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**BENEFÍCIOS COGNITIVOS DA PARTICIPAÇÃO ESPORTIVA
E APTIDÃO CARDIORRESPIRATÓRIA EM MULHERES
JOVENS**

Londrina

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Tese apresentada ao Programa de Pós-Graduação Associado em Educação Física UEM/UEL do Centro de Educação Física e Esporte da Universidade Estadual de Londrina, como requisito à obtenção do Título de Doutor em Educação Física.

Orientador: Prof. Dr. Marcos Roberto Queiroga

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RESUMO

Objetivo: Este estudo tem como objetivo analisar a relação entre aptidão cardiorrespiratória (ACR), engajamento esportivo, fator neurotrófico derivado do cérebro (BDNF) e controle cognitivo em jovens do sexo feminino. **Métodos:** O estudo possui desenho transversal. A amostra foi composta por 33 mulheres jovens com idade entre 18 e 30 anos que foram submetidas a medidas antropométricas, avaliação da composição corporal, mediante densitometria por dupla emissão de raios X (DXA), avaliação da ACR usando um sistema de calorimetria indireta, avaliação bioquímica do BDNF e dosagem de estradiol. Também foram obtidas informações sociodemográficas, engajamento esportivo, função cognitiva (controle inibitório e memória de trabalho) e condição de saúde reprodutiva. Para a análise dos dados foi empregada a regressão linear, regressão quadrática e modelos de mediação. Sendo adotada significância de 5%. **Resultados:** o presente trabalho evidenciou que existe uma curva de “U” invertido entre a ACR e o controle inibitório, sendo que a regressão quadrática apresenta uma variância compartilhada de 16,1%. Bem como a prática esportiva apresenta relações lineares significativas com a memória de trabalho. Entretanto, a ACR pode mediar essa relação, apresentando apenas efeitos indiretos sobre a relação da prática esportiva e a memória de trabalho. Por fim, o tempo semanal gasto em treinamento esportivo apresenta uma relação linear e positiva com os níveis de BDNF circulante em repouso. **Conclusão:** Os resultados confirmaram que a ACR possui efeitos sobre quase todas as variáveis de controle cognitivo. E o tempo despendido em práticas esportivas está ligado aos níveis de BDNF circulante. Ademais, as práticas esportivas podem ser um bom meio para aumentar a ACR e principalmente podem aumentar os níveis de BDNF circulante.

Palavras Chaves: Aptidão física; Função executiva; Desempenho cognitivo; Escolares.

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ABSTRACT

Objective: This study aims to analyze the relationship between cardiorespiratory fitness (CRF), sports engagement, brain-derived neurotrophic factor (BDNF), and cognitive control in young females. **Methods:** The study employs a cross-sectional design. The sample comprised 33 young women aged 18 to 30 years, who underwent anthropometric measurements, body composition assessment via dual-energy X-ray absorptiometry (DXA), and evaluation of resting energy expenditure using an indirect calorimetry system. Additionally, biochemical assessments of BDNF and estradiol levels were conducted. Data on sociodemographic information, sports engagement, cognitive function (inhibitory control and working memory), and reproductive health status were also collected. Data analysis utilized linear regression, quadratic regression and mediation models. A significant level was set at 5%. **Results:** The study highlighted a significant inverted “U” relationship between CRF and inhibitory control, with both variables sharing a variance of 16.1%. Furthermore, sports engagement demonstrated a linear relationship with working memory; however, CRF mediates this relationship, indicating only an indirect effect between sports practice and working memory. Lastly, the number of weekly hours spent on sports practice was positively correlated with serum BDNF levels. **Conclusion:** The results confirm the impact of CRF on cognitive control variables. Additionally, time spent on sports practice is associated with BDNF levels. Overall, engaging in sports appears to be an effective way to improve both CRF and BDNF levels.

Keywords: BDNF; Estradiol; Sports; Female; Cardiorespiratory fitness; Reproductive health.

Ilustrações

| | |
|---|-----|
| Figura 1 – Modelos teóricos e lacunas referentes a aptidão cardiorrespiratória e prática esportiva com desfechos cognitivos..... | 19 |
| Figura 2 – PRISMA FlowDiagram..... | 39 |
| Figura 3 – Proposed pathways found in this scoping review between aerobic exercise and sports with cognitive outcomes..... | 61 |
| Figura 4 – Quadratic regression between cardiorespiratory fitness and inhibitory control..... | 89 |
| Figura 5 – Linear regression between hours of training and BDNF..... | 112 |
| Figura 6 – Mediation model between sports practice, cardiorespiratory fitness and working memory..... | 113 |

Abreviações

| | |
|---------------------|--|
| AF | Atividade física |
| ATP | Adenosine triphosphate |
| ACR | Aptidão cardiorrespiratória |
| BDNF | Fator neurotrófico derivado do cérebro |
| CB | Tarefa de blocos de corsi |
| CRF | Cardiorespiratory fitness |
| DXA | Absorciometria por raios-X com Dupla Emissão |
| DMO | Densidade mineral óssea |
| ER | Estrogen Receptor |
| E2 | Estradiol |
| ELISA | Enzyme-Linked Immunosorbent Assay |
| fMRI | Functional magnetic resonance imaging |
| GXT | Teste escalonado máximo |
| HIIT | High-intensity interval training |
| HR | Frequência Cardíaca |
| PCC | Population Concept Context |
| RER | Respiratory exchange ratio |
| RT | Reaction time |
| VEGF | Vascular endothelial growth factor |
| VO ₂ max | Consumo máximo de oxigênio |

SUMÁRIO

CAPÍTULO 1

| | | |
|----------|---|-----------|
| 1 | INTRODUÇÃO | 11 |
| 1.1 | INATIVIDADE FÍSICA, APTIDÃO CARDIORRESPIRATÓRIA E PRÁTICA ESPORTIVA | 11 |
| 1.2 | DESFECHOS COGNITIVOS | 12 |
| 1.3 | APTIDÃO CARDIORRESPIRATÓRIA E DESFECHOS COGNITIVOS | 14 |
| 1.4 | PRÁTICA ESPORTIVA E DESFECHOS COGNITIVOS | 15 |
| 1.5 | FUTUROS DIRECIONAMENTOS | 17 |
| 1.6 | OBJETIVOS E ESTRUTURA DO PROJETO | 20 |

CAPÍTULO 2

| | | |
|----------|--|-----------|
| 2 | PROCEDIMENTOS METODOLÓGICOS | 22 |
| 2.1 | AMOSTRA | 22 |
| 2.2 | COLETA DE DADOS | 23 |
| 2.3 | ANTROPOMETRIA | 23 |
| 2.4 | COMPOSIÇÃO CORPORAL | 24 |
| 2.5 | AVALIAÇÃO SOCIOECONÔMICA | 24 |
| 2.6 | SAÚDE REPRODUTIVA | 24 |
| 2.7 | ATIVIDADE FÍSICA | 24 |
| 2.8 | TESTES COGNITIVOS | 25 |
| 2.8.1 | Blocos de Corsi | 25 |
| 2.8.2 | Stroop test | 25 |
| 2.9 | FATOR NEUROTRÓFICO DERIVADO DO CÉREBRO (BDNF) E ESTRADIOL (E2) | 26 |
| 2.10 | APTIDÃO CARDIORRESPIRATÓRIA | 26 |
| 2.11 | ANÁLISE ESTATÍSTICA | 29 |

CAPÍTULO 3

| | | |
|----------|---|-----------|
| 3 | Scoping Review | 31 |
| 3.1 | ARTIGO 1: ROLE OF CARDIORESPIRATORY FITNESS, AEROBIC EXERCISE AND SPORTS PARTICIPATION IN FEMALE COGNITION: A SCOPING REVIEW | 31 |
| 3.2 | BACKGROUND | 32 |
| 3.3 | METHODS | 36 |
| 3.3.1 | Inclusion and Exclusion criteria | 36 |
| 3.3.2 | Search Strategy | 37 |
| 3.3.3 | Data extraction and synthesis | 38 |
| 3.4 | RESULTS | 38 |
| 3.4.1 | Cardiorespiratory fitness and cognitive-related outcomes | 47 |

| | | |
|-------|--|----|
| 3.4.2 | Aerobic exercise and cognitive-related outcomes..... | 47 |
| 3.4.3 | Sports practice and cognitive-related outcomes | 48 |
| 3.4.4 | Menstrual cycle influence on the relationship between cardiorespiratory fitness, aerobic exercise, sports and cognitive-related outcomes | 49 |
| 3.4.5 | Pregnancy influence on the relationship between cardiorespiratory fitness, aerobic exercise, sports and cognitive-related outcomes | 50 |
| 3.5 | DISCUSSION | 51 |
| 3.5.1 | Cardiorespiratory fitness | 51 |
| 3.5.2 | Aerobic exercise | 53 |
| 3.5.3 | Sports participation | 55 |
| 3.5.4 | Menstrual cycle..... | 57 |
| 3.5.5 | Pregnancy..... | 59 |
| 3.6 | LIMITATIONS | 60 |
| 3.7 | CONCLUSION | 60 |
| 3.8 | FUTURE RESEARCH..... | 61 |
| 3.9 | REFERENCES..... | 62 |

CAPÍTULO 4

| | | |
|----------|---|-----------|
| 4 | Artigo Original | 75 |
| 4.1 | ARTIGO 2: WHAT IS THE OPTIMAL LEVEL OF CARDIORESPIRATORY FITNESS FOR COGNITIVE OUTCOMES: THE INVERTED “U” THEORY | 75 |
| 4.2 | BACKGROUND | 76 |
| 4.3 | METHODS..... | 78 |
| 4.3.1 | Antropometric measurements..... | 79 |
| 4.3.2 | Demographic assessment | 79 |
| 4.3.3 | Reproductive health..... | 79 |
| 4.3.4 | Cognitive Tests | 80 |
| 4.3.4.1 | Corsi Block test..... | 80 |
| 4.3.4.2 | Stroop test | 81 |
| 4.3.5 | Brain derived neurotrophiv factor (BDNF) and estradiol (E2) | 82 |
| 4.3.6 | Cardiorespiratory Fitness..... | 82 |
| 4.3.7 | Statistical Analysis | 84 |
| 4.4 | RESULTS | 84 |
| 4.5 | DISCUSSION | 90 |
| 4.6 | CONCLUSION | 92 |
| 4.7 | SUPPLEMENTARY TABLE | 94 |
| 4.8 | REFERENCES..... | 95 |

CAPÍTULO 5

| | | |
|----------|------------------------------|------------|
| 5 | Artigo Original | 101 |
|----------|------------------------------|------------|

| | | |
|---------|--|-----|
| 5.1 | ARTIGO 3: COGNITIVE BENEFITS OF SPORTS PARTICIPATION: INVESTIGATING BDNF LEVELS AND EXECUTIVE FUNCTIONS IN FEMALE | 101 |
| 5.2 | BACKGROUND | 102 |
| 5.3 | METHODS | 104 |
| 5.3.1 | Antropometric measurements | 105 |
| 5.3.2 | Physical Activity and Sports engagement questionnaire | 105 |
| 5.3.3 | Cognitive Tests | 106 |
| 5.3.3.1 | Corsi Block test | 106 |
| 5.3.3.2 | Stroop test | 106 |
| 5.3.4 | Brain derived neurotrophiv factor (BDNF) | 107 |
| 5.3.5 | Cardiorespiratory Fitness | 107 |
| 5.3.6 | Statistical Analysis | 108 |
| 5.4 | RESULTS | 109 |
| 5.5 | DISCUSSION | 114 |
| 5.6 | CONCLUSION | 116 |
| 5.7 | REFERENCES | 117 |

CAPÍTULO 6

| | | |
|----------|-----------------------------|-----|
| 6 | Considerações finais | 123 |
|----------|-----------------------------|-----|

| | |
|--------------------|-----|
| REFERÊNCIAS | 125 |
|--------------------|-----|

| | |
|------------------|-----|
| APÊNDICES | 144 |
|------------------|-----|

Capítulo 1

1 INTRODUÇÃO

1.1 INATIVIDADE FÍSICA, APTIDÃO CARDIORRESPIRATÓRIA E PRÁTICA ESPORTIVA

Na sociedade atual, a falta de atividade física (AF) e os baixos níveis de aptidão cardiorrespiratória (ACR) têm criado desafios à saúde pública. A inatividade física é a quarta causa de mortalidade no mundo, seguido pelo índice de massa corporal (IMC) acima de 25 kg/m² (World Health Organization, 2009). A inatividade física e um elevado IMC estão associados com a síndrome metabólica, baixa saúde óssea, que promovem um impacto negativo na saúde mental (World Health Organization, 2009). Ademais, a inatividade física está associada a maiores níveis de depressão e ansiedade, particularmente em mulheres (Puccinelli *et al.*, 2021). A aptidão cardiorrespiratória (ACR) é um componente essencial da saúde física e está diretamente relacionada à capacidade do corpo de fornecer oxigênio às células e remover metabólitos (Caspersen; Powell; Christenson, 1985; Ozemek *et al.*, 2018). Níveis baixos de ACR têm efeitos prejudiciais sobre a saúde da população, exacerbados pelo aumento do comportamento sedentário durante a pandemia de COVID-19 (Bertrand *et al.*, 2021; Clemmensen; Petersen; Sørensen, 2020; Shuval *et al.*, 2022).

Aproximadamente 47% da população adulta não atinge os níveis recomendados de AF, sendo os maiores níveis de inatividade encontrados entre as mulheres (Guthold *et al.*, 2018). Esse problema de saúde pública foi exacerbado pela recente pandemia causada pelo SARS-CoV-2, na qual uma maior parcela da população adotou um estilo de vida inativo, com um maior tempo em comportamento

sedentário e com um decréscimo no engajamento em esportes recreacionais (Bertrand *et al.*, 2021; García-Tascón *et al.*, 2020; Stockwell *et al.*, 2021). Similarmente, com o decréscimo da ACR, os níveis de depressão significativamente aumentam (Dishman *et al.*, 2012).

Um método para alterar esse decréscimo nos níveis de ACR é estar engajado em práticas esportivas regulares. Uma vez que esportes têm sido identificados como uma forma eficaz de melhorar a ACR (Castagna; Krstrup; Póvoas, 2020; Khan *et al.*, 2012; Oliveira *et al.*, 2017). Mais ainda, os esportes podem aumentar o prazer da atividade física ao melhorar as interações sociais (Khan *et al.*, 2012). Além disso, a adesão aos esportes pode ser maior em comparação com outras formas de atividade física devido à maior intensidade e ao tempo reduzido necessário para atender às recomendações de atividade (Khan *et al.*, 2012; Rhodes; Warburton; Murray, 2009).

1.2 DESFECHOS COGNITIVOS

Dentro das áreas de estudo da saúde mental, uma parte busca analisar o controle cognitivo e sua relação com atividade física, aptidão física e exercício (McMorris, 2016). O controle cognitivo se refere a uma série de processos cerebrais com o objetivo de regular interações intrínsecas e extrínsecas com a função de realizar metas (Botvinick *et al.*, 2001). O mesmo, também é conhecido por funções executivas e se referem a aspectos cognitivos caracterizados por processos direcionais com um objetivo que envolvem planejamento, coordenação e programação de possíveis interações ambientais, e incluem processos como inibição, memória de trabalho e flexibilidade mental (Botvinick *et al.*, 2001; Hillman; Biggan, 2017; Mourão Junior; Melo, 2011). Sendo a função executiva essencial para as

atividades diárias (Vaughan; Giovanello, 2010) e para as conquistas acadêmicas (de Bruijn *et al.*, 2018).

Ademais, processos executivos são dependentes das conexões cerebrais, principalmente do córtex pré-frontal, hipocampo e os gânglios da base (Meeusen *et al.*, 2017). Nesse sentido, o Brain-Derived Neurotrophic Factor (BDNF) é responsável pela plasticidade sináptica, potenciais de longa duração e memória longa, promovendo uma maior ativação neural e uma melhor conectividade cerebral, a qual resulta em um processamento mais rápido das tarefas (Cunha; Brambilla; Thomas, 2010; Lewin; Carter, 2014).

O BDNF tem como função a formação de memórias longas, essenciais para o controle top-down, além de estar relacionada à formação de novos neurônios. O BDNF apresenta sua maior concentração sobre as estruturas do hipocampo, corpo estriado e amígdala, quando ativado inicia uma série de processos elétricos juntamente com o AMP cíclico, o qual é um neurotransmissor que amplifica a ativação cerebral, sendo esses responsáveis pela formação de novos neurônios e memórias (ligações sinápticas) (McMorris, 2016; Meeusen *et al.*, 2017).

Mais do que ser um marcador neural, o BDNF está relacionado com a recuperação tecidual. Logo após o exercício físico, BDNF é expresso na musculatura e se liga aos tecidos para reparação (Yu *et al.*, 2017). Do mesmo modo, a expressão de BDNF e seu receptor tropomyosin-related kinase B (TRKb) aumenta durante a remodelação óssea, aumentando as conexões BDNF-TRKb e melhorando a formação óssea (Kilian *et al.*, 2014). Essas informações demonstram a importância dessa proteína para o corpo humano.

1.3 APTIDÃO CARDIORRESPIRATÓRIA E DESFECHOS COGNITIVOS

O benefício da ACR sobre a saúde mental pode ser explicado pela ativação de regiões do cérebro, especialmente o hipocampo, e pelo aumento na liberação de fatores neurotróficos como o BDNF, cuja expressão está diretamente relacionada à ACR (De Sousa *et al.*, 2021; McMorris, 2016; Whiteman *et al.*, 2014). Ademais, a ACR é diretamente relacionada a proteínas associadas com o desenvolvimento e manutenção neural, como o fator de crescimento endotelial vascular (VEGF), responsável pela vascularização cerebral, e o BDNF (Hillman; Erickson; Kramer, 2008; McMorris, 2016; Meeusen *et al.*, 2017; Whiteman *et al.*, 2014). Mais ainda, um aumento da ACR, também está associado a alterações morfológicas no cérebro, como maior volume do hipocampo e maior irrigação sanguínea em regiões cerebrais responsáveis pelo controle cognitivo (Chaddock-Heyman *et al.*, 2015; Ortega *et al.*, 2017). Tanto a ACR quanto o BDNF são fortemente e positivamente relacionados ao controle cognitivo (Vaynman; Ying; Gomez-Pinilla, 2004; Whiteman *et al.*, 2014). Ainda, a relação entre a ACR e as conquistas acadêmicas são mediadas pelas funções executivas (de Bruijn *et al.*, 2018; Martinez-Vizcaino *et al.*, 2021).

No entanto, a relação entre ACR e desempenho cognitivo apresenta variações. Estudos sugerem que existe uma relação em forma de "U invertido", onde níveis extremamente altos de ACR podem estar associados a um desempenho cognitivo piorado, possivelmente devido ao excesso de estímulos neurais que geram "ruído" no processamento cerebral (McMorris, 2016; McMorris; Hale, 2012; Wang; Guo, 2022). Isso pode ocorrer em atividades de alta intensidade, que elevam os níveis de neurotransmissores excitatórios e hormônios como o cortisol, levando a conflitos no processamento neural (McMorris; Hale, 2012; Świątkiewicz *et al.*, 2023).

Além disso, durante o exercício aeróbico, as contrações musculares e a recuperação muscular têm um papel essencial na liberação e modulação do BDNF (Matthews *et al.*, 2009; Yu *et al.*, 2017). O BDNF atua, também, na neuroproteção, neurogênese e consolidação da memória (Cunha; Brambilla; Thomas, 2010; Miranda *et al.*, 2019; Rothman; Mattson, 2013). Essa relação complexa sublinha a necessidade de um equilíbrio na intensidade do exercício para maximizar os benefícios cognitivos sem alcançar níveis prejudiciais de ACR. Entretanto, os estudos são preliminares e mais informações são necessárias sobre este fato, principalmente em mulheres.

Além disso, a pesquisa sobre a ACR e os resultados cognitivos frequentemente carece de representação feminina. Hormônios reprodutivos nas mulheres influenciam significativamente a função cognitiva e a excitabilidade cerebral, o que pode levar a respostas cognitivas distintas em comparação aos homens (Barha *et al.*, 2019; Barha; Liu-Ambrose, 2020; Pluchino *et al.*, 2013). A variação hormonal ao longo do ciclo menstrual pode impactar negativamente a liberação de BDNF, especialmente em momentos de baixos níveis de estradiol (Nose *et al.*, 2019; Pluchino *et al.*, 2013; Scharfman; MacLusky, 2006). Ademais, é importante destacar que a promoção da saúde cognitiva com exercícios durante a idade adulta pode ser protetora contra os efeitos prejudiciais da idade, da redução dos hormônios sexuais e de disfunções químicas sobre as funções cognitivas (Barha; Liu-Ambrose, 2020; Furley; Schütz; Wood, 2023; McMorris, 2016). Assim, futuras investigações devem considerar essas diferenças e o papel dos hormônios reprodutivos na relação entre ACR e função cognitiva.

1.4 PRÁTICA ESPORTIVA E DESFECHOS COGNITIVOS

A participação crônica em esportes tem demonstrado melhorar a cognição, possivelmente devido aos altos níveis de aptidão cardiorrespiratória (ACR) resultantes dessa prática (Caspersen; Powell; Christenson, 1985; Khan *et al.*, 2012). No entanto, os benefícios cognitivos da participação esportiva não se restringem apenas à ACR. Estudos indicam que a atividade esportiva pode ser relacionada às funções executivas, uma vez que exige uma ativação mais elevada do córtex pré-frontal e demanda mais funções executivas em comparação a outras formas de atividade física (Furley; Schütz; Wood, 2023).

Pesquisas demonstram efeitos positivos da participação esportiva no controle inibitório e do BDNF circulante, ambos fundamentais para a saúde cognitiva (Weber *et al.*, 2024). A prática esportiva também promove a ativação de regiões cerebrais e uma possível liberação de fatores neurotróficos, como o BDNF, que são essenciais para a neurogênese e a formação de memórias e desempenho de tarefas diárias (McMorris, 2016; Weber *et al.*, 2024).

Mais do que aumentar a ACR, a prática esportiva impacta positivamente as funções executivas, dados indicam que há uma melhora na performance em tarefas que dependam de controle inibitório para praticantes de esportes (Formenti *et al.*, 2021; Voss *et al.*, 2010). Os efeitos da prática esportiva nas funções executivas podem ser relacionados a utilização de tarefas motoras mais complexas para uma melhor performance. Também, durante a prática esportiva, há uma necessidade de integrar atenção e a memória de trabalho para decisões em tempo real, e uma maior demanda de controle inibitório para garantir a ação correta (Formenti *et al.*, 2021; McMorris, 2016; Voss *et al.*, 2010; Zhou; Xi; Qin, 2020).

Ao considerar os diferentes tipos de esportes, a distinção entre esportes de habilidades abertas e fechadas se torna relevante. Esportes de habilidades abertas,

requerem que os atletas respondam a um ambiente dinâmico e em constante mudança, exigindo atenção e memória de trabalho para a tomada de decisões em tempo real (Diamond; Ling, 2016). Já esportes de ambientes fechados são realizados de forma cíclica, consistente e sem interferências externas (Allard; Burnett, 1985). Um estudo específico, observou, que os atletas de futebol apresentaram tempos de reação mais rápidos durante tarefas inibitórias em comparação com grupos que praticavam esportes aeróbicos ou não praticavam esportes. Essa diferença pode ser atribuída a uma melhor conectividade funcional e ativação de áreas cerebrais específicas, como os núcleos basais e o córtex frontal, que são fundamentais para o controle motor e a ação inibitória (Shi *et al.*, 2020).

É essencial que futuras investigações considerem esses fatores influentes e elucidem como as funções executivas podem ser aprimoradas especificamente pela prática esportiva (Furley; Schütz; Wood, 2023).

1.5 FUTUROS DIRECIONAMENTOS

A falta de engajamento esportivo ou exercício aeróbico pode aumentar a obesidade, a qual negativamente impacta marcadores bioquímicos relacionados à atividade neural (i.e., BDNF; VEGF) (Engel; Velloso, 2022). Dado a prevalência de obesidade, que foi exacerbada durante a pandemia do SARS-CoV-2 (Clemmensen; Petersen; Sørensen, 2020), é necessário elucidar seu efeito nos diferentes aspectos da cognição. Além disso, os impactos da obesidade nos marcadores bioquímicos neurais são inconsistentes na literatura (Sandrini *et al.*, 2018), sendo necessário avaliar os possíveis efeitos mediadores da gordura corporal.

Mesmo que 95% do crescimento cerebral ocorra até os seis anos de idade, processos sinápticos, crescimento neural, e consolidação de memória persistem durante a vida (Khan; Hillman, 2014; Meeusen *et al.*, 2017). Desse modo, a estimulação do cérebro por meio de esportes e exercício aeróbico durante a fase adulta pode ser uma janela de oportunidade para promover a saúde cerebral e reduzir os impactos da idade, níveis hormonais e adiposidade no futuro (Barha; Liu-Ambrose, 2020).

Muitos estudos avaliaram apenas o efeito do exercício aeróbico agudo e sua relação com as funções cognitivas. Entretanto, estudos que avaliaram as relações entre prática esportiva, ACR, composição corporal e marcadores bioquímicos neurais são escassos, e lacunas de informações surgem conforme apresentado na Figura 1. Ademais, os efeitos da prática esportiva sobre a cognição podem ser dependentes da ACR, fazendo com que a ACR seja um possível mediador dessa relação. Essa lacuna na literatura deve ser investigada, uma vez que menores níveis de ACR podem resultar em piores desfechos cognitivos, e a prática esportiva pode ser usada como intervenção para alterar esses desfechos, já que apresenta um maior engajamento que outros tipos de atividade física. Assim, o presente projeto visa elucidar o efeito independente da prática esportiva e ACR sobre a cognição em mulheres jovens adultas e o possível efeito mediador da ACR e da gordura corporal.

1.6 OBJETIVOS E ESTRUTURA DO PROJETO

A estrutura da tese seguiu o modelo escandinavo, incluindo três artigos científicos. A presente tese tem uma introdução expandida e três artigos científicos. A pesquisa dessa tese foi desenvolvida no *Adamo Lab* (University of Ottawa) em colaboração com o Laboratory of Experimental and Applied Physiology to Physical Activity (LAFEAF). A coleta de dados foi realizada entre outubro de 2023 e janeiro de 2024. Esse estudo tem como objetivo avaliar a relação entre a aptidão cardiorrespiratória, prática esportiva, estradiol e fator neurotrófico derivado do cérebro, e controle cognitivo em mulheres adultas jovens. Esse estudo também evidenciara os efeitos da saúde reprodutiva sobre as variáveis apresentadas anteriormente.

Para responder o principal objetivo da tese, foi proposto os seguintes manuscritos científicos. Os títulos dos manuscritos, assim como os respectivos objetivos são os seguintes:

Artigo 1: Role of cardiorespiratory fitness, aerobic exercise and sports participation in female cognition: a scoping review

Objetivo principal: Mapear a literatura sobre os efeitos do exercício aeróbico, prática esportiva e aptidão cardiorrespiratória em mulheres adultas jovens, com subtópicos relacionados à gestação e ciclo menstrual.

Artigo 2: What is the optimal level of cardiorespiratory fitness for cognitive outcomes: The inverted “U” theory.

Objetivo principal: Analisar a relação entre a aptidão cardiorrespiratória e desfechos cognitivos e controlar as relações pelos níveis de estradiol.

Artigo 3: Cognitive benefits of sports participation: Investigating BDNF levels and executive functions in females.

Objetivo principal: Investigar os efeitos da prática esportiva nas funções executivas e nos níveis de BDNF em mulheres. Bem como, explorar a relação entre duração e intensidade dos esportes e os desfechos cognitivos.

Capítulo 2

2 PROCEDIMENTOS METODOLÓGICOS

2.1 AMOSTRA

O presente projeto é um estudo transversal aprovado pelo comitê de ética da University of Ottawa, sobre parecer de nº H-01-23-8825 (apêndice 1). A coleta de dados foi realizada entre Outubro de 2023 e Janeiro de 2024. A amostra do estudo foi composta por jovens mulheres adultas, com idade entre 18 e 30 anos. Os participantes foram recrutados através de flyers (apêndice 2).

Os Voluntários que enviaram e-mail demonstrando interesse, receberam todas as informações do estudo por meio do e-mail. Os participantes foram pré-avaliados para garantir que atendiam todos os critérios de inclusão e exclusão. Aos potenciais participantes foi enviado o termo de consentimento antes de realizar o agendamento da coleta de dados. Caso os participantes necessitassem de esclarecimentos adicionais, um membro da equipe fornecia as informações requeridas por e-mail, telefone ou conferência online, antes do início da coleta de dados. Todos os participantes assinaram o termo de consentimento livre e esclarecido (apêndice 3)

Os critérios de inclusão foram: mulheres entre 18 e 30 anos; não podiam ser gestantes, não poderiam apresentar contraindicação para realizar o DXA scan, precisariam se comunicar em inglês, francês ou português. Não poderiam usar drogas (i.e. maconha, substancias psicoativas).

Os critérios de exclusão foram: apresentar qualquer patologia ou condição óssea, baixa mobilidade, uso de substância psicoativa, gestação, ser diagnosticado com hiperatividade/ansiedade/depressão, não possuir inglês, francês ou português como língua materna.

O tamanho da amostra foi calculado a priori utilizando o software GPower 3.1[®] para regressão linear múltipla. O tamanho de efeito utilizado foi de $f^2=0.212$ (SCHMALHOFER *et al.*, 2019), poder de 0.8, alfa de 0.05, e 3 preditores. O cálculo amostral resultou em 31 sujeitos. O tamanho da amostra final foi de 33 indivíduos.

2.2 COLETA DE DADOS

A coleta de dados foi realizada em uma visita, com duração de aproximadamente 100 minutos. A coleta de dados foi realizada na seguinte ordem: questionários (sociodemográfico; saúde reprodutiva, atividade física), performance cognitiva, medidas antropométricas e composição corporal (massa magra, gordura e densidade mineral óssea), coleta sanguínea, e aptidão cardiorrespiratória. A descrição de cada variável está presente nos seguintes tópicos:

2.3 ANTROPOMETRIA

Medidas antropométricas de composição corporal foram avaliadas por uma balança com precisão de 0,1kg (Tanita, BWB-800, Lanchine, QC). A estatura foi avaliada por meio de um estadiômetro com precisão de 0,1cm (Tanita, HR-200, Lanchine, QC). Para avaliação da massa corporal, solicitou que

as participantes estivessem com roupas leves e descalço. Para medir a estatura as participantes se mantiveram em posição ortostática.

2.4 COMPOSIÇÃO CORPORAL

A composição corporal foi estimada pela técnica de Absorciometria por raios-X com Dupla Emissão (DXA) (Lunar Prodigy, GE). Gordura corporal e massa livre de gordura foram determinadas examinando o corpo inteiro do avaliado. O equipamento foi calibrado no início de cada dia de coleta seguindo as recomendações do fabricante e um técnico de laboratório com experiência nessa avaliação realizou a calibração.

2.5 AVALIAÇÃO SOCIOECONÔMICA

Todos as participantes completaram um questionário para avaliação do nível socioeconômico (apêndice 4) referente a etnia, status civil, último nível educacional obtido, renda bruta anual (i.e. bolsa de estudos, bolsas governamentais, suporte parental).

2.6 SAÚDE REPRODUTIVA

A saúde reprodutiva foi avaliada por meio de questionário focado em avaliar o uso de hormônios contraceptivos, período menstrual, gestação e doenças reprodutivas (i.e. síndrome do ovário policístico, endometriose) (Apêndice 5).

2.7 ATIVIDADE FÍSICA

O questionário de Baecke (BAECKE; BUREMA; FRIJTERS, 1982), foi utilizado para avaliar a prática esportiva e os níveis de atividade física (apêndice 6). O questionário é composto por 16 questões sobre a prática de atividade física em diferentes contextos, relacionado a prática de esportes, especificamente o tipo de esporte e frequência. Para a avaliação dos scores de esporte, atividade física no tempo livre e atividade física no trabalho, seguiu-se as recomendações do questionário, o qual leva em conta o tempo praticado, a intensidade e quais modalidades eram praticadas.

2.8 TESTES COGNITIVOS

Os testes cognitivos foram conduzidos em um ambiente silencioso e isento de estímulos audiovisuais. Ambas as avaliações ocorreram no mesmo dia, com um intervalo de descanso entre a aprendizagem e o teste propriamente dito. A aplicação dos testes foi realizada por meio de computadores.

2.8.1 Blocos de Corsi

Para verificar a memória de trabalho viso-espacial, o teste de blocos de Corsi foi realizado. Todos os participantes tiveram uma tentativa de adaptação e aprendizagem. Essa tarefa consiste em memorizar uma sequência de cubos que piscam na tela do computador. Para uma correta resposta, os participantes precisam reproduzir a mesma ordem apresentada pelo computador. Se os participantes não memorizassem os cubos em duas respostas consecutivas, o

teste era automaticamente encerrado. Último nível atingido e o score total foram adotados com indicadores de performance (BRUNETTI *et al.*, 2018).

2.8.2 Stroop test

O teste de Stroop foi realizado por respostas congruentes e incongruentes por meio de um computador. O teste possui duas possíveis tarefas; a primeira sendo congruente: quando a cor escrita é a mesma da pintada; a segunda incongruente: quando a cor escrita é diferente da pintada. O sujeito realizou 100 respostas com estímulos congruentes e incongruentes de maneira aleatória. Foram avaliados os seguintes scores: acurácia (percentual de respostas corretas); controle inibitório (acurácia congruente menos incongruentes), e tempo de reação (BARBAROTTO *et al.*, 1998; SCARPINA; TAGINI, 2017). Todos os indivíduos tiveram uma tentativa de adaptação e aprendizagem.

2.9 FATOR NEUROTRÓFICO DERIVADO DO CÉREBRO (BDNF) E ESTRADIOL (E2)

A coleta sanguínea foi realizada por um profissional habilitado, e aproximadamente 10ml foram coletados em tubos para a separação do sêrum. O sangue foi subsequentemente centrifugado a 2500 rpm durante 10 minutos a 4°C para separação do sêrum e após isso foi armazenado a -80°C. O BDNF e E2 foram analisados pelo método de *Sandwich Enzyme-Linked Immunosorbent Assay* (ELISA). Ambas as análises seguiram a instrução do fabricante para o *Human BDNF Elisa* (Invitrogen, ThermoFisher) e para o E2 (OriGene Technologies, Inc.). Para o E2, o percentual de inibição foi calculado uma vez que uma menor absorvância demonstra maior concentração. Todas as amostras

foram analisadas e o coeficiente de variação se manteve menor do que 10% para todos os sujeitos.

2.10 APTIDÃO CARDIORESPIRATÓRIA (CRF)

A aptidão cardiorrespiratória foi avaliada por meio do padrão ouro para consumo máximo de oxigênio (VO_{2max}) testado por meio de um calorimétrico indireto. Um teste máximo escalonado (GXT) a partir do teste modificado do protocolo de Balke (BALKE; WARE, 1959) determinou o VO_{2max} . Gases utilizados (i.e. O_2 ; CO_2) foram coletados por meio de um sistema metabólico portátil (K5, COSMED s.r.l., Rome, Italy). Uma máscara da Hans Rudolph (Hans Rudolph Inc, Kansas, USA) foi ajustada ao participante e conectada à unidade do K5. Antes do início do teste, os participantes se familiarizaram com a esteira por meio de um aquecimento de 5 minutos. Os participantes iniciaram o protocolo modificado de Balke a uma velocidade de 4.0 milhas por hora (mph) e foram incentivados a aumentar a velocidade até que se encontrasse uma velocidade confortável entre 5.0 – 7.0 mph. A velocidade da esteira foi baseada na frequência cardíaca (HR) que o participante atingiu durante o período de aquecimento. Para os participantes que atingiram uma HR maior que 75% da sua frequência cardíaca de reserva durante o aquecimento a velocidade se manteve a mesma do aquecimento. Se o participante atingisse uma HR entre 60 a 75% da HR durante o aquecimento, a velocidade da esteira seria de 0,5 mph mais rápida do que a velocidade de aquecimento. Para os participantes que atingissem menos de 60% da HR, a esteira seria ajustada 1 mph mais rápido do que o aquecimento. A frequência cardíaca de reserva foi determinada utilizando o método de Karvonen: $HR_{max} - HR_{rest}$. Enquanto existe um debate referente a

acurácia em determinar a HR_{max} , quando combinada com a $HR_{reserva}$ pode ser útil para estabelecer a velocidade para o GXT. HR_{max} foi determinada pela seguinte equação: $208 - 0.7 * age$ (TANAKA; MONAHAN; SEALS, 2001). A velocidade do teste podia ser alterada pela experiência em corrida do participante e em consulta com o avaliador

Imediatamente após a determinação da velocidade inicial do teste, o participante foi ajustado a máscara do K5. Após a fixação da máscara o participante se manteve em pé por 3-5 minutos para coleta dos valores metabólicos e para que o indivíduo se acostumasse com o aparato. Os primeiros 2 minutos do teste consistia em uma corrida na velocidade pré-determinada com uma inclinação de 0%. O teste consistia na inclinação de 2% a cada 2 minutos até que a razão de conversão de oxigênio (RER) de 1.0 fosse atingida; então a esteira era inclinada por 1% a cada minuto até a fadiga, nesse momento o teste era terminado. Ao final de cada estágio do teste os participantes reportaram a sua percepção subjetiva de esforço (PSE) utilizando a escala de borg.

Foram tomadas todas as precauções para minimizar o desconforto e os riscos de cada participante. Ocasionalmente, por questões de segurança, o teste poderia ser terminado antes de atingir o VO_{2max} ou fadiga. O participante foi instruído que ele poderia parar o teste a qualquer momento sem prejuízo. Os critérios para finalização do teste foram os seguinte (AMERICAN COLLEGE OF SPORTS MEDICINE, 2018):

- Angina (dor no peito)
- Sinais de baixa perfusão sanguínea– dor de cabeça leve, confusão, palidez, náusea, frio, cianose
- Interrupção do teste por meio do participante

- Fadiga
- Falha nos equipamentos
- Respiração curta, câimbra
- Falha em aumentar a HR com o aumento da intensidade do exercício

Diversos indicadores diretos e subjetivos foram utilizados para confirmar o esforço máximo durante o GXT. Os seguintes indicadores foram utilizados para confirmar o $VO_2\text{max}$.

- Falha em aumentar a HR com o aumento da intensidade do exercício
- Um platô no consumo de oxigênio (>150 ml/min) com o aumento o esforço físico
- Um RER maior de 1.15
- Uma PSE maior ou igual a 18 (escala 6 a 20)

2.11 ANÁLISE ESTATÍSTICA

Os dados foram testados para normalidade utilizando assimetria e curtose. As comparações foram realizadas por meio do teste de ANOVA, já as variáveis que não apresentaram normalidade foram comparadas pelo teste de Kruskal-Wallis. As relações foram realizadas por meio de uma matrix de correlação com as correlações de Pearson (r). A regressão linear múltipla foi aplicada para as variáveis que apresentassem $p < 0.157$ (HEINZE; DUNKLER, 2017), e diagnóstico de colinearidade e efeitos residuais também foram verificados. As variáveis também foram testadas por meio das curvas de estimações, e o modelo quadrático foi avaliado para análise de “U” invertido. Todas as análises foram controladas

pelas variáveis demográficas e saúde reprodutiva que apresentaram correlações significantes com as variáveis dependentes e independentes.

As análises de mediação seguiram pressupostos previamente descritos (Baron; Kenny, 1986) e o procedimento de bootstrapping foi realizado com 5000 repetições da amostra, também a classificação dos modelos de mediação e não-mediação seguiu uma árvore de decisões (Zhao; Lynch; Chen, 2010).

Capítulo 3

3. Scoping Review

3.1 **Artigo 1:** ROLE OF CARDIORESPIRATORY FITNESS, AEROBIC EXERCISE AND SPORTS PARTICIPATION IN FEMALE COGNITION: A SCOPING REVIEW

Abstract

Background: The impact of cardiorespiratory fitness (CRF) on cognition is thought to be mediated by brain-derived neurotrophic factor (BDNF). Aerobic exercise can increase CRF through various activities, including sports participation. The relationship between these factors in females has yet to be elucidated. **Objective:** This review aims to map the current literature on the effects of aerobic exercise, sports participation, and CRF in healthy adult females, with sub-topics of pregnancy and menstrual cycle periodicity. **Methods:** A scoping review of the literature was conducted following PRISMA guidelines and the PCC mnemonic (Population, Concept, and Context). The following five databases were screened: CINAHL, Medline, Web of Science, SPORTDiscus, and Scopus. Eligible articles included healthy adult females, investigated aerobic exercise, sports participation or CRF, and linked outcomes to cognition. Data from included manuscripts was extracted and analyzed. Two sub-population groupings (pregnant individuals and menstrual cycle) were established to further aid the interpretation of the findings. **Results:** Of the 300 titles and abstracts screened, 74 were eligible for full-text screening, and 28 were included in the scoping review. Of the 28 included, 14 did not control for or report on menstrual cycle phase or sex hormones. **Conclusion:** This scoping review found an inverse ‘U’ relationship between aerobic exercise and cognition, demonstrating an optimal dose of aerobic exercise to benefit cognitive functions. As estrogen may impact the relationship between CRF and neural growth factors, more research is needed on this pathway, independent of the menstrual cycle, to determine potential beneficial effects. It is currently unknown whether sports participation can independently impact cognition.

Keywords: Executive Function, Cognition, Sports, Fitness, Aerobic Exercise, Female

3.2 BACKGROUND

Low levels of cardiorespiratory fitness (CRF) have detrimental effects on population health and have been exacerbated with the rise in sedentary behavior during the COVID-19 pandemic (Bertrand et al., 2021; Clemmensen; Petersen; Sørensen, 2020; Shuval et al., 2022). Low levels of CRF are associated with obesity (Carbone et al., 2019), metabolic syndrome (Myers; Kokkinos; Nyelin, 2019), poor bone health (Arena et al., 2022), and anxiety and depression (Dishman et al., 2012; Ortega et al., 2008; Shuval et al., 2022). Pertaining to mental health, CRF is directly related to the expression of the molecule brain-derived neurotrophic factor (BDNF) (De Sousa et al., 2021; McMorris, 2016; Whiteman et al., 2014); where low levels of this protein are associated with major depression (De Sousa et al., 2021; Kim et al., 2007).

BDNF contributes on neuroprotection, neurogenesis, memory consolidation, brain excitability, and neural connectivity (Cunha; Brambilla; Thomas, 2010; Miranda et al., 2019; Rothman; Mattson, 2013). Moreover, the effects of CRF on cognition seem to be mediated by BDNF levels (Piepmeier; Etnier, 2015; Vaynman; Ying; Gomez-Pinilla, 2004). When examining aspects of cognition, the executive function appears to be most influenced by CRF (Hillman; Erickson; Kramer, 2008; Scott et al., 2016; Weber et al., 2022). Executive function refers to series of cognitive processes responsible for action plans and decision making; its features include domains such as inhibitory control (i.e., inhibit distraction stimulus that can lead to a wrong action), working memory, and mental flexibility (Diamond; Ling, 2016; Hillman; Biggan, 2017), and are essential for daily tasks (e.g., Managing money; Managing home) (Vaughan; Giovanello, 2010) as well as academic achievement (de Bruijn et al., 2018).

One way to improve CRF is by engaging in habitual aerobic exercise (Caspersen; Powell; Christenson, 1985). A category of aerobic exercise is sports participation. Individuals exposed to sports training that involve physical exertion, especially aerobic exercises, usually exhibit increased CRF (Khan et al., 2012; Oliveira et al., 2017). More than that, sports participation can be divided in open (i.e., basketball, soccer, hockey) and closed skills sports (i.e., swimming, running). Open skill sports are those which players are required to consistently react and adapt to an unpredictable environment. Whereas closed skill sports are defined by sports with a stable environment, during which players have a predetermined movement pattern (Allard; Burnett, 1985).

More than being physically demanding, sports participation can also require the high utilization of different cognitive aspects (e.g., attention, inhibitory control, cognitive flexibility) (Furley; Schütz; Wood, 2023). To significantly improve sports performance it is necessary to integrate these cognitive functions and enhance the top-down processing (i.e., utilize past experiences to guide an activity or reaction) (Logan et al., 2022; Voss et al., 2010). During sports participation, players must be attentive to different environmental changes, and adapt to complex and quickly changing conditions (Diamond; Ling, 2016). However, there is a lack of literature examining the relationship between sport-based and non-sport physical activity and cognition (Castells-Sánchez et al., 2021). What remains to be clarified or determined is whether or not engaging in sports participation offers cognitive advantages over regular engagement in physical activity, since executive functions are correlated to health related variables (i.e. physical fitness) (Furley; Schütz; Wood, 2023).

During aerobic exercise, skeletal muscle contractions upregulate BDNF release (Matthews et al., 2009; Yu et al., 2017), which can result in BDNF being stored in blood platelets (Fujimura et al., 2002). Additionally, blood platelets promote homeostasis by repairing vessels, promoting clotting, and increasing inflammatory responses (Zucker, 1980). There is an effect of CRF on platelet activity owing to muscular and vascular adaptations to habitual physical activity/training (Currie et al., 2009; Heber et al., 2016). Moreover, in animals models, circulating BDNF can cross the blood-brain barrier, and peripheral BDNF (e.g. serum BDNF) is strongly related to the amount of BDNF in the brain (Klein et al., 2011). Another protein related to cardiorespiratory fitness (CRF), muscle contraction, and brain health is Vascular Endothelial Growth Factor (VEGF). VEGF plays a crucial role in promoting angiogenesis. Increasing VEGF dynamics with exercise (Hoier; Hellsten, 2014), may enhance cerebral blood flow, which is essential for supporting neurogenesis (Fabel et al., 2003).

Exposure to aerobic exercise results in hormonal changes. Strenuous activities can increase cortisol levels, catecholamine release, and decrease energy resources. These alterations in whole body homeostasis can overstimulate cognitive functions. For example, during a strenuous exercise, the body increases catecholamine levels and glucose consumption (Kjær; Secher; Galbo, 1987); these patterns can result in neural noise due to high levels of catecholamines (McMorris, 2016; McMorris; Hale, 2012) or decreasing brain excitability by decreasing energetic resources during/after intense activities (Quistorff; Secher; Van Lieshout, 2008; Tomporowski, 2003). Therefore, determining what the optimal dose of aerobic exercise for improvements in cognitive function is necessary.

Biological sex is an important consideration when examining CRF as well as aspects of cognition as there are known between-sex differences. These differences occur mainly because of sex hormones since estrogen is strongly related to BDNF (Pluchino et al., 2013). Also, engaging in exercise may have more significant impacts on cognition in females (Barha; Liu-Ambrose, 2020). The promotion of cognitive health with exercise during adulthood may be protective against the deleterious effects of age, reduction of sex hormones and chemical dysregulations on cognitive functions (Barha; Liu-Ambrose, 2020; Furley; Schütz; Wood, 2023; McMorris, 2016). During adulthood, menstruation and pregnancy are uniquely female experiences that may play a role in cognitive functions and hormone release. All these aspects must be addressed to elucidate the possible female-centric impact of CRF/aerobic activity on cognitive-related outcomes. Cognitive-related outcomes are measures/effects related to the function of brain and mental process which encompass cognitive function, growth factors and other biomarkers that may influence cognitive function and brain imaging.

The available literature predominantly focuses on males or mixed samples, creating a gap in research regarding the effects of CRF, aerobic exercise, and cognition specifically in the female population. It is important to highlight that males and females experience significantly different impacts on cognition (Barha; Liu-Ambrose, 2020; Castells-Sánchez et al., 2021) and CRF (Kind et al., 2019) through their lifespan. These differences complicate the application of findings across the sexes. Therefore, the purpose of this study is to map the research done and identify the gaps related to the effects of aerobic exercise, sports participation, and cardiorespiratory fitness on cognition in healthy

adult females, with sub-topics related to menstrual cycle periodicity and pregnancy. Considering the wide scope of our topic and the limited existing literature, a scoping review is one of the most suitable methods for identifying and analyzing gaps in the literature (Munn et al., 2018)

3.3 METHODS

3.3.1 Inclusion and exclusion criteria

A scoping review was conducted, using the PCC mnemonic (Population, Concept, and Context) to develop the research question (Munn et al., 2018), to elucidate the state of the literature on the relationship between aerobic exercise, sports participation, cardiorespiratory fitness, and cognition in a healthy female population. This study followed the recommendations of PRISMA-ScR checklist (Tricco et al., 2018).

Eligible articles included the following aspects: 1) healthy adult female individuals; 2) investigated any aerobic exercise, sports participation, or cardiorespiratory fitness; and 3) the outcomes were linked to cognition. Articles that included male participants, pathology, animals, elderly, and when the objective of the study was to verify the effects of illicit or admissible/legal drug use on cognition, were excluded.

3.3.2 Search strategy

The initial search was performed on October 30th, 2022, and a second search, to refine the articles was performed on September 13th, 2023. The following databases were screened: Cinahl, Medline, Web of Science, Sport

Discus, and Scopus. The keywords, MeSH terms, and Boolean operators used to facilitate the search are detailed in Table 1. For this review no restriction for language and date was utilized. The articles eligible for the title/abstract screening were transferred to Covidence, and duplicate articles were automatically removed. Two reviewers independently screened the manuscripts by title and abstract; if any conflict was identified, a third review was consulted. The reference lists of included articles were checked for potentially relevant studies that met our inclusion criteria.

Table 1. Search strategy for Medline

| Key Term | Search Strategy | Retrieved Articles |
|---------------------------|---|---------------------------|
| Aerobic Exercise | ("Sports" OR "Sport" OR "Athletes" OR "Physical Fitness" OR "Cardiorespiratory Fitness" OR "Aerobic Exercise") | 370,317 |
| Cognitive outcomes | ("Brain-Derived Neurotrophic Factor" OR "Nerve Growth Factors" OR "Vascular Endothelial Growth Factors" OR "Executive Function" OR "Inhibitory Control" OR "Stroop Task" OR "Working Memory" OR "receptor TrkB" OR "Cognitive Flexibility") | 135,124 |
| Females | ("Woman" OR "Female" OR "Pregnant women" OR "Menstrual Cycle" OR "Reproductive Health") | 9,913,245 |
| | Above searches combined with AND | 1456 |
| AND NOT | ("Male" OR "Elderly" OR "Aged" OR "Older" OR "Children" OR "Child" OR "Adolescents" OR "Concussion" OR "Dementia" OR "Alzheimer") | 97 |

3.3.3 Data extraction and synthesis

After reviewing the full text, information was extracted from the included manuscripts utilizing the Covidence software, and the following information was summarized: author, country, study design, study population, outcomes, and summary of main findings. To address the research question, the reviewers grouped the findings by the predictor variables (i.e., aerobic exercise, sports participation, and cardiorespiratory fitness) to summarize the main findings. The two reviewers also analyzed the relationship between aerobic exercise, sports participation, cardiorespiratory fitness, and cognition in two female sub-populations (i.e., pregnant individuals, individuals with menstrual cycle variations). The sub-population groupings were used to aid in the interpretation of findings to answer the research question.

3.4 RESULTS

The database search and references screening identified a total of 435 articles (427 from database search and 8 from references screening), of which 135 were duplicates. A total of 300 titles and abstracts were screened, and 74 studies were eligible for full-text screening. Of the remaining articles identified, 28 studies were included in the scoping review. All stages of the screening process are presented in Figure 1.

Of the 28 articles included, 14 did not control for or report information on the menstrual cycle phase or sexual hormones of the participants included. Additional information and a summary of the findings from individual studies can be found in Tables 2 and 3. Table 2 summarizes the association between aerobic

exercise, sports participation, cardiorespiratory fitness, and cognition in a healthy female population. Table 3 includes a summary of the effect of pregnancy and menstrual cycle periodicity on the relationship between aerobic exercise, sports participation, cardiorespiratory fitness, and cognition in a healthy female population.



PRISMA 2009 Flow Diagram

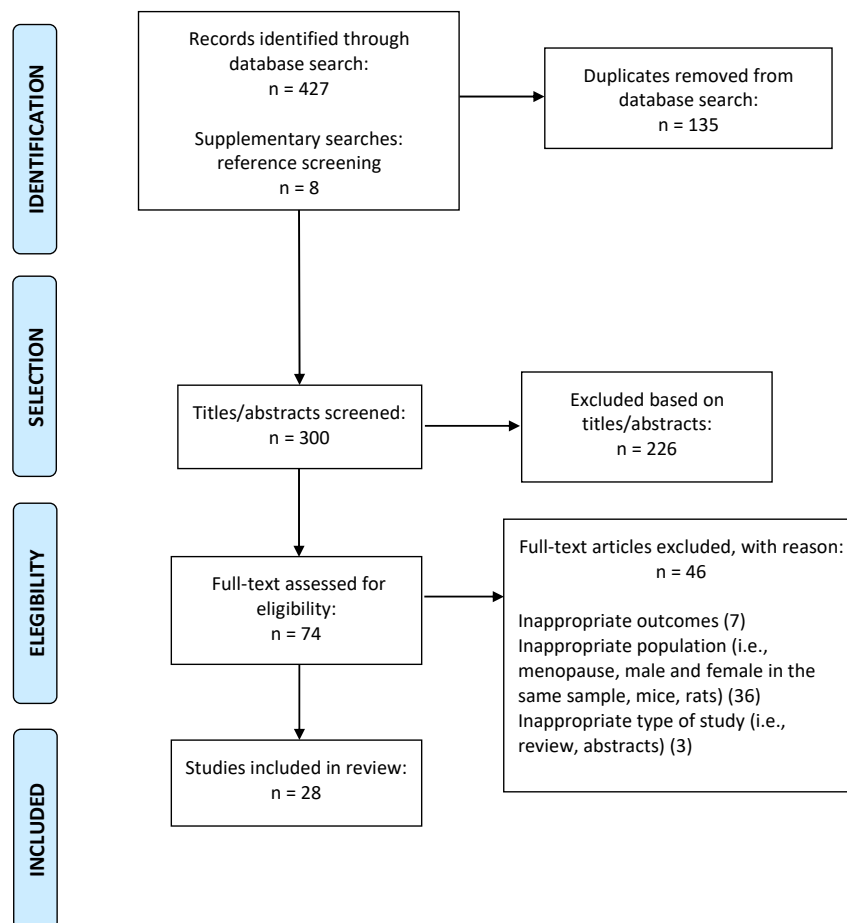


Figure 2 - PRISMA flow diagram

Table 2- Characteristics of studies analyzing the effects of cardiorespiratory fitness, aerobic exercise and sports on cognition.

| Author (year)/ country | Study type | Total sample | Context | Cognitive outcome | Main findings |
|---|-----------------|--------------|---|-------------------------------------|--|
| Cardiorespiratory fitness and cognitive outcomes in healthy female individuals | | | | | |
| Scott et al., (2016) USA | Cross-sectional | 120 | Cardiorespiratory fitness | Executive function | VO ₂ peak is positively associated to attention ($P<0.01$), shifting ($P<0.01$) and working memory ($P<0.01$) |
| Li et al., (2019) China | Cross-sectional | 24 | Cardiorespiratory fitness | Executive function and Brain images | High-fit group showed greater brain activation in the anterior cortex and has higher accuracy ($t(11)= 2.315; p=0.03$). |
| Schmalhofer., (2019) Germany | Cross-sectional | 822 | Cardiorespiratory fitness | Serum BDNF (pg/ml) | VO ₂ peak is positively associated with BDNF ($\beta: 2.35; CI: 1.17 - 3.52$) |
| Cui et al., (2020) China | Cross-sectional | 115 | Cardiorespiratory fitness and acute moderate exercise (30min) | Inhibitory control and Brain images | Acute exercise decreases the RT of low-fit group. High-fit group showed greater brain activation than the low-fit group in the post-rest imaging, mainly in the anterior cortex. |
| Aerobic exercise and cognitive outcomes in healthy female individuals | | | | | |

| | | | | | |
|--|-----------------|-----------------------------------|---|-------------------------------|---|
| Nofuji et al., (2012) Japan | Cross-sectional | 8 controls 8 physically active | Acute low, moderate, and maximum aerobic exercise (30min) | Serum BDNF (pg/ml) | BDNF increased immediately after maximal and moderate exercise for the sedentary and active groups ($p < 0.01$). BDNF decreased for active group after 30 (-15%) and 60 minutes (-25%) of maximum exercise. |
| Schmidt-kassow et al., (2012) Germany | Cross-sectional | 20 | Acute low-intensity and high-intensity aerobic exercise (30min) | Serum BDNF (pg/ml) | Increase of BDNF during high intensity exercise Exercise: 31392.1 baseline: 30221.5 |
| Li et al., (2014) China | Cross-sectional | 15 | Acute moderate-intensity aerobic exercise (30min) | Functional working memory | MRI, Acute exercise activates prefrontal cortex but not changes working memory performance ($P > 0.05$) |
| Lieberman et al., (2014) USA | Longitudinal | 109 | Basic combat training (BCT)/Military (10 weeks) | Reaction time, Working memory | Increase in RT after BCT $d: 0.47$; $P = 0.016$ |
| Hwang et al., (2016) USA | Cross-sectional | 14 | Acute high-intensity aerobic exercise (20min) | Serum BDNF (pg/ml) | Increase of BDNF immediately after high intensity exercise and decreases during recovery Exercise: 23492 Baseline: 20989 |

| | | | | | | |
|---------------------------------------|-----------------------------|----|---|---------------------|--|--|
| | | | | | | Recovery: 19919 |
| Lowe et al., (2016) Canada | Cross-sectional | 51 | Acute moderate-intensity aerobic exercise (20min) | Inhibitory control | | Better performance after acute exercise ($F(1,49) = 13.729$, $P=0.001$) |
| Jurimae et al., (2018) Estonia | Cross-sectional | 15 | Acute sub-maximal exercise (1h) | Plasma VEGF (pg/ml) | | VEGF significant increases immediately after post-exercise compared to pre-exercise. CV: 1.70 ES: 0.19 |
| Rentería et al., (2020) USA | Randomized controlled trial | 17 | Short-term HIIT program (4 weeks) and GXT | Serum BDNF (pg/ml) | | HIIT increases BDNF before GXT compared to control ($P<0.05$) Decreases of BDNF after GXT for HIIT group are higher ($P<0.001$) |
| Luo et al., (2021) China | Randomized controlled trial | 70 | HICT program (12 weeks) | Inhibitory control | | Faster incongruent RT after HICT ($d:0.38$; $P=0.047$) |

Aerobic exhaustion exercise and cognitive outcomes in healthy female individuals

| | | | | | | |
|-------------------------------------|-----------------|----|--------------------------|--|--|---|
| Bue-estes et al., (2008) USA | Cross-sectional | 26 | Maximal aerobic exercise | Reaction time, Working memory, Visual spatial Memory | | Working memory significantly lower when intensity was up to 50% of VO_2 max. Higher working memory after recovery time (after 30min) |
|-------------------------------------|-----------------|----|--------------------------|--|--|---|

| | | | | | |
|--|-----------------|----|--|--|--|
| García-Suárez et al., (2020) Mexico | Cross-sectional | 17 | Acute effect of GXT and HIIT | Serum BDNF (ng/ml), cortisol (μ g/dl) | HIIT increases BDNF post-exercise $d: 0.17$ GXT decreases BDNF post-exercise $d: -0.26$ The ratio of cortisol and BDNF increases after exertion. |
| Conkright et al., (2021) USA | Cross-sectional | 15 | Physical exertion (TMT) / Military (3 days) | Plasma BDNF (pg/ml) and Serum cortisol (μ g/dl) | TMT did not change BDNF levels TMT increases cortisol ($p: <0.05$) |
| Armstrong et al., (2022) UK | Cross-sectional | 10 | Physical exertion (3-h loaded march)/ Military | Inhibitory control, working memory, military tasks | High and Very-high loaded reduced working memory Inhibitory control was reduced in high loaded. |

Sports practice and cognitive outcomes in healthy female individuals

| | | | | | |
|------------------------------------|-----------------|---|--------------------------|-----------------------------|---|
| Schor et al., (2019) Brazil | Cross-sectional | 15 professional judo fighters | Training session and GXT | Plasma BDNF (pg/ml) | BDNF increases after both tests. Delta BDNF was higher during training session ($P=0.003$). |
| Shi et al., (2020) China | Cross-sectional | 20 soccer athletes 15 aerobic athletes | sports practice | Inhibitory control and fMRI | The soccer and aerobic groups presented with lower RT than control. However, the soccer group presented with lower inhibitory RT. The soccer group presented |

| | | | | | |
|--|-----------------|-------------------|-------------|------------------------------|---|
| | | 15 controls | | | more activation of basal nuclei than aerobic groups |
| Pradas et al., (2021) Spain | Cross-sectional | 14 padel athletes | Competition | Blood BDNF ng/ml | Padel competition increased BDNF (pre: 1531.12 x post: 1769.56; $d:1.527$; $p<0.05$) |
| Yu et al., (2023) China | Cross-sectional | 38 ice hockey | Skill level | fNIRS and executive function | The accuracy and reaction time is better for elite players ($p=0.001$). Also, the elite group had higher activation of prefrontal ($p=0.026$) and frontal cortex ($p=0.03$) |

Note: BDNF – Brain Derived Neurotrophic Factor; fMRI – Functional magnetic resonance imaging; fNIRS – Functional near-infrared spectroscopy; GXT – Graded exercise texting; HICT – high-intensity circuit training; HIIT – high-intensity interval training; N.S. - Not Significant; RT – Reaction time; VEGF – Vascular endothelial growth factor; VO2 max – maximum oxygen consumption; VO2 peak – Peak oxygen consumption.

Table 3 - Characteristics of studies analyzing the effects of menstrual cycle and pregnancy on the relationship between cardiorespiratory fitness, aerobic exercise, and sports with cognition

| Author (year) Country | Study type | Total sample | Context | Cognitive outcome | Main findings |
|--|-----------------|------------------|---|---|--|
| Relationship between cardiorespiratory fitness, aerobic exercise, cognitive outcomes, and menstrual cycle periodicity | | | | | |
| Melin et al. (2019) Denmark and Sweden | Cross-sectional | 16 EUM 14 AM | Acute maximal aerobic exercise (2 bouts) | BDNF ($\mu\text{g/L}$), Cortisol (nmol/L) | Acute exercise increased cortisol (+98.6) and BDNF (+96.5) only in AM group |
| Nose et al. (2019) Japan | Cross-sectional | 132 EUM 63 AM | Elite Athletes | Serum BDNF (ng/ml), serum estradiol (pg/ml) | AM presented lower BDNF than EUM (median: 22.9 x 25.2) A significant relationship between BDNF and estradiol ($r: 0.209$) |
| Dirk et al. (2020) Canada | Longitudinal | 15 EUM | Acute aerobic exercise during Follicular and Luteal Phase (20min) | Inhibitory control RT | Acute exercise decreased RT for both menstrual phases ($P:0.003$) Menstrual phase did not impact RT |
| Poli et al. (2021) Brazil | Longitudinal | 14 EUM | Acute HIIE during Follicular and Luteal Phase (20min) | Inhibitory control, serum BDNF (pg/ml) | BDNF increased after HIIE for both conditions (LUT:+8.22; FOL:+7.29) VO ₂ max is related to Δ BDNF |

after HIIE during follicular phase
(r: -0.539)

Relationship between cardiorespiratory fitness, aerobic exercise, cognitive outcomes, and pregnancy

| | | | | | |
|--|-----------------|--|---|--|--|
| Vega et al., (2010) Germany | Cross-sectional | 20 3 rd trimester | Sub maximum GXT (150 bpm) pre- and post-partum | Serum BDNF (ng/dl), VEGF (pg/ml), cortisol (μg/dl) | BDNF increased during sub-maximum exercise for pregnant individuals (p = 0.048). BDNF is higher and cortisol is lower after childbirth (p<0.001) |
| LeMoyne et al. (2014) Canada | Cross-sectional | 52 pregnant (1 st trimester 15, 2 nd trimester:18; 3 rd trimester: 10) 15 control | Cardiorespiratory fitness | Inhibitory control | Inhibitory control is negatively impacted by pregnancy (F: 2.86; p=0.04). VO ₂ max changes during the pregnancy (F:4.61; p=0.006) |
| Ferrari et al. (2018) Germany | Longitudinal | 19 intervention 15 control | Moderate combined exercise from 14 th week to 30 th week of gestation | Serum BDNF (pg/ml) | BDNF is higher in the exercise group compared to the control group (control: 3371.2 x INT: 6540.7; p<0.001). |

Note: EUM - eumenorrheic; AM - Amenorrheic; BDNF – Brain Derived Neurotrophic Factor; GXT - Grade exercise testing; FOL - Follicular phase; HIIE - high intensity interval exercise; LUT - Luteal phase; RT - reaction time; VEGF - Vascular Endothelial Growth Factor; VO₂ max – maximum oxygen consumption.

3.4.1 Cardiorespiratory fitness and cognitive-related outcomes

A limited number of studies (n=4) were found that examined the effects of cardiorespiratory fitness on markers of cognition (Cui et al., 2020; Li et al., 2019; Schmalhofer et al., 2019; Scott et al., 2016). All assessed cardiorespiratory fitness by maximal oxygen consumption (VO₂max), during a graded exercise test, and none of these studies controlled for menstrual phase or sexual hormones. In one study (Schmalhofer et al., 2019), a positive relationship was shown between CRF and serum BDNF. Also, females categorized as the high-fit group (VO₂max in the 50th percentile or above) had higher activation of the anterior cortex during executive function tasks and better accuracy during rest (Cui et al., 2020; Li et al., 2019). Similar to the other findings, CRF was related to different aspects of executive function, namely working memory and shifting attention (Scott et al., 2016).

3.4.2 Aerobic exercise and cognitive-related outcomes

The impact of aerobic exercise on cognition was examined in 9 articles, of which 6 assessed the effect of acute aerobic exercise (Hwang et al., 2016; Jürimäe; Vaiksaar; Purge, 2018; Li et al., 2014; Lowe; Kolev; Hall, 2016; Nofuji et al., 2012; Schmidt-Kassow et al., 2012) and 3 assessed the effect of chronic aerobic intervention (Lieberman et al., 2014; Luo et al., 2021; Rentería et al., 2020).

The results from four studies showed that an acute (single) bout of aerobic exercise (>60% of VO₂peak intensity) can increase serum BDNF, vascular endothelial growth factor (VEGF) (Hwang et al., 2016; Nofuji et al., 2012;

Schmidt-Kassow et al., 2012) and increase inhibitory control (50% of maximum heart rate) (Lowe; Kolev; Hall, 2016). No effects of light-intensity aerobic activity were found for neural markers. Also, moderate exercise (60-70% of maximum heart rate) appears to modulate brain areas responsible for executive functions, for example, activating the prefrontal cortex (Li et al., 2014).

In the recovery period (15-30 min) following a graded exercise test (GXT), BDNF levels were found to be significantly decreased over those measured at rest (Nofuji et al., 2012; Schmidt-Kassow et al., 2012). Different from an acute exercise exposure, high intensity aerobic training can increase resting levels of BDNF (Rentería et al., 2020) and promote faster reaction time during an inhibitory control task (Luo et al., 2021).

The effects of strenuous aerobic exercise on cognition were evaluated in four manuscripts (Armstrong et al., 2022; Bue-Estes et al., 2008; Conkright et al., 2021; García-Suárez et al., 2020), two of which were conducted among female military members (Armstrong et al., 2022; Conkright et al., 2021). The results of these studies consistently identified that exhaustion following aerobic exercise results in poorer cognitive function (i.e., reduced working memory). Additionally, two studies found that cortisol levels increased after a bout of maximal exercise (Conkright et al., 2021; García-Suárez et al., 2020). Evidence indicates that following exhaustive aerobic exercise, working memory assessments decrease by approximately 20% compared to resting values (Bue-Estes et al., 2008). Similarly, after 3-hours of physical exertion, inhibitory control was reduced by 25% when compared to a less intense activity (Armstrong et al., 2022).

3.4.3 Sports practice and cognitive-related outcomes

Four studies assessed the effects of sports in different conditions: i) martial arts training session (Schor et al., 2019); ii) comparing open and close skills (soccer and endurance athletes) (Shi et al., 2020); iii) a Padel (racket sport) competition (Pradas et al., 2021); iv) skill level of ice hockey players (Yu et al., 2023). Results showed that in the recovery period recovery (30 min) following one training session of martial arts (Schor et al., 2019) and a single Padel competition (Pradas et al., 2021), serum BDNF levels were significantly higher than at rest. Moreover, differences in response were noted between elite and novice hockey players, with elite players showing higher activation of prefrontal and frontal cortex and performing better on executive functions task than their novice peers. (Yu et al., 2023)

Another study compared brain activity and inhibition capacity in participants engaged in open and closed skill sports to those in a control group (lack of specific sports training); sports groups had a better reaction time compared to the control group, independent of the type of sport (Shi et al., 2020). However, open-skill sports (e.g., soccer) lead to higher activation in a particular brain region, the basal nuclei (as measured by fMRI) when compared to closed skills (e.g., aerobic athlete) (Shi et al., 2020).

3.4.4 Menstrual cycle influence on the relationship between cardiorespiratory fitness, aerobic exercise, sports and cognitive-related outcomes.

Regarding reproductive health, two studies evaluated differences between eumenorrheic and amenorrheic (absence of a menstrual cycle) females (Melin et al., 2019; Nose et al., 2019), and another two assessed the impacts of the

menstrual phase on cognitive-related outcomes (de Poli et al., 2021; Dirk; Belfry; Heath, 2020).

After maximal aerobic exercise, BDNF (+96.5%) and cortisol only increased in the amenorrheic group (Melin et al., 2019). At rest, eumenorrheic females showed higher values of BDNF in comparison to those experiencing amenorrhea. Moreover, BDNF positively correlates with estradiol, a significant female reproductive health hormone that is high in the follicular phase triggering events leading to ovulation. (Nose et al., 2019)

When analyzing inhibitory control, acute aerobic exercise decreased reaction time after exercise, independently of the menstrual phase (Dirk; Belfry; Heath, 2020). BDNF increased after a 20-min bout of vigorous physical activity for both phases (Luteal and follicular) (de Poli et al., 2021). Conversely, VO₂max is negatively correlated with the change in BDNF after a GXT only for follicular phase ($r=-0.539$) (de Poli et al., 2021).

3.4.5 Pregnancy influence on the relationship between cardiorespiratory fitness, aerobic exercise, sports and cognitive-related outcomes.

Three studies investigated the effects of aerobic fitness and exercise on cognitive-related outcomes (biomarkers and cognitive function tests) during pregnancy and after childbirth. Among these 3 studies, one evaluated the impact of an acute bout of submaximal exercise on BDNF (Rojas Vega et al., 2011); the second study a 16-week intervention that incorporated moderate exercise and BDNF (Ferrari et al., 2018); and the last study investigated the impacts of

cardiorespiratory fitness on inhibitory control (Lemoyne; Curnier; Elleberg, 2014).

After an acute bout of moderate intensity aerobic exercise in pregnant females, serum BDNF increased immediately after exercise. About 10-12 weeks post-delivery, BDNF levels increased and cortisol levels decreased during rest and post-exercise compared to their levels during pregnancy period (Rojas Vega et al., 2011). Following a 16 week exercise intervention, resting serum BDNF increased (+1574.1 pg/ml), while the level of BDNF in the control group, decreased (-691.9 pg/ml) (Ferrari et al., 2018).

Examining inhibitory control responses during pregnancy, Lemoyne and colleagues showed decreased inhibitory control and VO₂max across all three trimesters. When VO₂max is inserted as a covariate in analyses, it does not change the effect of pregnancy on inhibitory control. These results demonstrate that CRF is not the explanatory variable leading to the decrease in inhibitory control over the course of pregnancy. Also, the non-pregnant control group had a better reaction time and VO₂max than the pregnant individuals (Lemoyne; Curnier; Elleberg, 2014).

3.5 DISCUSSION

3.5.1 Cardiorespiratory Fitness

The literature surrounding the relationship between CRF and BDNF, found in our scoping review, is inconsistent. While some studies reported an inverse relationship between CRF and BDNF (Currie et al., 2009; de Poli et al., 2021),

another study found a positive association between these variables (Schmalhofer et al., 2019). One explanation for the reported inverse relationship could be that BDNF has a fundamental role in tissue repair and formation (vessels, cardiac tissue, bones, skeletal muscles), in this sense circulating BDNF can be mobilized, directed to and taken up by tissues needing repair thereby decreasing circulating levels (Kilian et al., 2014; Pius-Sadowska; Machaliński, 2017; Yu et al., 2017). The positive associations observed between CRF and BDNF suggest a connection to increased engagement of muscle-type 1 fibers in the context of aerobic activities. It appears that the BDNF-TrkB complex plays a role in fat oxidation processes, crucial for energy generation during aerobic exercise (Matthews et al., 2009; Sakuma; Yamaguchi, 2011; Schmalhofer et al., 2019), consequently upregulating circulating BDNF levels.

When analyzing the relationship between CRF and executive function, results demonstrated a positive impact of CRF on the activation of the anterior cortex (Cui et al., 2020). The executive process depends on brain connections, mainly between the pre-frontal cortex, hippocampus, and basal ganglia (Meeusen et al., 2017). The release of BDNF can be upregulated due to muscular contractions (Matthews et al., 2009) and is consequently linked to CRF. When correlating BDNF with executive functions, it is responsible for synaptic plasticity, long-term potentiation, and long-term memory, promoting higher neuronal activation and improved brain connectivity. This enhancement results in faster processing of tasks (Aghjayan et al., 2021; Cotman; Berchtold, 2002; Hillman; Erickson; Kramer, 2008; Lewin; Carter, 2014). Moreover, increased serum BDNF levels are related to a higher hippocampus volume (Aghjayan et al., 2021). Taken

together these data CRF can increase brain activation and proteins responsible for better cognitive function.

This scoping review found that acute moderate exercise only changes RT among individuals with low fitness levels (Cui et al., 2020). Given there is an inverted-U relationship between exercise and cognitive functions, stimulation of the brain could be dependent on the intensity of the bout of exercise (Fortune et al., 2019; McMorris, 2016; McMorris; Hale, 2012). Thus, the cognitive functioning of individuals with higher fitness levels may be less impacted by low/moderate physical activity. In this sense, a higher-fitness individual seems to adapt to metabolic/hormonal changes caused by physical activity and needs more stimulus to promote cognitive gains.

3.5.2 Aerobic exercise

Our scoping review focused on females found a positive effect of acute (Hwang et al., 2016) and chronic (Lieberman et al., 2014) aerobic exercise on inhibitory control and working memory. The effects of aerobic exercise on executive functions are linked to an increase in neurotransmitters, which can stimulate certain brain areas (e.g., pre-frontal cortex) responsible for cognitive functions (Ogoh et al., 2014; Shansky; Lipps, 2013).

It was determined that there is a positive effect of acute aerobic activity on BDNF. In contrast, during recovery, many studies showed lower serum BDNF than baseline (Hwang et al., 2016; Nofuji et al., 2012; Rentería et al., 2020; Schmidt-Kassow et al., 2012). A potential explanation for lower BDNF levels during the recovery period is that muscle damage, which increases BDNF levels

in muscle tissue as a necessity for recovery (Murawska-Ciałowicz et al., 2021; Yu et al., 2017), leads to the depletion of stored BDNF in platelets. Moreover, in a rat model, the BDNF is upregulated in soleus after aerobic exercise (Yu et al., 2017). Thus, BDNF can bind to TrkB, triggering the repair of damage, increasing muscle regeneration (Sakuma; Yamaguchi, 2011; Yu et al., 2017), resulting in a decrease in BDNF circulation.

Acute aerobic exercise can lead to an increase in VEGF levels. VEGF is correlated to metabolic demand, with higher exercise efforts leading to higher circulating VEGF (Jürimäe; Vaiksaar; Purge, 2018). VEGF, stored in muscle fibers, can be secreted during an acute muscle contraction, increasing extracellular levels up to 5 times resting level. This circulating VEGF stimulates angiogenesis and consequently increases oxygen and metabolite delivery (Hoier; Hellsten, 2014). It is important to highlight the effect of VEGF on angiogenesis within the hippocampus and, consequently, on neurogenesis (Ben-Zeev; Shoenfeld; Hoffman, 2022; Cao et al., 2004; Fabel et al., 2003). In animal model, this increase in VEGF facilitates learning and memory, reducing latency during tasks (Cao et al., 2004). The activation of VEGF on brain can also be result from lactate-inducing VEGF. During exercise, lactate levels increase and bind its receptor on the brain (HCAR1). When HCAR1 is activated, it promotes subsequent activation of Vascular Endothelial Growth Factor A (VEGFA) and, consequently, brain angiogenesis, mainly in the hippocampus. (Morland et al., 2017).

A decline in cognitive functions (working memory and inhibitory control) and BDNF levels were seen following exhaustive aerobic exercise. (Armstrong et al., 2022; Bue-Estes et al., 2008; García-Suárez et al., 2020) . Moreover, cortisol

and the ratio of cortisol to BDNF increases after exertion (Conkright et al., 2021; García-Suárez et al., 2020), this increase in cortisol can act as an inhibitor of BDNF synthesis (García-Suárez et al., 2020; Murawska-Ciałowicz et al., 2021). This finding is important because exhaustive exercise upregulates plasma cortisol levels, increasing catecholamine synthesis, leading to neural noise due to overstimulation of the brain (McMorris, 2016; McMorris; Hale, 2012). Cortisol can stimulate the release of glutamate, which binds to NMDA receptors. This interaction can affect synaptic sensitivity and alter BDNF expression, primarily by influencing intracellular calcium influx through NMDA receptors, which can subsequently impact neurogenesis (Cotman; Berchtold, 2002; Gould; Tanapat, 1999; Lu, 2003). Moreover, the reduction in BDNF after exhaustive exercise could be related to a shift in the use of additional resources (e.g., lactate for the ATP synthesis) rather than the syntheses of BDNF (Müller et al., 2020; Quistorff; Secher; Van Lieshout, 2008).

Although sex disparities are not the focus of this review, it is important to highlight that studies showed a greater decline in the cognitive function and neurochemical markers of female individuals following exhaustive exercise compared to their male counterparts (Armstrong et al., 2022; Conkright et al., 2021). Females may be more susceptible to negative sequelae due to disparities in physical fitness and metabolic demands (Devries, 2016). Consideration should be given to sex disparities when developing training prescriptions.

3.5.3 Sports participation

Chronic sports participation can improve cognition, possibly related to high levels of cardiorespiratory fitness that results from the sports participation (Furley;

Schütz; Wood, 2023; Khan et al., 2012). But also, sports participation can be independently related to executive functions since it requires higher activation of the prefrontal cortex and higher executive function demand than other forms of physical activity (Furley; Schütz; Wood, 2023).

Of the four studies related to sports participation, one study compared with controls (non-sports participation) (Shi et al., 2020). At the same time, other studies analyze the effects of a training/competition session (Pradas et al., 2021; Schor et al., 2019) and the impact of skill level on cognition (Yu et al., 2023). The results of this review showed positive effects of sports participation on inhibitory control and serum/plasma BDNF. The one study examining different types of sports (open and closed skills), showed the aerobic and soccer groups had faster RT during easier tasks) (Shi et al., 2020). The values for RT during an inhibitory task (harder) were faster for the soccer group compared to aerobic and control. A possible explanation for the faster reaction times during inhibitory tasks among the soccer group could be better functional connectivity and activation of certain brain areas (e.g., the basal nuclei and the frontal cortex) (Shi et al., 2020). The basal nuclei are responsible for actions such as motor, spatial, visual, and affective. Specifically, the putamen region of the basal nuclei is responsible for motor and visual tasks, being activated during sports, and acting for better inhibitory control (Aron; Poldrack; Wise, 2010; Chaddock et al., 2010; Shi et al., 2020) and these regions are known to be enhanced during sports, mainly for open skill sports (Shi et al., 2020).

Moreover, the effects of sports participation, mainly open skills sports, on cognitive control may be related to more complex motor tasks that are required for successful performance in the sport. Open sports require attention and

working memory for real-time decision-making, and an increased demand for inhibitory control to ensure corrective action (Ballester et al., 2019; Diamond; Ling, 2016; Formenti et al., 2021; Voss et al., 2010).

In essence, there is a lack of comprehensive research concerning how sports impact cognition. This gap stems from the unique cognitive demands of each sport, whether open or closed, and how they contribute to various improvements in aerobic fitness. As a result, the exact enhancements in executive functions linked to sports participation might not have been fully elucidated or might need deeper investigation to consider other influencing factors (Furley; Schütz; Wood, 2023).

3.5.4 Menstrual cycle

During the menstrual phase, oscillation in hormonal levels is noted, and estrogen levels are highest between 10 and 14 days of the menstrual cycle (de Jonge; Thompson; Ahreum, 2019). Circulating estradiol can cross blood-brain barriers, and estrogen receptors (ER) are widely distributed in the brain. ER on the membrane can activate signaling pathways responsible for neuroprotection and synaptic formation (Rettberg; Yao; Brinton, 2014; Scharfman; MacLusky, 2006). Moreover, estradiol can stimulate the brain's bioenergetic system, improving ATP availability (Rettberg; Yao; Brinton, 2014). Estrogen receptors can stimulate the hippocampus, leading to a beneficial effect related to learning, memory, neuronal survival, and neuronal activity (Pluchino et al., 2013; Scharfman; MacLusky, 2006). A significant positive association between serum BDNF and estradiol has been noted (Nose et al., 2019).

It is well known that excessive exercise and weight loss can create an energy deficit that may inhibit the synthesis of gonadal hormones, causing deficits

in sexual hormones and menstrual dysfunction (Warren, 1999). Approximately 25% of runners (Warren, 1999), 15% of ice hockey athletes (Gimunová et al., 2022) and 10% of futsal athletes can experience amenorrhea (absence of menstruation) or an irregular menstrual cycle (Queiroga et al., 2021). Among female individuals, reproductive characteristics have been shown to have an effect on cognition. One study suggested that amenorrheic female athletes had lower levels (at rest) of circulating BDNF compared to eumenorrheic female athletes (Nose et al., 2019). The presence of BDNF in the endometrium and the discharge associated with menstruation may justify the presences of lower BDNF levels among amenorrheic female individuals. The endometrium may be a source of BDNF synthesis (Pluchino et al., 2013; Russo et al., 2012) or act as a stimulus for endometrial cell proliferation (Wang et al., 2022). Given amenorrheic individuals do not shed their endometrium cyclically (if at all), there is less demand for BDNF, downregulating circulating BDNF levels, with the possibility to decrease the availability of BDNF for the brain once blood BDNF can cross the blood-brain barrier.

Another study found an elevation of BDNF and cortisol levels after aerobic exercise only among amenorrheic athletes (Melin et al., 2019), possibly suggesting a lack of aerobic stimulus in the eumenorrheic group. Since catecholamines (epinephrine, norepinephrine, dopamine) are regulated by cortisol, and these neurotransmitters/hormones stimulate brain regions (Shansky; Lipps, 2013) regulating metabolite supply (Hackney; Walz, 2013) this could be an avenue for the increase in BDNF.

This review highlights the effect of acute aerobic exercise on inhibitory control and serum BDNF during both menstrual phases (follicular and luteal),

suggesting a beneficial effect of aerobic exercise, independent of menstrual phase (de Poli et al., 2021; Dirk; Belfry; Heath, 2020). However, this study did not verify the menstrual phase by hormonal dosage (de Poli et al., 2021). This is a short-coming in the study design, as the presence of menstruation does not equate to normal hormone levels (de Jonge; Thompson; Ahreum, 2019).

3.5.5 Pregnancy

The studies in this scoping review reveal decreased cognitive-related outcomes during pregnancy, characterized by reduced baseline BDNF levels, diminished inhibitory control, and elevated cortisol levels compared to non-pregnant individuals (Lemoyne; Curnier; Elleberg, 2014; Rojas Vega et al., 2011). A possible explanation for these lower levels of BDNF (Rojas Vega et al., 2011) and inhibitory control (Lemoyne; Curnier; Elleberg, 2014), could be related to higher levels of cortisol during pregnancy (Rojas Vega et al., 2011), with the increase in cortisol down-regulating neurogenesis (Gould; Tanapat, 1999), and affecting neurotransmitters. A single bout of aerobic exercise in pregnancy showed a significant increase immediately after the exercise (Rojas Vega et al., 2011) and exposure to a moderate-intensity aerobic exercise intervention resulted in increased BDNF levels compared to the control group whose levels decreased from baseline (Ferrari et al., 2018).

Aerobic exercise can increase BDNF levels during pregnancy (Ferrari et al., 2018) and can reduce the deleterious effect of pregnancy on BDNF. Moreover, animal studies have shown higher BDNF levels in offspring from mothers who practiced exercise throughout gestation (Ferrari et al., 2018) offering a potential intergeneration benefit. Currently, there is a gap in the

literature; investigating the effects of aerobic exercise or CRF on BDNF levels and its receptor in the human placenta, to determine whether there are better metabolic and neurotrophic markers in offspring of mothers who practiced exercise throughout gestation (Rojas Vega et al., 2011). Maternal adaptations in response to environmental factors (e.g., exercise) can be transmitted to the fetus through the placenta, facilitating the provision of nutrients, hormones, and immunological communications (Brett et al., 2014; Goudreau et al., 2021). Finally, BDNF/TRKb can contribute to enhanced fetal growth and may be associated with the management and prevention of fetal growth disturbances (Mayeur et al., 2010).

3.6 LIMITATIONS

While the aim of this scoping review was to summarize and unveil gaps in the literature related to the benefit of aerobic exercise and sports on cognitive-related outcomes and the possible effect of the menstrual phase or pregnancy on these relationships, it is not without limitations. The review did not assess the quality of the included studies or provide a detailed synthesis of evidence. Additionally, it did not address the heterogeneity among studies. Also, the number of cross-sectional studies limited the interpretation of causality.

3.7 CONCLUSION

The possible pathways and covariates found in this scoping are elucidated in Figure 2. The scoping review shows an inverse 'U' relationship between the aerobic exercise and cognitive functions, demonstrating an optimal amount and

intensity of aerobic exercise to benefit cognitive functions. Also, CRF is significantly related to serum BDNF, but more information is needed to confirm the beneficial effects of CRF on cognitive-related outcomes independent of the menstrual phase since there is a possible effect of estrogen on this relationship. Lastly, no study was found that clearly illustrates the effects of CRF on the BDNF receptor (TrkB) and whether sports practice is independently related to cognitive-related outcomes in females.

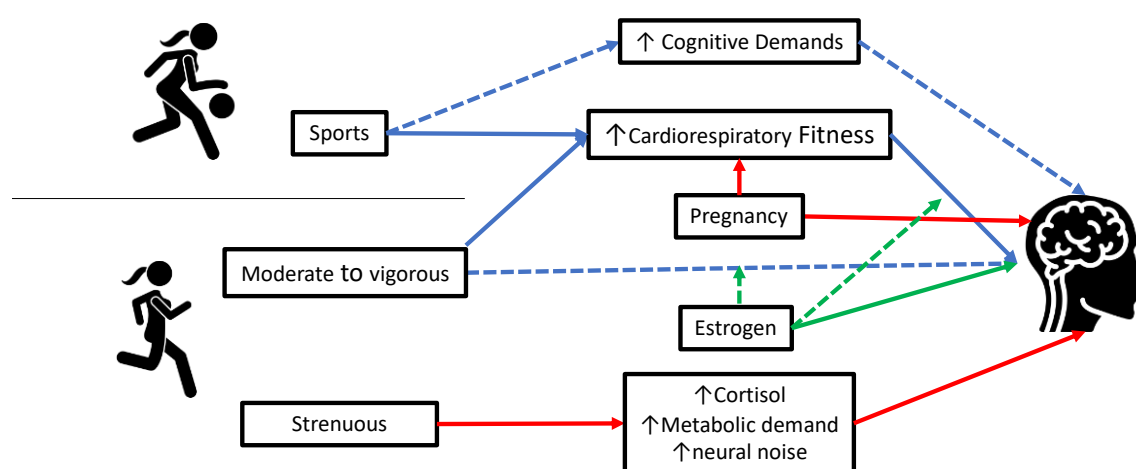


Figure 3- Proposed pathways found in this scoping review between aerobic exercise and sports with cognitive outcomes. The continuous line shows consolidated information between variables, whereas dotted lines represent possible pathways that must be elucidated. Blue lines: improvements in outcome; green lines: possible covariates; red lines: deleterious effect on outcome. *Icons used from Flaticon.com

3.8 FUTURE RESEARCH

Recommendations relating to further research into the roles of cardiorespiratory fitness, aerobic exercise and sports practice in female cognition are presented below:

- Implement precise, objective methods to control for menstrual phases and hormonal variations when analyzing their impact on cognitive performance.
- Investigate the influence of cardiorespiratory fitness on estrogen-cognition dynamics.
- Explore cardiorespiratory fitness as a mediator in sports participation and cognitive-related outcomes.
- Conduct randomized controlled trials to evaluate how aerobic exercise and cardiorespiratory fitness influence cognitive-related outcomes.
- Study the interaction between aerobic exercise/cardiorespiratory fitness and TRKb
- Assess the impact of aerobic exercise/cardiorespiratory fitness on BDNF during pregnancy and in the placenta.

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Capítulo 4

4. Artigo Original

4.1 **Artigo 1:** WHAT IS THE OPTIMAL LEVEL OF CARDIORESPIRATORY FITNESS FOR COGNITIVE OUTCOMES: THE INVERTED "U" THEORY.

Abstract

Background: Cardiorespiratory fitness (CRF) is related to health outcomes and has been linked to cognitive function improvement through mechanisms such as increased brain activation and hormone release. However, an inverted "U" relationship suggests that extremely high CRF levels may negatively impact, and further studies need to elucidate this theory. **Objective:** This study aimed to explore the relationship between CRF and cognitive outcomes in females while controlling for estradiol levels. **Methods:** Thirty-three females aged 18-30 years underwent assessments including CRF measurement using a graded exercise test and an indirect calorimeter, cognitive tests (Corsi Block, Stroop), and blood collection for Brain Derived Neurotrophic Factor (BDNF) and estradiol quantification. Data were analyzed using multiple linear and quadratic regressions, controlling for covariates such as fat mass and estradiol. **Results:** Significant correlations were found between CRF and working memory (Block span: $r=0.415$; Total score: $r=0.462$), and between estradiol and BDNF ($r=0.39$). Linear regression showed that CRF independently predicted variations in working memory ($R^2=21.4\%$) despite covariates. Quadratic regression indicated an inverted "U" relationship between CRF and inhibitory control accuracy, suggesting optimal cognitive performance at approximately $47 \text{ ml.kg}^{-1}.\text{min}^{-1}$ of VO_2max . **Conclusion:** This study underscores the importance of maintaining optimal CRF levels to foster cognitive health. The findings support an association between CRF and working memory, while highlighting the complex relationship with inhibitory control. Future research should focus on intervention studies to establish causal relationships.

Keywords: Cardiorespiratory fitness, Cognitive function, estradiol, Female

4.2 BACKGROUND

Cardiorespiratory fitness (CRF) is a health-related component of physical fitness. CRF characterizes the body's capacity to supply oxygen to the cells (i.e., mitochondria) and remove the metabolites after oxygen consumption (Caspersen; Powell; Christenson, 1985; Ozemek et al., 2018). Research indicates that higher CRF levels can mitigate cardiovascular and metabolic disease (Fowles et al., 2014; Ozemek et al., 2018), as well as mental health disorders such as depression (Kandola et al., 2019).

CRF may alleviate depression by enhancing brain activation, particularly in the hippocampus, as well as increasing neurotransmission and BDNF release. These changes can improve brain function and reduce depressive symptoms (Kandola et al., 2016, 2019). The activation of certain brain regions and the release of neural substances, including neuroplasticity proteins like BDNF and excitatory hormones such as catecholamines, not only safeguard against mental health problems but also enhance cognitive functions like inhibitory control, working memory, and reaction time (Aron; Poldrack; Wise, 2010; Cotman; Berchtold; Christie, 2007; Leckie et al., 2014; Miranda et al., 2019). It is important to highlight that the effects of CRF on executive functions depend on brain changes induced by CRF, such as improved gray and white matter function (Callow et al., 2022; Opel et al., 2019; Rosario et al., 2024); increased BDNF release (Hwang; Castelli; Gonzalez-Lima, 2017; Schmalhofer et al., 2019) and enhanced brain activation (Won et al., 2024). These findings suggest that CRF leads to multilevel changes that boost executive function (Stillman et al., 2016).

There is some evidence to suggest a worsening of cognitive function when extremely high levels of CRF are achieved, implying an inverted "U" relationship

(McMorris, 2016; McMorris; Hale, 2012; Wang; Guo, 2022). This phenomenon may occur because high-intensity acute aerobic exercise, necessary to reach high levels of CRF, exposes individuals to elevated levels of excitatory factors such as glutamate, cortisol, and norepinephrine; potentially resulting in neural noise resulting in chronic signal processing conflicts in the brain (McMorris; Hale, 2012; Świątkiewicz et al., 2023). Existing literature on this topic remains inconclusive, as some authors suggest that sustained improvements in CRF levels are necessary to maintain the cognitive benefits associated with aerobic exercise (Fortune et al., 2019).

Another research gap in this area is the lack of female representation, as most published data have been collected from male-only or mixed-gender samples. It is well documented that female reproductive hormones significantly impact cognitive function and brain excitability (Barha; Liu-Ambrose, 2020; Baskaran et al., 2017; Bayer et al., 2018; Pluchino et al., 2013), thus cognitive responses to CRF may differ between males and females (Barha et al., 2019, 2021; Barha; Liu-Ambrose, 2020). In addition, as reproductive hormones fluctuate over an ovulatory cycle, females tend to experience impairment in neural stimulation or BDNF release when estradiol is at its lowest before menstruation or in those with irregular cycles (Nose et al., 2019; Pluchino et al., 2013; Scharfman; MacLusky, 2006). A recent scoping review from our group identified only four studies examining the effects of CRF on cognitive outcomes in females and of those, none controlled for hormonal levels (Weber et al., 2024).

There is a clear need for more comprehensive exploration of the potential positive effects of CRF on cognitive outcomes, independent of reproductive hormones. The objective of this study is to elucidate the relationship between

CRF and cognitive outcomes while controlling for estradiol. Our hypothesis is that CRF has an independent relationship with cognitive functions and possibly provides protection against the deleterious effects of lower estradiol.

4.3 METHODS

The present study performed at the University of Ottawa (Canada) included females between 18 and 30 years of age. The project was approved by the University of Ottawa Ethics Board (file number: H-01-23-8825). Participants were recruited through flyers attached on university boards. The data collection was performed individually and was collected in the following order: questionnaires, cognitive tests, blood collection, anthropometrics and body composition analysis, cardiorespiratory fitness. All tests were performed in one session which lasted 100 minutes for each participant.

The inclusion and exclusion criteria were verbal assessed during the recruitment process. The inclusion criteria were, not be pregnant, otherwise healthy and without contraindications to exercise or receiving a dual-energy x-ray absorptiometry (DXA) scan. Participants also needed to be able to communicate in English, French, or Portuguese. The exclusion criteria were any pathology that could impair the physical test (e.g. arthritis, back pain, heart disease, asthma, diabetes), bone condition, low mobility, use of any psychoactive substance, a diagnosis of ADHD, anxiety, and/or depression, and known vision deficiency.

The sample size of 31 was calculated using Gpower 3.1 for multiple linear regression, with effect size set at 0.212 (Schmalhofer et al., 2019), power

of 0.8, alpha of 0.05, and 3 predictors. A total of 33 participants were used in this study for the data collection.

4.3.1 Anthropometric measurements

A Body mass and height were measured with a scale (Tanita, BWB-800, Lanchine, QC) and a stadiometer (Tanita HR-200, Lanchine, QC), respectively. Body composition, including fat mass and fat-free mass, were assessed using DXA. The DXA machine (Lunar Prodigy, GE) was calibrated before each day of data collection and all measurements were conducted by trained research personnel.

4.3.2 Demographic Assessment

Each participant completed a demographics questionnaire which was used to assess socioeconomic status, ethnicity, civil status, highest level of education obtained, and total financial support received annually (e.g., scholarships, government bursaries and loans, parental support).

4.3.3 Reproductive health

Reproductive health characteristics were assessed using a questionnaire developed by our research team (supplementary document 1). The use of birth control hormones, days from last period, and reproductive disease (e.g., Polycystic ovarian syndrome, Endometriosis) were assessed. To include these variables as a co-variates in the analysis, the information of days from last period

were inserted as a continuous variable and the use of birth control and reproductive disease were transformed as a dummy variable. However, none of the variables presented significance on the correlation matrix (supplementary table 1), so only estradiol (E2) was inserted as a reproductive health co-variate.

4.3.4 Cognitive Tests

The cognitive tests (Corsi Block, Stroop test) were performed in an environment without external audiovisual stimuli. All participants participated in a learning phase for each test and were given time to ask any questions they might have. Additionally, all participants had a rest period between the learning phase and the official attempt

4.3.4.1 Corsi Block test

To probe visuospatial working memory, the Corsi block-tapping task was performed. This task consists of memorizing a sequence of cubes that flash on the computer screen. The test involves memorizing a sequence of cubes flashing on a computer screen. It begins with two cubes flashing in the middle of a layout of nine cubes (encoding phase), with each cube flashing for 250 ms. The participant then attempts to reproduce the sequence in the same order as the cubes appeared (forward condition) during the recall phase, without a time limit. After the response, feedback was displayed for 1000 ms before the start of a new encoding phase. For correct responses, participants needed to reproduce the same order as the order the computer established. All participants had one trial for adaptation and learning before beginning the test trial. If participants did not

memorize the cubes for two consecutive answers, the test ended. Block span (latest level completed) and total score (latest level complete x number of correct answers) were adopted as performance indicators (Brunetti et al., 2018).

4.3.4.2 Stroop test

The Stroop test was performed using the PsyToolkit web-based method (Stoet, 2010, 2017). The Stroop test was translated for the main language of each participant (English, French or Portuguese). The Stroop test consisted of the congruent and incongruent condition. In the congruent condition, the ink of the presented color word (e.g., green) matched the meaning of the color word (e.g., green). In contrast, in the incongruent condition the ink of the presented color word (e.g., green) did not match the meaning of the color word (e.g., red). The participants were asked to perform 50 incongruent and 50 congruent trials of the Stroop test, which were presented in a randomized order. Each word was displayed for 2000 ms, during which participants were required to respond with the correct color. If the participant took longer to respond or provided an incorrect answer, it was recorded as an error. A fixation cross was shown for 500 ms between each word. Accuracy (i.e., percentage of correct answers), reaction time (i.e., how fast did the participant respond), and inhibitory control performance (i.e., the difference in accuracy and reaction time in congruent and incongruent conditions) were used as indices of executive performance. When the difference between congruent and incongruent tasks (inhibitory control) is minimal (close to 0), the score suggests superior inhibitory control performance, indicating minimal discrepancy between executing congruent and incongruent tasks (Barbarotto et al., 1998; Scarpina; Tagini, 2017).

4.3.5 Brain derived neurotrophic factor (BDNF) and estradiol (E2)

A 10 ml sample of blood was drawn by a qualified phlebotomist and collected in serum tubes. Blood was subsequently centrifuged at 2500 rpm for 10 minutes at 4°C for the serum separation process and stored at -80°C for future analysis. Serum BDNF and E2 were quantified through a sandwich Enzyme-Linked Immunosorbent Assay (ELISA). Both analyses followed the manufacturer instructions for Human BDNF Elisa (Invitrogen, ThermoFisher) and E2 (OriGene Technologies, Inc.). For E2, a percentage of inhibition was calculated as lower absorbance means higher concentration. The sample was analyzed in duplicates and the coefficient of variation remained under 10% for all the subjects.

4.3.6 Cardiorespiratory Fitness

CRF was assessed with an indirect calorimeter (K5, COSMED, Rome, Italy) during a graded exercise test (GXT) using a Modified Balke Protocol (Balke; Ware, 1959). The GXT started with a 5-minute warm-up, during which the speed of the test was determined. The speed of the test was selected based on a comfortable speed chosen by the participant, between 5.0 – 7.0 mph; if the heart rate (HR) reserve was greater than 75% during the warmup, the test was performed with the same speed. If the HR reserve was between 60 – 75%, the initial speed was increased by 0.5 mph, and when the HR reserve was below 60%, the initial speed was increased by 1.0 mph.

Before each test the equipment was calibrated following the recommendations of the manufacturer. The participant was then fitted to the K5

gas analyzer with the specific mask. An initial 3-5 minutes in a standing position was used to check basal metabolic values. The first 2 minutes of the treadmill test consisted of running at the pre-determined speed at an initial grade of 0%. After that, the treadmill incline increased by 2% every 2 minutes until a respiratory exchange ratio (RER) of 1.0 is achieved. When an RER value of 1.0 was measured, the treadmill incline increased by 1% every minute until volitional fatigue, at which time the test was terminated. At the end of each 2-minute test increment, up to when an RER value of 1.0 was achieved, the participants provided a rating of their perceived exertion using the Borg Scale (6 to 20) (Borg, 1982). Criteria for the termination and maintain participant safeness during the VO₂max test included all the symptoms or values previously described by American College Sports Medicine (American College of Sports Medicine, 2018) (e.g. Onset of angina or angina-like symptoms; shortness of breath, wheezing, leg cramps, or claudication; signs of poor perfusion: light-headedness, confusion, ataxia, pallor, cyanosis, nausea, or cold and clammy skin; failure of HR to increase with increased exercise intensity; noticeable change in heart rhythm by palpation or auscultation; subject requests to stop; physical or verbal manifestations of severe fatigue); the participants were also able to stop the test at any time or if they met indicators confirming VO₂max as described below.

Various objective and subjective indicators were utilized to confirm that maximal effort has been elicited during the GXT. The following indicators were used to confirm VO₂max (American College of Sports Medicine, 2018):

- failure of HR to increase with further increases in exercise intensity
- a plateau in oxygen uptake (or failure to increase oxygen uptake by 150 ml/min) with increased workload

- an RER greater than 1.15
- an RPE of more than 18 (6 to 20 scale)

4.3.7 Statistical Analysis

The participant characteristics are presented as mean and standard deviation. A correlation matrix was performed with the dependent and independent variables. Multiple linear regression and quadratic regressions were performed to determine relationships, and the Durbin-Watson method was utilized to check the residual effects of the linear regression. The demographic and reproductive health variables were tested as possible covariates, and those that presented $p < 0.1$ were included as controls in the analyses. For quadratic regressions, only the significant variables are presented in graphs, and the vertex was calculated using the formula $X = -B/2A$ ($Y = Ax^2 + Bx + C$). Significance was set at $p < 0.05$. All the analyses were performed using SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Macintosh, Version 27.0. Armonk, NY: IBM Corp).

4.4 RESULTS

The participant characteristics are presented in Table 1. The sample comprised 33 females with a mean age of 22.4 years. The participants were predominantly (81.8%) English-speaking as their primary language. Regarding reproductive health, 66.7% were not using hormonal birth control, and 15.2% reported irregular cycles.

Table 1 - Sample characterization (n=33)

| | Mean \pm Standard deviation |
|---|-------------------------------|
| Age (Years) | 22.4 \pm 2.7 |
| Weight (kg) | 64.1 \pm 8.6 |
| Height (cm) | 166.6 \pm 8.5 |
| Lean mass (kg) | 43.0 \pm 5.2 |
| Fat mass (%) | 29.0 \pm 5.8 |
| VO ₂ max (ml.kg ⁻¹ .min ⁻¹) | 45.9 \pm 8.3 |
| BDNF (ng/ml) | 102.2 \pm 32.5 |
| E2 (pg/ml) | 37.9 \pm 47.4 |
| | N (%) |
| Ethnicity | |
| White | 27 (81.8) |
| Black | 2 (6.1) |
| South Asian | 4 (12.1) |
| Primary Language | |
| English | 20 (60.6) |
| French | 3 (9.1) |
| English and French | 9 (27.3) |
| Portuguese | 1 (3.0) |
| Annual household income | |
| Less than 20,000 | 13 (39.4) |
| 20,000-40,000 | 10 (30.3) |
| 40,000-60,000 | 6 (18.2) |
| 60,000-80,000 | 2 (6.0) |
| >80,000 | 2 (6.0) |
| Highest degree completed | |
| Less than high school | 0 (0) |
| High school | 14 (42.4) |
| College/CEGEP | 4 (12.1) |
| Undergraduate | 12 (36.3) |
| Post-graduate | 3 (9.1) |
| Use of reproductive hormones | |
| No | 22 (66.7) |
| Yes | 11 (33.3) |
| Menstrual cycle length (days) | |
| 1-3 | 2 (6.0) |
| 3-5 | 22 (66.7) |
| >5 | 9 (27.2) |
| Days from last period (n) | |
| 1-5 | 4 (12.1) |
| 6-12 | 11 (33.4) |
| 12-16 | 6 (18.1) |
| 17-28 | 7 (21.2) |
| >40 | 5 (15.2) |

Table 2 illustrates the correlation matrix. The CRF was significantly correlated with fat mass ($r=-0.70$; $p<0.001$) and working memory (Block span $r=0.415$; $p=0.016$; Total score $r=0.462$; $p=0.007$). A positive relationship was identified between E2 and BDNF ($r=0.39$; $p=0.029$).

Table 3 presents the linear regression analysis. The VO₂max and working memory presented a shared variance (R^2) of 17.2% (Block span; $p=0.016$) and for total score the R^2 is 21.4% ($p=0.007$). When co-variables were inserted in the model working memory and VO₂max remains significantly independent of the co-variables (fat mass and serum E2). This indicates that this relationship is not impacted by the co-variables.

Table 2 – Correlation matrix

| Variables | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|-------|-------|--------------|-------------|-------------|-------|--------------|--------------|--------------|--------------|-------------|-------------|------|----|
| 1-Age (Years) | 1 | | | | | | | | | | | | | |
| 2-Lean mass (kg) | -0.06 | 1 | | | | | | | | | | | | |
| 3-Fat mass (kg) | -0.09 | -0.13 | 1 | | | | | | | | | | | |
| 4-VO ₂ max (ml.kg ⁻¹ .min ⁻¹) | 0.03 | 0.22 | -0.70 | 1 | | | | | | | | | | |
| 5-BDNF (ng/ml) | 0.15 | 0.29 | -0.11 | 0.11 | 1 | | | | | | | | | |
| 6-E2 (pg/ml) | -0.29 | 0.22 | -0.04 | -0.28 | 0.39 | 1 | | | | | | | | |
| <i>Corsi Block (Working Memory)</i> | | | | | | | | | | | | | | |
| 7-Block span | 0.31 | 0.07 | -0.23 | 0.41 | 0.19 | 0.19 | 1 | | | | | | | |
| 8-Total score | 0.31 | 0.04 | -0.27 | 0.46 | 0.23 | 0.22 | 0.95 | 1 | | | | | | |
| <i>Stroop test (Inhibitory Control)</i> | | | | | | | | | | | | | | |
| 9-Accuracy Congruent (%) | -0.06 | 0.13 | -0.26 | 0.10 | 0.23 | 0.18 | -0.09 | -0.07 | 1 | | | | | |
| 10-Accuracy Incongruent (%) | -0.16 | 0.23 | 0.04 | -0.03 | -0.03 | -0.21 | -0.42 | -0.43 | 0.24 | 1 | | | | |
| 11-RT Congruent (ms) | 0.10 | -0.05 | 0.28 | -0.14 | 0.04 | 0.03 | -0.21 | -0.18 | 0.22 | 0.16 | 1 | | | |
| 12-RT Incongruent (ms) | 0.07 | -0.11 | 0.31* | -0.23 | 0.01 | 0.06 | -0.21 | -0.15 | 0.11 | -0.03 | 0.92 | 1 | | |
| 13-Inhibitory control RT (ms) | -0.01 | -0.17 | 0.22 | -0.29* | -0.03 | 0.08 | -0.10 | -0.01 | -0.15 | -0.40 | 0.31 | 0.65 | 1 | |
| 14-Inhibitory control accuracy (%) | -0.02 | -0.14 | 0.12 | 0.08 | -0.09 | -0.04 | 0.12 | 0.07 | -0.62 | -0.40 | -0.13 | -0.03 | 0.18 | 1 |

Note: Bold values for $P < 0.05$; * for $p < 0.1$

Table 3 – Relationship between cardiorespiratory fitness and working memory and inhibitory control

| | VO ₂ max (ml.kg ⁻¹ .min ⁻¹) | | VO ₂ max (ml.kg ⁻¹ .min ⁻¹) + Model 1 | | VO ₂ max (ml.kg ⁻¹ .min ⁻¹) + Model 2 | |
|---|---|--------------|--|--------------|--|--------------|
| | β | 95% CI | B | 95% CI | β | 95% CI |
| Working memory (Corsi Block) | | | | | | |
| Block span (u) | 0.04 | 0.01 – 0.08 | 0.05 | 0.01 – 0.11 | 0.05 | 0.01 – 0.09 |
| Total Score (u) | 1.05 | 0.31 – 1.78 | 1.22 | 0.16 – 2.28 | 1.15 | 0.37 – 1.92 |
| Inhibitory control (Stroop test) | | | | | | |
| RT (ms) | -1.42 | -3.13 – 0.28 | -1.31 | -3.77 – 1.15 | -1.43 | -0.26 – 0.39 |

Note: Model 1 – Fat mass (%) included as control; Model 2 – E2 included as control.

Figure 1 presents the quadratic regressions. Figure 1A shows an inverted “U” relationship between incongruent accuracy, measured by the Stroop Test, and VO₂max; the quadratic regression vertex shows an optimal accuracy point around 47 ml.kg⁻¹.min⁻¹ of VO₂max. Moreover, the inhibitory control accuracy (with values close to zero denoting better inhibitory control) has a significant quadratic relationship with VO₂max, with the vertex around 45 ml.kg⁻¹.min⁻¹.



Figure 1 - Quadratic Regression between cardiorespiratory fitness and inhibitory control

4.5 DISCUSSION

The present study investigated relationships between CRF and cognitive outcomes. The results underscore a direct association between CRF and working memory, and an inverted "U" relationship between CRF and inhibitory control. Moreover, our findings contribute to the understanding of the impact of estrogen on brain function.

The observed correlation between estradiol and BDNF in this study align with previous literature, indicating a direct correlation between these markers ($r=0.209$; $p=0.004$) (Nose et al., 2019). This relationship can be attributed to the effect of estradiol on brain excitability, leading to increased neurotransmission and enhanced BDNF release (El-Sayes et al., 2019; Scharfman; MacLusky, 2006). Furthermore, estradiol's ability to cross the blood-brain barrier and act with BDNF, modulating gene transcription and promoting neuronal survival and growth (Rettberg; Yao; Brinton, 2014; Scharfman; MacLusky, 2006), resulting in a higher connectivity, memory consolidation, and better cognitive outcomes.

Our study found a significant positive association between CRF and working memory without significant impacts of co-variables (fat mass and estradiol). Consistent with our findings, the literature suggests that higher CRF results in high working memory performance in young adult females (Li et al., 2019). Aerobic capacity may influence working memory through stimulation and oxygenation of brain regions responsible for short-term memory storage, such as the prefrontal and posterior parietal regions and the hippocampus (Bunge; Wright, 2007; Kesner; Hopkins, 2001; Mora-Gonzalez et al., 2019), thereby facilitating myelination and synaptic strengthening (Bunge; Wright, 2007). Moreover, it is important to highlight the possible mediator effects of brain

structure (i.e., hippocampus volume, basal nuclei and gray matter) on the relationship of CRF and executive functions (Stillman et al., 2016). The association between CRF and cognitive performance may not be direct; thus, multilevel analyses should be anticipated to explore these variables. Future studies should aim to clarify this relationship, considering the possible moderating impact of brain structures, and employ comprehensive analytical tools.

Distinct patterns were observed for accuracy in inhibitory control and incongruent responses on the Stroop test. The results suggest the inverted "U" relationship between CRF and inhibitory control, with a shared variance of 16.1% observed in incongruent accuracy when quadratic models are applied ($p=0.045$), peaking at approximately 47 ml.kg⁻¹.min⁻¹. This finding is consistent with the inverted U-shaped curve that has been observed for the association between CRF and academic achievement in the pediatric age group (e.g., female and male children) (Hansen et al., 2014). Also, a VO₂max of 47 ml.kg⁻¹.min⁻¹ is the value corresponding to the 95th percentile of females aged between 20-24 years old (Hoffmann et al., 2019), which suggests that extremely high levels of CRF do not provide an additional benefit concerning specific measures of cognitive performance. The inverted "U" theory posits that increased neural stimulation may produce excess neurotransmitter and noise (McMorris; Hale, 2012). Whether there is a detrimental association between extremely high levels of CRF and cognitive performance (as assumed in an inverted U-shaped association) needs to be investigated in further detail because there are only a few participants from our sample whose CRF would be classified as extremely high. Unlike working memory, inhibitory control relies heavily on neural connections, potentially leading to challenges in coordination and planning with the increased

neural noise. Another hypothesis surrounding our findings involves the shifting of metabolic resources to produce energy instead of neuron production (Müller et al., 2020; Quistorff; Secher; Van Lieshout, 2008), especially in sustaining extremely high levels of CRF (>95th percentile of CRF), which occur from rigorous aerobic training.

Strengths of this study include the focus on female participants and accounting for variables such as the menstrual cycle and reproductive hormones. Additionally, the study sheds light on the inverted "U" theory in the context of more complex cognitive tasks as they relate to CRF. However, limitations include that the sample size calculations were tailored to linear regression, hence caution is warranted in interpreting results from quadratic regressions. Another limitation is that causation cannot be established due to the cross-sectional design. Nevertheless, this study lays a conceptual foundation the development of targeted training interventions to enhance cognitive outcomes. These interventions should focus on increasing cardiorespiratory fitness without being overly strenuous. Additionally, maintaining healthy levels of estradiol is crucial for optimizing cognitive performance. Future research could explore specific training regimens and hormonal management strategies to further refine these interventions.

4.6 CONCLUSION

In conclusion, our study highlights the relationship between CRF and cognitive function, revealing an association with working memory and an inverted "U" relationship with inhibitory control. Additionally, our findings highlight that estrogen may influence cognitive processes, as evidenced by correlations with

BDNF. These insights underscore the importance of maintaining optimal CRF levels for cognitive health, particularly in female populations that experience hormonal fluctuations across the menstrual cycle. While our study contributes valuable insights, further research, including the prospective testing of interventions, is needed to determine a cause-effect relationship and unveil the underlying neurobiological mechanisms through which CRF influences cognitive function. Finally, based on the normative values for a Canadian population, we found a maximal oxygen consumption in the 90th percentile, for this study age, as the optimal point for cognitive outcomes.

4.7 SUPPLEMENTARY TABLE

Supplementary table – Correlation between reproductive health characteristics and main variables

| Variables | Birth Control Use | Days from last period (n) | Diagnosed with reproductive disease ³ |
|--|-------------------|---------------------------|--|
| 1- Age (Years) | 0.304* | -0.233 | 0.147 |
| 2-Lean mass (kg) | -0.101 | 0.004 | 0.107 |
| 3-Fat mass (kg) | 0.128 | -0.170 | >0.001 |
| 4-VO _{2max} (ml.kg ⁻¹ .min ⁻¹) | -0.09 | 0.199 | -0.080 |
| 5-BDNF (ng/ml) | -0.172 | 0.147 | -0.077 |
| 6-E2 (pg/ml) | -0.340 | 0.479 | 0.154 |
| 7-Block span | 0.019 | 0.243 | 0.015 |
| 8-Total score | 0.096 | 0.197 | 0.108 |
| 9-Accuracy Congruent (%) | -0.115 | 0.199 | 0.099 |
| 10-Accuracy Incongruent (%) | -0.120 | -0.226 | 0.162 |
| 11-RT Congruent (ms) | 0.297 | -0.187 | -0.160 |
| 12-RT Incongruent (ms) | -0.243 | -0.211 | -0.080 |
| 13-Inhibitory control RT (ms) | -0.277 | -0.269 | -0.173 |
| 14-Inhibitory control accuracy (%) | -0.223 | -0.153 | -0.067 |

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Capítulo 5

5. Artigo Original

5.1 Artigo 2: COGNITIVE BENEFITS OF SPORTS PARTICIPATION: INVESTIGATING BDNF LEVELS AND EXECUTIVE FUNCTIONS IN FEMALES

Abstract

Background: Physical inactivity is a major global health issue, contributing significantly to mortality rates. Engaging in sports can mitigate these risks by enhancing physical activity levels, improving cardiorespiratory fitness (CRF), and positively influencing cognitive functions and brain-derived neurotrophic factor (BDNF) levels. **Objectives:** This study aims to investigate the effects of sports practice on executive functions and serum BDNF levels in female participants, as well as to explore the relationship between the duration and intensity of sports engagement and cognitive outcomes. **Methods:** A cross-sectional study was conducted with 33 female participants aged 18-30. Participants were classified into three groups: closed skill sports (n=13), open skill sports (n=10), and sedentary (n=10). Data collection included physical activity assessments, cognitive tests (Corsi Block and Stroop tests), serum BDNF levels via ELISA, and CRF measurement through a graded exercise test. **Results:** Participants in the closed skill sports group had a higher VO₂max ($52.45 \pm 5.57 \text{ ml.kg}^{-1}.\text{min}^{-1}$) compared to the open skill sports and sedentary groups. The sedentary group exhibited significantly lower working memory scores on the Corsi Block test ($p < 0.01$) compared to both sports groups. A positive correlation was identified between sport index and working memory ($\beta = 2.29$; $p = 0.04$). Mediation analysis indicated that CRF significantly mediated the relationship between sports practice and working memory performance (indirect effect: $\beta = 1.07$). Also, a positive relationship was found between volume of training and BDNF levels ($\beta = 2.21$; $p = 0.04$). **Conclusions:** This study highlights the beneficial effects of sports practice on cognitive functions and BDNF levels in women, emphasizing the role of regular sports training in enhancing CRF and executive functions. Increasing weekly training volume is positively related to serum BDNF levels.

Keywords: Sports practice, Inhibitory control, Working memory, cardiorespiratory fitness, female.

5.2 BACKGROUND

Physical inactivity is a significant global health issue, being the fourth leading risk of all-cause mortality (World Health Organization, 2009), and impacting over a quarter of adults worldwide (Guthold et al., 2018). To mitigate mortality risk, individuals are recommended to engage in 150 to 300 minutes of moderate-intensity or 75 to 150 minutes of vigorous-intensity aerobic physical activity per week. Participation in sports can effectively reduce sedentary behavior and increase overall physical activity (Khan et al., 2012; World Health Organization, 2020). Moreover, sports can enhance the enjoyment of physical activity by integrating social interactions (Khan et al., 2012). Adherence to sports may be higher compared to other forms of physical activity due to the higher intensity and the reduced time required to meet the activity recommendations (Khan et al., 2012; Rhodes; Warburton; Murray, 2009).

In addition to reducing physical inactivity, sports practice is responsible for increasing cardiorespiratory fitness (CRF) (Castagna; Krstrup; Póvoas, 2020; Khan et al., 2012; Oliveira et al., 2017) and brain activity (Diamond; Ling, 2016; Voss et al., 2010; Weber et al., 2024). The literature provides evidence of the positive impacts of CRF on brain morphology (e.g., increased hippocampal volume and greater cortical area) (Chaddock-Heyman et al., 2016; Hillman; Erickson; Kramer, 2008; Pensel et al., 2018), brain oxygenation (McMorris, 2016; Salzman; Dupuy; Fraser, 2022), levels of brain-derived neurotrophic factor (BDNF) (McMorris, 2016; Schmalhofer et al., 2019), brain activation (Hillman; Erickson; Kramer, 2008), and executive functions (Scott et al., 2016; Weber et al., 2024). The effects of CRF on executive functions appear to be dependent on multilevel alterations (Stillman et al., 2016). When BDNF is activated, a series of

electrical processes are initiated and cyclic AMP is upregulated. Cyclical AMP is a neurotransmitter that amplifies brain activation, and is responsible for the formation of new neurons and synaptic connections, improving executive functions (McMorris, 2016; Miranda et al., 2019). Executive functions are necessary for a better academic achievement and for daily tasks (de Bruijn et al., 2018; Vaughan; Giovanello, 2010). However, the literature lacks evidence on the specific effects of sports practice on cognitive outcomes (Castells-Sánchez et al., 2021).

Sports practice can positively impact executive functions and brain structures due to the complex motor tasks involved, the need to integrate attention and working memory for real-time decision-making, and the increased demand for inhibitory control to ensure accurate task execution (Diamond; Ling, 2016; Formenti et al., 2021; Logan et al., 2022; McMorris, 2016; Voss et al., 2010). Sports can be categorized into two groups: open or closed skill, both of which require different brain actions (Formenti et al., 2021; Shi et al., 2020). Open skill sports demand continuous adaptation to unpredictable environments (i.e. soccer, basketball), whereas closed skill sports involve a stable environment with predetermined movement patterns (i.e. running, cycling) (Allard; Burnett, 1985). The need for the constant use of executive functions is more pronounced in open skill sports; however, few studies have compared the differences in cognitive functioning between those who practice open sports, closed sports and those who do not practice sports.

Alternatively, the effects of sport practice on executive functions might be related to the CRF improvements resulting from sports practice, suggesting that CRF could mediate these relationships (Weber et al., 2024). The potential impact

of sports practice on cognition and the possible mediating effect of CRF require further investigation. It is important to highlight the insufficient representation of females, as the majority of published data have been derived from male-only or mixed-gender samples. Therefore, if the hypothesis that sports practice promotes better cognitive functions is confirmed, engaging in sports during adulthood may offer protective benefits against the deleterious effects of hormonal reduction and chemical dysregulation that females experience over the years. (Barha; Liu-Ambrose, 2020; Furley; Schütz; Wood, 2023; Weber et al., 2024). Therefore, the aim of this investigation is i) to elucidate the effects of sports practice on executive functions and serum BDNF concentrations in females, and ii) explore the relationship between the amount of time spent on sports practice and cognitive-related outcomes in females.

5.3 METHODS

The present study was conducted at the University of Ottawa (Canada) and approved by the uOttawa Ethics Board (file number: H-01-23-8825). Thirty-three female participants aged 18-30 were included in the study. Participants' primary language was predominantly English (60.6%), bilingual (English and French) (27.3%), followed by French (9.1%), and Portuguese. Among the participants, 54.5% had completed high school or college, while the 45.5% remainder had at least a graduation degree. Regarding household income, 60.6% of participants earned a maximum of \$30,000 per year, 27.3% earned between \$30,000 and \$70,000 annually, and 12.1% earned more than \$70,000 per year. The use of hormonal birth control was reported by 33.3% of participants.

Testing sessions lasted approximately 100 minutes per session and included questionnaires, cognitive tests, blood collection, anthropometrics, body composition analysis, and cardiorespiratory fitness assessment. For detailed inclusion and exclusion criteria and better description of the sample and tests, refer to Weber et al. (unpublished).

5.3.1 Anthropometric measurements

Body mass and height were measured with a scale (Tanita, BWB-800, Lanchine, QC) and a stadiometer (Tanita HR-200, Lanchine, QC), respectively. Body composition, including fat mass and fat-free mass, were assessed using DXA. The DXA machine (Lunar Prodigy, GE) was calibrated before each day of data collection and all measurements were conducted by trained research personnel.

5.3.2 Physical Activity and Sports engagement questionnaire

The Baecke questionnaire (Baecke; Burema; Frijters, 1982) was utilized to evaluate physical activity levels across leisure time, work, and sports. The questionnaire also gathers details on the type, duration, and frequency of sports participation. The simple-sport score index was computed by multiplying the intensity, duration, and proportion of sports activities. Whereas sports index takes into account questions related to leisure time habits. For participants who did not engage in sports, a score of 0 was assigned. Sports intensity was classified based on energy expenditure, following the questionnaire's guidelines: low

(~181.6 Kcal/h), moderate (~301.1 Kcal/h), and high (~420.6 Kcal/h). Each sport was categorized according to its energy costs (Herrmann et al., 2024).

5.3.3 Cognitive Tests

To assess working memory and inhibitory control, participants completed the Corsi blocks test and the Stroop test. For both tests, participants were given a practice trial. The cognitive tests were administered through a computer-based system in an environment free from external audio-visual stimuli.

5.3.3.1 Corsi Block test

To assess visuospatial working memory, participants completed the Corsi block-tapping task, where they memorized and reproduced a sequence of squares shown on a computer screen. Each participant had one trial for practice before the test began. The test ended if they failed to recall the sequence correctly twice in a row. Performance was measured by block span (the highest level completed) and total score (block span multiplied by the number of correct answers at that level) (Brunetti et al., 2018; Kessels et al., 2000)

5.3.3.2 Stroop test

The Stroop test was conducted on a computer, featuring both congruent and incongruent tasks. In the congruent task, the color of the text matched the word, while in the incongruent task, the color differed from the word. Participants completed 100 randomized trials with both task types (50 congruent, 50

incongruent). Performance was assessed based on accuracy (percentage of correct answers), inhibitory control (difference in accuracy and reaction time between congruent and incongruent tasks), and reaction time. Better inhibitory control was indicated by results closer to zero, reflecting minimal discrepancy between congruent and incongruent task performance (Barbarotto et al., 1998; Scarpina; Tagini, 2017).

5.3.4 Brain derived neurotrophic factor (BDNF)

A 10 ml blood sample was drawn by a trained phlebotomist into serum tubes. The blood was then centrifuged at 2500 rpm for 10 minutes at 4°C to separate the serum, which was stored at -80°C for later analysis. Serum BDNF levels were measured using a sandwich Enzyme-Linked Immunosorbent Assay (ELISA) with a 1:20 dilution for analysis, following the manufacturer's instructions for the Human BDNF ELISA (Invitrogen, ThermoFisher). Each sample was analyzed in duplicate, and the coefficient of variation was below 10% for all subjects.

5.3.5 Cardiorespiratory Fitness

Cardiorespiratory fitness (CRF) was measured using an indirect calorimeter (K5, COSMED, Rome, Italy) during a graded exercise test (GXT) conducted with the Modified Balke Protocol (Balke; Ware, 1959). The GXT began with a 5-minute warm-up to determine the test speed, which was selected based on the participant's comfort between 5.0 and 7.0 mph. If the heart rate (HR) reserve exceeded 75% during the warm-up, the test continued at the same

speed. If the HR reserve was between 60% and 75%, the speed was increased by 0.5 mph. For an HR reserve below 60%, the speed was increased by 1.0 mph.

The treadmill test commenced with 2 minutes of running at the predetermined speed and a 0% incline. Subsequently, the incline increased by 2% every 2 minutes until a respiratory exchange ratio (RER) of 1.0 was reached. Once an RER of 1.0 was achieved, the incline increased by 1% per minute until the participant reached volitional fatigue, at which point the test was stopped.

5.3.6 Statistical Analysis

The variables were assessed for normality using the Shapiro-Wilk test, and data were reported as mean and standard deviation. Comparisons among the open, closed, and sedentary groups were conducted using ANOVA for parametric data and the Kruskal-Wallis test for non-parametric data. Linear regressions were performed to examine the relationships between Baecke questionnaire scores and cognitive-related outcomes (inhibitory control, working memory, BDNF). Residual effects and collinearity diagnostics were checked for the linear regressions. Significant regressions were further tested using a mediation model with VO₂max as the mediator. Mediation analyses followed the framework previously proposed (Baron; Kenny, 1986), and a bootstrapping procedure with 5000 resamples was applied. Mediation and non-mediation types were determined based on a decision tree (Zhao; Lynch; Chen, 2010). All analyses were conducted using SPSS Version 27, with significance set at $p < 0.05$.

5.4 RESULTS

The sample's characterization and comparisons between sports classifications (open and closed) and sedentary behaviors are presented in Table 1. The study compared physiological and cognitive parameters among participants engaged in different types of physical activities: Closed Skills (n=13), Open Skills (n=10), and Sedentary (n=10). Significant differences were observed in several variables. Fat mass was significantly higher for sedentary group ($p=0.003$) compared to open and closed skills sports. Higher $VO_2\text{max}$ values were found for closed skills sports when compared to open skills sports (Mean difference (MD): 7.95; $p=0.007$) and sedentary (MD:13.38; $p<0.001$).

The sports groups did not differ in inhibitory control outcomes (accuracy and reaction time) measured by the Stroop test. However, lower values in working memory (Corsi Blocks) were found for the sedentary group compared to both open (MD: -18.24; $p=0.017$) and closed skills sports (MD: -23.10; $p=0.005$).

Based on the results presented in Table 2. There were no significant relationships between sports score (measured by the Baeck questionnaire) and inhibitory control outcomes. However, higher Simple sport-score was associated with increased performance in both Block Span ($\beta = 0.11$, 95% CI [0.01, 0.22]; $R^2=14.5\%$) and Total Score ($\beta = 2.29$, 95% CI [0.08, 4.50]; $R^2=12.6\%$) measures. The same pattern is observed for the Sports Index.

Table 1 – Sample characterization and comparisons between sports skills

| Variables | Closed Skills (n=13) ¹ | Open Skills (n=10) ² | Sedentary (n=10) ³ | Total |
|--|-----------------------------------|---------------------------------|-------------------------------|-----------------|
| Age (years) | 21.95 ± 3.06 | 22.81 ± 2.16 | 22.58 ± 3.18 | 22.40 ± 2.70 |
| Weight (kg) | 65.45 ± 10.00 | 61.79 ± 9.01 | 64.71 ± 7.20 | 64.11 ± 8.60 |
| Height (cm) | 172.0 ± 7.95 | 163.74 ± 8.49 ¹ | 162.55 ± 6.58 ¹ | 166.6 ± 8.50 |
| Fat mass (%) | 25.65 ± 4.84 | 28.90 ± 6.15 | 33.61 ± 3.87 ¹⁻² | 29.04 ± 5.80 |
| Lean mass (kg) | 46.13 ± 5.39 | 41.47 ± 4.47 ¹ | 40.61 ± 4.30 ¹ | 43.05 ± 5.21 |
| VO₂max (ml.kg⁻¹.min⁻¹) | 52.45 ± 5.57 | 44.50 ± 9.74 ¹ | 39.07 ± 2.23 ¹ | 45.98 ± 8.30 |
| Stroop Test | | | | |
| Congruent Accuracy (%)* | 98.10 ± 2.65 | 97.69 ± 2.74 | 96.05 ± 3.73 | 97.36 ± 3.07 |
| Incongruent Accuracy (%)* | 97.88 ± 2.28 | 95.69 ± 3.83 | 98.39 ± 1.76 | 97.37 ± 2.87 |
| RT Congruent (ms) | 606.57 ± 73.18 | 605.88 ± 100.69 | 610.40 ± 80.99 | 607.52 ± 81.90 |
| RT Incongruent (ms) | 651.56 ± 81.58 | 667.55 ± 139.75 | 653.38 ± 94.95 | 656.96 ± 102.83 |
| Inhibitory control Accuracy (%) | 2.29 ± 2.41 | 2.73 ± 2.14 | 3.16 ± 2.92 | 2.69 ± 2.45 |
| Inhibitory control RT (ms) | 45.08 ± 31.69 | 62.04 ± 60.84 | 42.97 ± 28.74 | 49.58 ± 41.48 |
| Corsi Blocks | | | | |
| Block Span (u)* | 7.08 ± 0.86 | 7.40 ± 0.51 | 6.20 ± 0.91 ² | 6.91 ± 0.91 |
| Total Score (u) | 76.85 ± 21.49 | 81.70 ± 11.20 | 58.60 ± 15.73 ¹⁻² | 72.79 ± 19.30 |
| BDNF (ng/ml) | 112.33 ± 34.70 | 96.23 ± 35.86 | 93.13 ± 39.85 | 102.2 ± 32.5 |
| Estradiol (pg/ml)* | 42.30 ± 53.62 | 42.38 ± 52.14 | 25.73 ± 37.29 | 37.91 ± 47.4 |
| Baeck Questionary | | | | |
| Work index | 2.27 ± 0.46 | 2.86 ± 0.65 | 2.81 ± 1.01 | 2.61 ± 0.75 |
| Simple Sport Score | 4.82 ± 1.15 | 4.69 ± 3.52 | 0,0 ± 0,0 ¹⁻² | 3.32 ± 2.98 |
| Sport index | 4.24 ± 0.54 | 4.09 ± 1.14 | 2.45 ± 0.68 ¹⁻² | 3.65 ± 1.12 |
| Leisure time index | 3.40 ± 0.37 | 2.82 ± 0.48 ¹ | 2.97 ± 0.51 ¹ | 3.09 ± 0.51 |
| Total Physical activity | 3.30 ± 0.31 | 3.26 ± 0.55 | 2.74 ± 0.41 ¹⁻² | 3.12 ± 0.48 |
| How many hours do you play sports? | 9.85 ± 4.33 | 6.70 ± 5.98 | 0.0 ± 0.0 ¹⁻² | 5.91 ± 5.87 |

Note: *=Data without normality, comparisons performed with Kruskal-wallis; ¹Statistical difference from Closed-skills; ²Statistical difference from Open-skills

Table 2 – Regression analysis between physical activity domains (Baecke questionnaire) and cognitive-related outcomes

| | Simple Sport-Score | Sport Index | Work Index | Leisure-time index |
|---------------------------------|---------------------------|---------------------------|-------------------------|------------------------|
| Stroop Test | | | | |
| Congruent Accuracy (%) | 0.30 (-0.60 – 0.66) | 0.45 (-0.53 – 1.43) | -0.28 (-1.78 – 1.21) | -0.39 (-2.59 – 1.80) |
| Incongruent Accuracy (%) | -0.11 (-0.46 – 0.23) | -0.45 (-1.37 – 0.47) | 0.13 (-1.26 – 1.54) | 0.877 (-1.16 – 2.91) |
| RT Congruent (ms) | -4.37 (-14.28 – 5.53) | -21.30 (-46.76 – 4.16) | 12.51 (-52.22 – 27.19) | -1.55 (-60.23 – 57.11) |
| RT Incongruent (ms) | -5.41 (-17.86 – 7.02) | -23.59 (-55.89 – 8.70) | -16.80 (-66.61 – 32.99) | -1.26 (-74.93 – 72.40) |
| Inhibitory control RT (ms) | -0.97 (-6.04 – 4.09) | -2.16 (15.62 – 11.30) | -4.21 (-24.39 – 15.97) | 0.23 (-29.48 – 29.94) |
| Inhibitory control Accuracy (%) | -0.03 (-0.33 – 0.26) | -0.06 (-0.85 – 0.73) | -0.06 (-1.25 – 1.13) | -0.02 (-1.78-1.73) |
| Corsi Blocks | | | | |
| Block Span (u) | 0.11 (0.01 – 0.22) | 0.34 (0.07 – 0.61) | -0.11 (-0.55 – 0.33) | -0.23 (-0.88 – 0.41) |
| Total Score (u) | 2.29 (0.08 – 4.50) | 6.98 (1.25 -12.71) | -3.28 (-12.62 – 6.06) | -5.08 (-18.78 – 8.61) |
| BDNF (ng/ml) | 2.74 (-1.61 – 7.11) | 2.11 (-9.75 – 13.98) | -3.34 (-21.15 -14.46) | 9.75 (-16.20 – 35.72) |

Note: Bold values represent $p < 0.05$

The relationship between hours of sports practice and BDNF levels is illustrated in Figure 1. Linear regression analysis revealed a direct relationship between these variables, with a shared variance of 12.7% ($p=0.04$).

Based on the significant linear regressions found in Table 2 and Figure 1, mediation models were tested, incorporating $VO_2\text{max}$ as a mediator. Models meeting the criteria are presented in Figure 2. The mediation model reveals a significant indirect effect where maximum oxygen consumption ($VO_2\text{max}$) mediates the relationship between Simple Sport-Score and working memory (Corsi Blocks Total Score) (indirect effect: $\beta=1.07$ [0.17, 2.67]).

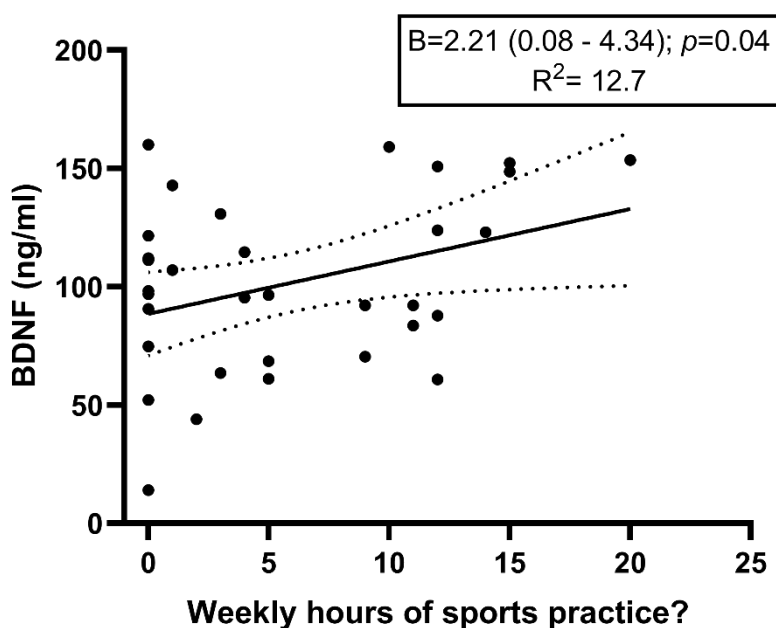


Figure 1 - Linear regression between hours of training and BDNF

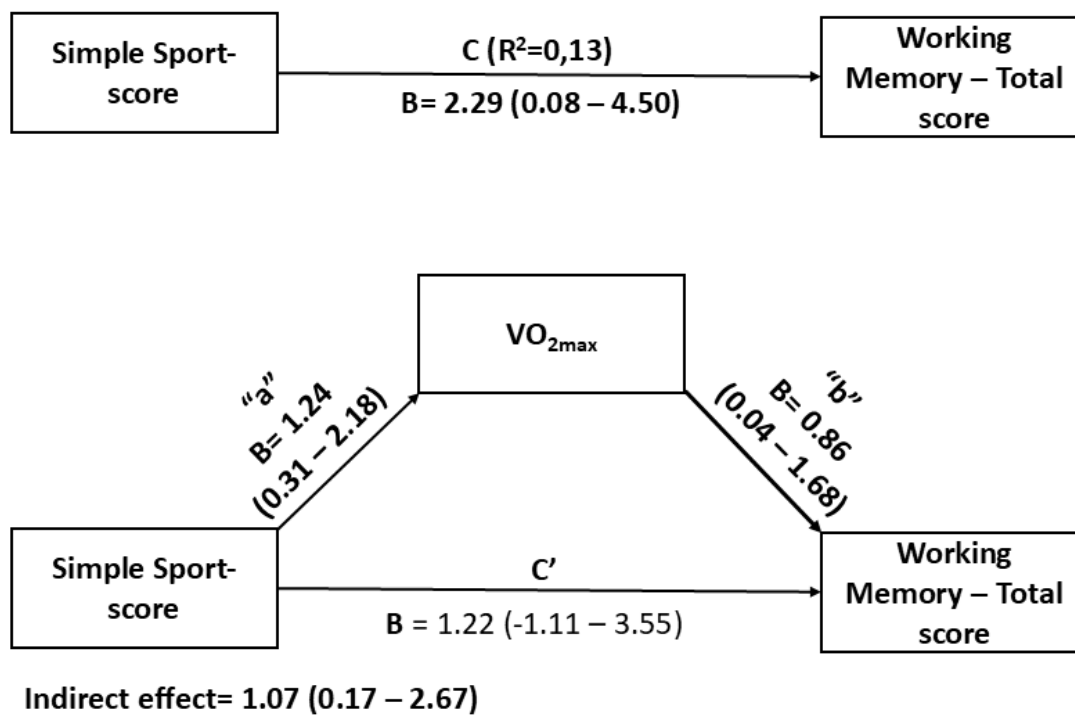


Figure 2 - Mediation model between sports practice, cardiorespiratory fitness and working memory

5.5 DISCUSSION

This study aimed to examine the relationship between sports practice and cognitive outcomes (specifically executive functions and BDNF levels) and to identify potential differences between open and closed sports. Closed skill and open skill presented higher working memory compared to sedentary group. The results indicate a positive association between the product of time and intensity spent in sports (sports index) and working memory. Additionally, a positive correlation was found between the amount of training and BDNF levels. Finally, a mediation analysis revealed a significant impact of cardiorespiratory fitness on the relationship between the sports index and working memory, highlighting an indirect-only mediation effect.

The comparisons in this study revealed higher working memory values for the sports groups compared to sedentary individuals. Literature on cognitive-related outcomes comparing female sports groups with sedentary groups is scarce. However, one study supports our findings, indicating that the soccer group (open skills) and aerobic group (closed skills) performed significantly better in reaction time than the sedentary group (Shi et al., 2020). These differences between sports practice (open or closed skills) and sedentary group are justified due to a better motor control and functional connectivity of the frontal lobe, which can reduce reaction time (Shi et al., 2020). These results can also be linked to the concept of brain utilization during sports practice, as sports are played in a constantly unpredictable environment (McMorris, 2016). Participants need to store information about opponents and anticipate their next moves, making it necessary to utilize working memory to retain information for a short period (Diamond; Ling, 2016).

The regressions in this study found positive relationships between the sports index and working memory. However, when mediation analysis was performed, the results indicated that the significant relationships were only present due to an increase in cardiorespiratory fitness (indirect effect only). This suggests that the impacts of sports engagement on working memory are dependent on levels of cardiorespiratory fitness. Aerobic capacity can stimulate brain areas responsible for short-term memory storage (Bunge; Wright, 2007; Mora-Gonzalez et al., 2019). Moreover, aerobic exercise can increase myelination and axon thickness, which consequently promotes better working memory and enhances connectivity between the prefrontal cortex and other regions of the brain (Bunge; Wright, 2007; Cotman; Berchtold, 2002; McMorris, 2016; Uysal et al., 2005). This enhanced cerebral network, resulting from higher neuronal efficiency (due to myelination), can mediate the relationship between cardiorespiratory fitness and executive functions (Callow et al., 2022). These findings support the idea that cardiorespiratory fitness may impact cognition in a multilevel manner, due to various alterations in the brain (both morphological and functional) (Stillman et al., 2016). Overall, the findings of this study also suggest a multilevel impact of sports practice on cognition.

Our findings elucidate a positive relationship between weekly hours of sports practice and BDNF levels. However, no associations were found between cardiorespiratory fitness and BDNF, which differs from the findings of a previous study conducted in females (Schmalhofer et al., 2019). The increase in circulating BDNF may be attributed to the fact that muscular contractions can stimulate the release of BDNF (Matthews et al., 2009). BDNF also plays a fundamental role in muscle and bone recovery, binding to its receptor (TrkB) to repair damage in

target tissues (Kilian et al., 2014; Yu et al., 2017). Additionally, platelets, which modulate and activate during exercise, are essential for tissue repair (Skouras et al., 2023; Yu et al., 2017). Platelets can store circulating BDNF and release it upon activation during exercise (Fujimura et al., 2002). Together, these factors may explain the upregulating effect of weekly hours of sports practice on serum BDNF levels.

The strengths of this study lie in its focus on female participants and its examination of both open and closed skill sports, as well as a sedentary group. Moreover, it provides insights into the influence of sports practice on working memory by analyzing the mediating effect of cardiorespiratory fitness in this relationship, making it the first study to address this topic within a female population. This study is limited by its cross-sectional design, which restricts causal effect analysis. Furthermore, the morphological and functional aspects of the brain were not investigated.

5.6 CONCLUSION

In conclusion, this study provides evidence of the beneficial effects of sports practice on cognitive functions and BDNF levels, regardless of the type of sport. It emphasizes the importance of regular sports training in enhancing cardiorespiratory fitness and, consequently, executive functions. Furthermore, our findings indicate that increasing the volume of weekly training is positively related to serum BDNF levels. Together, these findings underscore the significance of sports engagement in boosting cardiorespiratory fitness, executive functions and BDNF levels. While this study contributes to the literature on the effects of sports participation and the mediating role of cardiorespiratory fitness, future

research should investigate the morphological and functional changes in the brain resulting from sports practice, controlled by CRF.

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Capítulo 6

6 Considerações Finais

Essa tese buscou avançar no entendimento da relação da aptidão cardiorrespiratória (ACR) e prática esportiva com desfechos relacionados a cognição, mais específico do controle inibitório, da memória de trabalho e dos níveis de BDNF, bem como de quais são os efeitos do estradiol e da composição corporal sobre essas relações. A tese buscou responder essa lacuna por meio de um artigo de revisão e dois artigos originais.

O primeiro artigo de revisão evidenciou uma lacuna de estudos que avaliem os impactos da aptidão cardiorespiratória e da prática esportiva sobre desfechos cognitivos. A revisão demonstrou que informações a respeito da prática esportiva, principalmente quando se expande aos seus domínios (habilidades abertas e fechadas), são escassas e nenhum artigo avaliou os impactos da prática esportiva controlando os efeitos da ACR.

Com o intuito de responder a lacuna evidencia na revisão sistemática os artigos originais foram desenvolvidos. O primeiro artigo original da tese evidenciou que existe uma curva de “U” invertido entre a ACR e o controle inibitório, indicando que existe um ponto ótimo para melhores desfechos cognitivos. Ademais, os níveis de estradiol não mostraram impactos sobre as relações entre ACR e a memória de trabalho ou o controle inibitório. No segundo artigo original foi encontrado que o VO₂máx e a o engajamento esportivo são preditores das funções cognitivas. Os resultados também demonstram que o VO₂máx realiza uma mediação entre a relação da prática esportiva e a memória

de trabalho. Por fim, encontrou-se que o tempo gasto em práticas esportivas está linearmente relacionado aos níveis de BDNF circulante.

Dessa maneira, as lacunas de estudos que avaliem a relação da ACR e da prática esportiva sobre os desfechos cognitivos foram exploradas, e os resultados confirmaram que a ACR possui efeitos sobre quase todas as variáveis de controle cognitivo. E o tempo despendido em práticas esportivas está ligado aos níveis de BDNF circulante. Tais informações podem subsidiar planos de intervenções com o objetivo principal de aumentar a ACR para promover maior controle cognitivo. Ademais, as práticas esportivas podem ser um bom meio para aumentar a ACR e principalmente podem aumentar os níveis de BDNF circulante.

Sugere-se que futuros estudos, realizem ensaios clínicos randomizados com intensidades de treinamentos controladas e verifiquem os desfechos cognitivos. Bem como, futuras intervenções ou políticas públicas devem evidenciar que mulheres jovens mantenham bons níveis de ACR para que tenham melhores desfechos cognitivos, mas nunca realizem atividades em níveis extremamente altos.

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APÊNDICES

APÉNDICE 1

03/04/2023

Université d'Ottawa

Bureau d'éthique et d'intégrité de la recherche

University of Ottawa

Office of Research Ethics and Integrity

CERTIFICAT D'APPROBATION ÉTHIQUE | CERTIFICATE OF ETHICS APPROVAL

| | |
|---|--|
| Numéro du dossier / Ethics File Number | H-01-23-8825 |
| Titre du projet / Project Title | Examining the relationship between cardiorespiratory fitness, sports engagement, body composition, and biochemical makers related to neural development in young female adults |
| Type de projet / Project Type | Projet indépendant d'étudiant / Independent student project |
| Statut du projet / Project Status | Approuvé / Approved |
| Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy) | 03/04/2023 |
| Date d'expiration (jj/mm/aaaa) / Expiry Date (dd/mm/yyyy) | 02/04/2024 |

Équipe de recherche / Research Team

| Chercheur / Researcher | Affiliation | Role |
|-------------------------------|--|---|
| Vinicius MULLER REIS WEBER | École des sciences de l'activité physique / School of Human Kinetics | Chercheur Principal / Principal Investigator |
| Kristi ADAMO | École des sciences de l'activité physique / School of Human Kinetics | Superviseur / Supervisor |
| Jessica PURANDA | École des sciences de l'activité physique / School of Human Kinetics | Co-chercheur / Co-investigator |
| Kevin SEMENIUK | École des sciences de l'activité physique / School of Human Kinetics | Coordonnateur de recherche / Research Coordinator |
| Velislava TZANEVA | École des sciences de l'activité physique / School of Human Kinetics | Coordonnateur de recherche / Research Coordinator |

Conditions spéciales ou commentaires / Special conditions or comments

550, rue Cumberland, pièce 154 550 Cumberland Street, Room 154
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613-562-5387 • 613-562-5338 • ethique@uOttawa.ca / ethics@uOttawa.ca
www.recherche.uottawa.ca/deontologie | www.recherche.uottawa.ca/ethics

APÉNDICE 2

Version Date: 06/10/2023



Principal Investigator: Vinicius M. R. Weber, PhD student
Supervisor: Kristi B. Adamo, Professor

Volunteers Needed!

Relationship between cardiorespiratory fitness, sports engagement, body composition, and biochemical makers related to neural development in young female adults

What is the study about?

The present research is expected to improve the comprehension of the relationship between **health-related factors, sports engagements, and neural markers and cognitive tasks**. In addition, this research could contribute to intervention policies that could create plans to encourage participation in sport and improve cognitive function.

Who can participate?

- We are looking for **young adult females**:
 - Without low mobility;
 - who do not habitually use of any psychoactive substance (i.e., marijuana, stimulants);
 - who speak English, French or Portuguese
 - not currently pregnant;
 - without a diagnosis of ADHD/anxiety/depression.
- Between the ages of 18-30 years
- BMI (weight in kg over height in m²) between 18.5 to 29.9 kg/m²

What is involved?

Volunteers must be willing to spend a maximum of one-hundred (100) minutes of their time participating in an in-person at uOttawa Lees Campus, involving body composition, bone mineral density, aerobic fitness, cognitive tests and neural markers (blood draw). This research project has been reviewed and received approval by the Research Ethics Boards at the University of Ottawa (file number H-01-23-8825). For more information about this study please contact:

Kevin Semeniuk
Research Coordinator
ksemeniu@uottawa.ca
613-562-5800 x1003

Vinicius Weber
Ph.D. Student
vmull050@uottawa.ca

*The sample size of this study is 48 females, so the first females who attend to our research will be included in the data collection.

APÊNDICE 3

**Université d'Ottawa**

Faculté des sciences
de la santé

École des sciences de
l'activité physique

University of Ottawa

Faculty of Health Sciences

School of Human Kinetics

In today's society, a lack of physical activity (PA) and low levels of



125 Université/University (350)
Ottawa ON K1N 6N5 Canada



Invitation to Participate

You have been invited to participate in this study because you are a young female, and between the ages of 18-30 years old. Your participation will be integral in helping us determine the main variables related to fitness, sports engagement, body composition and neural markers. Also, this study will help to validate a secure technique to assess bone mass density. This study will involve anthropometric and body composition measurements, blood collection, aerobic fitness test, and cognitive tests.

Participation in this study is strictly voluntary and will happen through in-person assessment sessions conducted by the uOttawa project team at Lees Campus (200 Lees Ave.). All assessments will be lead and carried out by members of the Adamo Lab research team. The research team has been trained to perform the data assessment, and clearly review all instructions with the participant prior to each required procedure. Please review this information carefully before you provide your consent. If you have any questions regarding this study, please contact the principal investigator or research coordinator listed below.

Assessment session

You are accessing the study information because you had expressed interest in participating in these research trials. You are being required to provide consent for your participation before the assessments take place. This consent form needs to be returned to our research team before performing any part of the evaluation. You can return it signed by email to the Research Coordinator (ksemeniu@uottawa.ca) or to an individual designated from our lab team. You can also decide to withdraw from the study at any time before or throughout the assessment sessions. Participants will be required to take part in one assessment sessions. The sessions that you are assigned to will be performed at a consensual time suitable for your participation and your involvement. The time range to schedule your assessment session is between 6:00 a.m. to 6:00 p.m. Before consenting, you need to know that potential identifiable information (i.e., age, socioeconomic status, occupation) will be a part of data collection, but your name will never be indicated (other than in this consent form). In addition, your contact information will not be shared with anyone outside of the research team to preserve your anonymity and confidentiality.

Steps Before the Assessment session

Besides completing this consent form and sending it back to the research team, you will receive i) the assessment recommendations and instructions, ii) the Demographic Information (e.g., age, menstrual cycle information, household income, education degree), and iii) Health Appraisal Questionnaire, that you will be required to complete. The Health Appraisal Questionnaire aims to make sure you have no contraindications to perform maximal exercise testing. You cannot take part in this study if you meet one of the following exclusion criteria: diabetes (any type), hypertension and untreated thyroid disease, cardiovascular diseases, being pregnant, contraindication to exercise (based on the Health Appraisal Questionnaire). Participants with any severe pathology, use of any psychoactive substance, non-English, French or Portuguese speaking, and being diagnosed with ADHD/anxiety/depression

Steps During the Assessment session

Before the assessments start, participants will have reviewed the test protocols and will have received all the instructions from the testers. There will be one in-person session with an expected maximal duration of 100 minutes. The day will include cognitive tests, questionnaires and blood draw, DXA, UltraScan650™, anthropometric, and exercise testing. Participants will be asked to perform the following assessments according to the sequence presented below:

I) Stroop Test: The Stroop test will be performed with congruent and incongruent answers. The test has two possible tasks; the first one is the congruent: the written color is painted the same color as described; the second is incongruent: the written color is painted in different color. The subject will perform 100 random answers with congruent and incongruent tasks, evaluating the accuracy of both tasks (percentage of correct answers, inhibitory control (accuracy congruent to incongruent), and reaction time). All individuals will have one test execution for adaptation.

II) Corsi Block Test: To verify the visuospatial working memory, the Corsi block-tapping task (CB) will be performed. All participants will have one trial for adaptation and learning. This task consists of memorizing a sequence of cubes that flash on the computer screen. For correct responses, participants need to reproduce the same order as the order the computer established. If participants did not memorize the cubes in two consecutive answers, the test ends. Block span and total score will be adopted as performance indicators.

III) Blood Markers: To verify neural and hormonal markers a blood sample will be collected before any tests commence. Blood samples will be processed and stored at -80°C for downstream quantification of estradiol, brain derived neurotrophic factor (BDNF) and tropomyosin related kinase B (TrkB).

IV) Socioeconomic Assessment: Each participant will complete a questionnaire to assess socioeconomic status regarding ethnicity, civil status, highest level of education obtained, total income of all members of the household.

V) Reproductive Health: Assessed with a short questionnaire which will focus on birth control hormones, point of menstrual cycle, pregnancy, and reproductive disease (i.e., Polycystic ovarian syndrome, Endometriosis).

VI) Sports Practice: The Baecke questionnaire (Baecke et al., 1982) will be used for the evaluation of sports practice and current levels of physical activity. The questionnaire is composed of 16 questions about the practice of physical activity in a variety of settings including, related to sports practice, specifically the type of sport practiced and frequency.

VII) Anthropometrics: A portable stadiometer will be used to measure height and a scale for body weight. Participants will be asked to remove their shoes and keep only light clothing.

VIII) Body Composition: Body composition will be estimated by the dual-energy x-ray absorptiometry (DXA) technique. Fat mass, fat-free mass and total and regional bone mass (bone mineral density (BMD) and bone mineral content) will be determined by examining the whole body. Equipment calibration will follow manufacturer's recommendations, and both calibration and analyses will be carried out by a laboratory technician with experience in this type of evaluation. DXA scans will assess total body, femur, spinal column, and forearm BMD, anatomical locations will be assessed with 4 separate scans (total body, femur, spinal column,

and forearm). BMD will also be assessed through UltraScan650™, a non-invasive tool that does not require specialized skill to operate. The length of the right forearm will be measured. The ulna position locator (UPL) will be placed (using its pair of pins) into a pair of holes in the base of the unit that are located along the scale at the same value as the ulna length. A hand positioning locator (HPL) must be placed on the UPL, so that the patient can maintain a consistent position and orientation of the hand/forearm. The sensors of the device and the forearm of the participant will be sprayed with 70% isopropyl alcohol. The participant will rest their elbow on a pad located on the right-side of the device. The forearm of the participant will be secured for the scan. The scan will be repeated 3-5 times as needed.

IX) Heart Rate Monitor: Polar Wear Link and coded transmitter (Polar Electro Canada Inc, Lachine, QC) to monitor heart rate will be fitted and secured around the chest beneath the participant's nipple line, next to the skin. The Polar H800 receiver (watch) will remain with the research staff performing data collection.

X) Aerobic Fitness: Will be measured using the gold-standard maximal oxygen uptake (VO_{2max}) testing based on indirect calorimeter. A graded treadmill exercise test (GXT) based on Modified Balke protocol (Balke and Ware, 1959) will be used to determine an individual's VO_{2max} . Expired gases will be collected and analyzed using a wearable and portable metabolic system (K5, COSMED s.r.l., Rome, Italy). A Hans Rudolph (Hans Rudolph Inc, Kansas, USA) facemask and head support will be fitted on the participant and attached to the K5 unit. Prior to the start of the test, participants will be permitted to familiarize themselves with treadmill running by warming up for a period of 5 minutes. Participants will commence running on the treadmill at a speed of 4.0 miles per hour (mph) and will be asked to gradually increase the speed until they reach a comfortable warm-up speed between 5.0 – 7.0 mph. The treadmill speed for the test will be based on the HR the participant attains during the warm-up period and in consultation with the tester. For the participants that attain a HR greater than 75% of their age-predicted heart rate reserve during the warm-up, the treadmill speed for the test will remain at the warm-up speed. If the participant attains a HR between 60 and 75% of their age-predicted heart rate reserve during the warm-up, the treadmill speed for the test will be set 0.5 mph faster than the warm-up speed. For participants attaining a HR less than 60% of their age-predicted heart rate reserve during the warm-up, the treadmill speed for the test will be set 1.0 mph faster than the warm-up speed. Age-predicted heart rate reserve is determined using the Karvonen method: $HR_{max} - HR_{rest}$. While there is debate regarding accurate determination of age-predicted HR_{max} , when combined with $HR_{reserve}$ it can be useful in establishing an evidence-based running speed for the GXT. HR_{max} is determined using the following equation: $208 - 0.7 * age$ (Tanaka, et al., 2001). Dependent upon the participant's previous running experience, the treadmill speed for the test could still be modified by the tester in consultation with the participant.

Immediately after the determination of initial running speed, the participant will be fitted to the K5 breathing apparatus. An initial 3-5 minutes in a standing position will be used to collect resting metabolic values, and will allow the individual to become accustomed to wearing and breathing through the mask, and also allow us to make sure the values we are collecting are representative prior to the actual test. The first 2 min of the treadmill test will consist of running at the pre-determined speed at an initial grade of 0%. After that, the treadmill incline will be increased by 2% every 2 min until a respiratory exchange ratio (RER) of 1.0 is achieved. When an RER value of 1.0 is achieved, the treadmill incline will be increased by 1% every minute until volitional fatigue, at which time the test will be terminated. At the end of each 2-min test increment, up to when an RER value of 1.0 is achieved, the participants will provide a rating of their perceived exertion using the Borg Scale. Rate of perceived exertion (RPE) has been found

to be a valuable and reliable indicator in monitoring an individual's exercise tolerance. RPE correlates highly with measured exercise HR and was developed to allow the exerciser to subjectively rate their feelings during exercise (ACSM, 2010).

Every effort will be made to conduct the test in a manner to minimize discomfort and risk to the participant. Occasionally, for safety reasons, the test may be terminated before reaching VO₂max or volitional fatigue. The participant will be notified that they may stop the test at any time without prejudice. Criteria for the termination of the VO₂max test will include any of the following (ACSM, 2010):

- onset of angina (chest pain) or angina-like symptoms
- signs of poor perfusion – light headedness, confusion, pallor (pale appearance to the skin), cyanosis (bluish discoloration); ataxia (failure of muscular coordination), nausea, or cold and clammy skin
- participant requests to stop
- volitional fatigue
- physical or verbal manifestations of severe fatigue
- failure of testing equipment
- shortness of breath, wheezing, leg cramps
- failure of HR to increase with increased exercise intensity

Various objective and subjective indicators are useful to confirm that maximal effort has been elicited during the GXT. The following indicators will be used to confirm VO₂max (ACSM, 2010):

- failure of HR to increase with further increases in exercise intensity
- a plateau in oxygen uptake (or failure to increase oxygen uptake by 150 ml/min) with increased workload
- an RER greater than 1.15
- an RPE of more than 18 (6 to 20 scale)

A complete aerobic fitness test (including preparation and warm-up) will take approximately 25 minutes per participant.

Possible Benefits and Risks Associated with Participating in this Study

The results of these tests will be summarized and shared with you and will allow you to be aware of your physical fitness level and body composition data. It can potentially be used to determine areas you should improve and the type of training you could engage to reach these improvements. The results from this study will help define focus areas (i.e., customized preventive techniques to enhance fitness) for future intervention.

We anticipate low levels of risk associated with your participation in the assessment session. The maximal treadmill exercise test may result in discomfort, nausea, dizziness, and/or muscle soreness. However, the protocols used in the present study will incorporate evidence-based exercise tests. The UltraScan650™ bone mineral density measurement is based on ultra-sound and this technique may offer a risk of a temperature rise in the exposed tissue (bone and soft tissues lying adjacent to it) making one susceptible to issues with fetal development. Also, a DXA scan for full body composition assessment exposes participants to low radioactivity levels equivalent to 1/20th of the radioactivity received over an 8-hour period in the sunlight. Inconveniences include the possibility of attracting participants that will be within half a day's drive (<4 hours one-way) to the assessment location. Blood drawing may cause some pain,

bruising, bleeding or infections at the site of the needle stick. A health care provider (e.g., nurse) or phlebotomist who has been trained in safely drawing blood will take all necessary precautions to avoid these complications.

The risk of an adverse event is minimized through use of the medical screening Health Appraisal Questionnaire, and the supervision of testing by qualified personnel (members of Adamo Lab team). In the unlikely event that you experience an injury or medical issues (e.g., chest pains, acute soft tissue injury) during the exercise assessments, the safety protocol already in place in the test locations will be enacted and the emergency response team will be contacted. Moreover, heart rate will be continuously monitored to ensure that participants do not reach an unsafe heart rate. Borg scale (6-20) will also be used to monitor the degree of perceived exertion during the exercise test. The research staff will make sure the treadmill is properly adjusted and participants will engage in a standard warm-up with technique coaching and cool-down to prevent injuries for the aerobic assessments.

The epidemiological existing evidence reassures as to the safety of routine ultrasound scanning and the risk of negative incidences is extremely low. Risk is further reduced by limiting exposure to the forearm area. Pregnant women will not be recruited, which nulls the potential issues with fetal development.

The Right to Withdraw

Participation in this study is completely voluntary. You have the right to leave the assessment session or not perform one of the tests asked to you at any time. You can withdraw your consent at any time before or during the period that you are participating in the assessment session without any repercussions. If you withdraw your consent, the study team will no longer collect your data and will not use the data for research purposes. Information collected for the study before you withdrawn from the study may still be used unless you request for it to be destroyed. You have the right to request for the information to be destroyed.

Confidentiality and Anonymity of Data Collected

Potential identifiable information (i.e., age, sex, sociodemographic information) will be part of data collection, but your name will never be indicated in any material produced with this data or shared. In addition, your contact information will not be shared with anyone else but the research team leading this project to preserve your anonymity and confidentiality. Therefore, your responses will remain anonymous, including for all data made public in research reports, journal papers, and presentations. The results of this study will be used for scholarly purposes and will be shared within the research team from the uOttawa and any possible external funding partner.

Data Conservation

All paper-based data collected (e.g., consent forms, data collection forms) will remain in a locked storage case access to which is controlled and kept by the lead researcher while performing testing. Hard copies of data will be transferred to a secure uOttawa location in the lab that is locked at all times and requires a key for access. Data will be housed for 5 years following the completion of the project at the uOttawa, when it will be destroyed in accordance with uOttawa procedures.

Contacts

Consent Form:
UO REB File

Page 6 of 8

The ethical aspects of this study have been reviewed and approved by the University of Ottawa Research Ethics Board (file number H-01-23-8825). Any questions about the ethical conduct of this study, you may contact:

Protocol Officer for Ethics in Research
University of Ottawa
Tabaret Hall
550 Cumberland Street, Room 154
Ottawa, ON, K1N 6N5
Tel.: 613-562-5387 (ethics@uottawa.ca).

Should you have any questions about the study, please contact the principal investigator, supervisor or research coordinator:

Vinicius Muller Reis Weber
Principal Investigator
Faculty of Health Sciences
University of Ottawa
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Kristi Adamo
Professor/Supervisor
Faculty of Health Sciences
University of Ottawa
Tel.: 613-562-5800 x1009 (kadamo@uottawa.ca).

Kevin Semeniuk
Research Coordinator
Faculty of Health Sciences
University of Ottawa
Tel.: 613-562-5800 x1003 (ksemeniu@uottawa.ca)

Informed Consent of Participant

I _____ (your name), hereby volunteer to participate in the study titled **“Relationship between cardiorespiratory fitness, sports engagement, body composition, and biochemical makers related to neural development in young female adults”**. I have read the information presented in the above background information form and I have had the opportunity to ask questions of the investigators. I understand that my participation in this study, or indeed any research, may involve currently unforeseen risks.

The researcher will also share the conclusions of this study with the scientific community through publications and presentations.

I have been given a copy of this Background Information and Consent Form for me to keep. I also understand that by consenting to participate in this study, I have not waived any rights to legal recourse in the event of direct research-related harm (cf. TCPS2, 3.2).

Signature of Participant

Date (DD/MM/YY)

Signature of Researcher

Date (DD/MM/YY)

APÊNDICE 4

K.B. Adamo – Research Survey

DEMOGRAPHICS

1. Participant ID:

2. What is your gender?

Male

Female

You do not have an option that applies to me. I identify as (please specify):

3. What is your date of birth?

4. What is your marital status?

Married

Living common-law

Widowed

Separated

Divorced

Single, never married

5. Are you an Aboriginal person, that is, First Nations, Métis or Inuk (Inuit)? First Nations includes Status and Non-Status Indians.

Yes

No

IF YES:

6. Are you First Nations, Métis or Inuk (Inuit)?

First Nations (North American Indian)

Métis

Inuk (Inuit)

Unsure

7. How do you describe your ethnicity and/or race? Choose all that apply.

White

South Asian (e.g., East Indian, Pakistani, Sri Lankan)

Chinese

Black

K.B. Adamo – Research Survey

- Filipino
- Latin American
- Arab
- Southeast Asian (e.g., Vietnamese, Cambodian, Malaysian, Laotian)
- West Asian (e.g., Iranian, Afghan)
- Korean
- Japanese
- Other – specify:

8. What language do you speak most often at home?

- English
- French
- Both
- Other – specify:

9. How much money have you received over the last 12 month period (e.g., income, scholarships, familial assistance)?

- Less than \$20,000
- \$20,000 to less than \$30,000
- \$30,000 to less than \$40,000
- \$40,000 to less than \$50,000
- \$50,000 to less than \$60,000
- \$60,000 to less than \$70,000
- \$70,000 to less than \$80,000
- \$80,000 to less than \$90,000
- \$90,000 to less than \$100,000
- \$100,000 to less than \$110,000
- \$110,000 to less than \$120,000
- \$120,000 or more

10. How many people are dependent of this household income?

11. What is the highest certificate, diploma or degree that you have completed?

K.B. Adamo – Research Survey

- Less than high school diploma or its equivalent
- High school diploma or its equivalent
- Trade certificate or diploma
- College, CEGEP or other non-university certificate or diploma
- University certificate or diploma
- Bachelor's degree (e.g. B.A., B.Sc., LL.B.)
- University post-graduate certificate, diploma, degree

APÊNDICE 5

General Demographics Information and Reproductive Health History Questionnaire

PARTICIPANT ID: _____

Section A: General Demographics

1. What is your current age? _____
2. Have you ever experienced a fracture in your right forearm?
 - a) Yes
 - b) No
3. Which is your dominant hand?
 - a) Right
 - b) Left

Section B: Reproductive Health History

4. Do you take hormone in the form of birth control (e.g., pills, intrauterine device (Mirena) – IUD) or for hormone replacement therapy?
 - a) Yes
 - b) No
5. Do you have regular periods (~28 days long) ?
 - a) Yes
 - b) No, they were never regular
 - c) No, they were irregular for a few months
 - d) No, I never had a period
6. When was the start date of you last period? _____
7. Typically, how many days is your period? _____
8. How old were you when you got your first period? _____
9. Have you been through menopause? () YES () NO

10. In the past, how many pregnancies did you have in which you completed 20 weeks gestation or more?

- a) 0
- b) 1
- c) 2
- d) 3
- e) 4+

11. Do you have a diagnosed reproductive disease (e.g., Polycystic ovarian syndrome (PCOS), Endometriosis)?
