UNIVERSITY OF CALIFORNIA, MERCED

Physical Activity and Cortisol Regulation: A Meta-Analysis

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

in

Psychological Sciences

by

Susette Alanna Moyers, M.A.

Committee in charge:
Professor Martin S. Hagger, Chair
Professor Linda Cameron
Professor Jan Wallander

2021

I dedicate this dissertation to all of the scientists studying the exercise-cortisol paradox. Your work made this dissertation possible and has inspired me beyond measure.

The dissertation of Susette Alanna Moyers is approved by, and is acceptable in quality and form for publication on microfilm and electronically:

Professor Jan Wallander, Committee Member Date

Professor Linda Cameron, Committee Member Date

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University of California, Merced

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Next, I want to thank the members of my committee, Dr. Linda Cameron and Dr. Jan Wallander. Jan, thank you for agreeing to be on my committee since the first semester of graduate school! As your student and as your teaching assistant, I learned so much from you about health psychology and teaching. Your questions have challenged my work and they have helped me develop all of my milestone projects into manuscripts that were publishable. Thank you for your support on all of the personal matters as well, you have been someone that I can come to for just about anything, and I am grateful for the relationship that we were able to build. Linda, thank you for stepping in to be my interim advisor when I needed you to be. I appreciate all of your guidance over the past two years and all of your thoughtful comments and questions. The clinical implications section in here is for you! I have learned so much from you and I appreciate your support along the way.

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Curriculum Vitae

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EDUCATION

Ph.D. University of California, Merced
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Dissertation: *Physical activity and cortisol regulation: A meta-analysis*

M.A. Pepperdine University 2014-2016
Master of Arts in Psychology (Cum Laude)
Thesis: *The effects of social interaction on sleep and cortisol in low socio-economic populations*

B.A. University of California, Los Angeles 2012-2014
Bachelor of Arts in Psychology with honors

A.A. Santa Monica College 2010-2012
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PUBLICATIONS

Smith, S. R., Hagger, M. S., Keech, J. J., **Moyers, S. A.**, Hamilton, K. (in preparation). Social cognition approaches to understanding and changing COVID-19 preventive behaviours. In (Eds.), *Frontiers of COVID-19: Scientific and Clinical Perspectives of the Novel SARS-CoV-2.* New York, NY: Springer.

Moyers, S. A. & Hagger, M. S. (in preparation). Physical activity and cortisol regulation: A meta-analysis.

Moyers, S. A., Hagger, M. S., Keech, J. J., Smith, S. R., Hamilton, K. (in preparation). Cross-lagged effects of loneliness and avoidant coping during the COVID-19 pandemic.

Moyers, S. A., Hagger, M. S., Keech, J. J., Smith, S. R., Hamilton, K. (in preparation). Short- and long-term moderating effects of stress on loneliness and avoidant coping during the COVID-19 pandemic. *Stress & Health.*

Hagger, M. S., Smith, S. R., Keech, J. J., **Moyers, S. A**., Hamilton, K. (under review). Predicting physical distancing during the COVID-19 pandemic over time: Testing an integrated model. *Psychology & Health*.

Smith, S. R., Hagger, M. S., Keech, J. J., **Moyers, S. A.**, Hamilton, K. (under review). Improving hand hygiene behavior using a novel theory-based intervention during the COVID-19 pandemic. *Journal of Experimental Psychology: Applied.*

Hamilton, K., Smith, S. R., Keech, J. J., **Moyers, S. A**., Hagger, M. S. (2020). Application of the Health Action Process Approach to social distancing behavior during COVID-19. *Applied Psychology: Health and Well-Being.* https://doi.org/10.1111/aphw.12231

Hagger, M. S., Smith, S. R., Keech, J. J., **Moyers, S. A**., Hamilton, K. (2020). Predicting social distancing intention and behavior during the COVID-19 pandemic: An integrated social cognition model. *Annals of Behavioral Medicine.* https://doi.org/10.1093/abm/kaaa073

Moyers, S. A. & Hagger, M. S. (2020). Planning and implementation intention interventions in physical activity. In (Eds.) *Handbook of Self-Regulation and Motivation in Sport and Exercise.* Oxford, UK: Taylor & Francis. https://books.google.com/books?hl=en&lr=&id=YnwpEAAAQBAJ&oi=fnd&pg=PA166&ots=x92H1zZaTJ&sig=ArOjHrZUy2NcJVUry1kobLGInR0#v=onepage&q&f=false

Moyers, S. A. & Hagger, M. S. (2020). Physical activity and sense of coherence: A meta-analysis. *International Review of Sport and Exercise Psychology.* https://www.doi.org/10.1080/1750984X.2020.1846068

Moyers, S. A. & Tiemensma, J. (2020). The association between physical activity, sleep, and quality of life in patients in bio-chemical remission from Cushing's Syndrome. *Quality of Life Research, 29*(8), 2089-2100. https://doi.org/10.1007/s11136-020-02480-y

McKinley, L. E., McAnally, K., **Moyers, S. A.**, & Hagger, M. S. (2020). Behavioral health theories, equity, and disparities in global health: A basic process model. In R. Haring, I. Kickbusch, D. Ganten & M. R. Moeti (Eds.), *Handbook of Global Health*. New York, NY: Springer.

Hagger, M, S., **Moyers, S**., McAnally, K., McKinley, L. E. (2020). Known knowns and known unknowns on behavior change interventions and mechanisms of action. *Health Psychology Review*, *14*(1), 199-212. https://doi.org/10.1080/17437199.2020.1719184

WORK EXPERIENCE

Teaching Fellow Spring 2021
Psychology 015-Research Methods in Psychology
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GradEXCEL Graduate Peer Mentor 2020-2021
University of California, Merced

Teaching Fellow Fall 2020
Psychology 180-Physiological Psychology
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Psychology 181-Clinical Neuropsychology
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Teaching Assistant Fall 2019
Psychology 120- Health Psychology
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Teaching Assistant Spring 2019
Psychology 001-Introduction to Psychology
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Teaching Assistant Fall 2018
Psychology 181-Clinical Neuropsychology
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Teaching Assistant Spring 2018
Psychology 143-Abnormal Child Psychology
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Teaching Assistant Fall 2017
Psychology 001-Introduction to Psychology
University of California, Merced

Research Associate 2016-2017

Sovereign Health Group
Performed upper-level psychometric ratings such as SCID-V, WAIS-IV, MMPI-2RF, and any other projective testing as appropriate for patient based on current and pending diagnoses, wrote relevant psychological reports at the completion of each visit for each patient, managed the collection of data and ensured that it was precise and accurate, conducted literature research for all relevant projects, conducted on-going testing of company cognitive products, created proposals and promoted company products in research-related capacities, coordinated collaborative work efforts between staff from different departments and clinical sites in order to maximize the efficiency and effectiveness of the patient's treatment plan.

ORAL PRESENTATIONS

Hamilton, K., Smith, S. R., Keech, J. J., **Moyers, S. A**., Hagger, M. S. (2021, September). Predicting physical distancing over time during the COVID-19 pandemic. *Presentation given in the Health Behavior Models and the COVID-19 Pandemic symposium*, at The European Health Psychology Society, 35th Annual Conference, Virtual.

Moyers, S. A. (2021, April). *Short- and long-term mediating effects of perceived stress on loneliness and avoidant coping during the COVID-19 pandemic*. Health Psychology in COVID-19: Showcase on research, practice, and policy, Australian Psychological Society, Virtual.

Moyers, S. A. & Hagger M. S. (2021, April). *Physical activity and sense of coherence: A meta-analysis.* Society of Behavioral Medicine, 42nd Annual Conference, Virtual.

Moyers, S. A. & Hagger M.S. (2021, March). *Predicting social distancing behavior and avoidant coping during* the *COVID-19 pandemic.* Presentation given at the Health Sciences Research Institute's COVID-19 Research at University of California, Merced research week event, University of California, Merced, Virtual.

Moyers, S. A. (2020, November). *Stress and Health*. Guest lecture given online to Psychology 180-Physiological Psychology undergraduate class, Merced, California.

Moyers, S. A. (2019, November). *Physical activity and sense of coherence: A meta-analysis.* Presentation given at University of California, Merced health psychology department colloquium.

Moyers, S. A. (2019, October). *Physical activity*. Guest lecture given at the University of California, Merced to Psychology 120- Health Psychology undergraduate class, Merced, California.

Moyers, S. A. (2019, April). *The association between exercise, sleep, and quality of life in patients in remission from Cushing' Syndrome*. Western Psychological Association, 99th Annual Conference, Pasadena, California.

Moyers, S. A. (2019, January). *The association between physical activity, sleep, and*

quality of life in patients in remission from Cushing' Syndrome. Presentation given at University of California, Merced health psychology department colloquium.

Moyers, S. A. (2018, April). *The association between physical activity, sleep, and quality of life in patients in remission from Cushing' Syndrome*. Presentation given at University of California, Merced health psychology department pre-candidacy thesis symposium.

Moyers, S. A. (2018, March). *Stress, Trauma, and PTSD in Children.* Guest lecture given at the University of California, Merced to Psychology 143-Abnormal Child Psychology undergraduate class, Merced, California.

Moyers, S. A. (2017, October). *Mechanisms of Memory*. Guest lecture given at the University of California, Merced to Psychology 001-Introduction to Psychology undergraduate class, Merced, California.

Moyers, S. A. (2017, March). *Graduate school acceptance.* Panel presentation at Pepperdine University Master of Arts in Psychology class, West Los Angeles, California. *Invited talk.*

Moyers, S. A. (2016, June). *The Effects of Social Bonding on Sleep and Cortisol in Low Socio-Economic Populations.* Presentation conducted at Pepperdine's first annual GSEP Student Research and Project Symposium, Los Angeles, California.

Moyers, S. A. & Thapar-Olmos, N. (2016, March). *Stress, Resilience, and Healthy Women in the Workplace.* Presentation conducted at the annual GSEP Women in Leadership Conference, Los Angeles, California. *Invited talk.*

Castañeda-Sound, C. L., Sanchez, J. A., **Moyers, S. A.**, & Venegas, S. S. (2015, June). *Training Experiences of Bilingual Therapists*. Presentation given at Pepperdine's first annual graduate school of education and psychology faculty research symposium, West Los Angeles, California.

POSTER PRESENTATIONS

Moyers, S. A. & Tiemensma, J. (2019, March). *The association between exercise, sleep, and quality of life in patients in remission from Cushing' Syndrome*. Society of Behavioral Medicine, 40th Annual Conference, Washington, D.C.

Castañeda-Sound, C. L., Sanchez, J. A., **Moyers, S. A.**, & Venegas, S. S. (2018, October). *Exploring the clinical skill development of bilingual trainees.* National Latina/o Psychological Association biennial conference, San Diego, California.

Pettit, C., **Moyers, S.**, Moss, I. K, Iturralde, E., Rodriguez, A., Corley, F., Ramos, M., & Margolin, M. (2017, April). *Co-rumination as a moderator between victimization and depressive symptoms.* Biennial Meeting of the Society for Research on Child Development, Austin, Texas.

Pettit, C., **Moyers, S.**, Moss, I. K, Iturralde, E., Rodriguez, A., Corley, F., Ramos, M., & Margolin, M. (2017, April). *Observed global irritability in dyadic peer*

discussions as predicted by depressive symptoms and negative life events. Biennial Meeting of the Society for Research on Child Development, Austin, Texas.

Moyers, S. A., Pettit, C., Kellerman, I., Ramos, M., Itturalde, E., Corley, F., Margolin, G. (2017, April). *The role of gender in adolescent depression and put down behaviors.* Society for Research in Child Development Biennial Meeting, Austin, Texas.

Harari, L. A., **Moyers, S. A.**, Raposa, E. B., & Hammen, C. L. (2014, May). *The role of early life stress, and parenting styles in predicting alcohol consumption.* Poster presented at the psychology undergraduate research conference, Los Angeles, California.

TRAINING/CERTIFICATIONS

Institute for Evidence-Based Teaching Practices in Support of Student Learning 2021
University of California, Merced, Center for Engaged Teaching and Learning
Certificate received

This six-part interactive workshop included topics such as why the classroom climate matters for student learning, how student's prior knowledge affects learning, why student development matters for student learning, how students organize knowledge for learning, motivation principles for student learning, and how to use feedback to enhance student learning.

Methods for Meta-Analysis 2020
Georgia State University, Center for International Business Education and Research
Certificate received

This workshop covered topics related to meta-analytic methods, including multi-level and structural equation modeling for meta-analysis.

Preparing to Teach in the Online Environment Workshop 2020
University of California, Merced, Center for Engaged Teaching and Learning
Certificate received

This three-part workshop included topics such as remote technologies for teaching, enriching the student remote learning experience, and enhancing the remote instructor experience to help prepare instructors to implement online instruction.

Improving Teaching by Assessing Learning Workshop 2018
University of California, Merced, Center for Engaged Teaching and Learning
Certificate received

This four-part practicum-style workshop included topics such as lesson/curriculum planning, rubric design, teaching portfolios and student evaluations, and crafting a teaching statement.

SERVICE

W-STEM Graduate Mentor 2020-Present
University of California, Merced

-Provided professional development and mentorship to UC Merced undergraduate students tailored to the specific challenges faced by women in STEM. W-STEM is an organization dedicated to the advancement and empowerment of women in science, technology, engineering, and mathematics (STEM) fields at The University of California, Merced.

Editorial Manager 2020-2021
Behavioral Sciences: Special Issue "Health Behavior Change: Theories, Methods & Interventions"

-Assisted with the editorial process for the special issue with invited guest editors.

Lab Manager – SHARPP Lab 2019-2021
University of California, Merced

-Facilitated lab meetings, coordinated with community members for collaboration on behalf of the lab, managed all lab projects, and ensured lab was stocked with all materials and resources needed.

Academic Journal Peer Reviewer 2019-Present
Stress and Health | Annals of Leisure Research | Annals of Behavioral Medicine | Psychology and Health

-Completed two peer reviews for the academic journal *Stress and Health,* one peer review for the academic journal *Annals of Leisure Research,* one peer review for the academic journal *Annals of Behavioral Medicine*, and one peer review for the academic journal *Psychology and Health.*

Program committee for University of California Health Psychology Consortium
University of California, Merced 2019-2020

-Committee member for University of California inter-campus health psychology consortium. Helped plan and facilitate event, held at the University of California, Merced.

Graduate Student "Buddy" 2019
University of California, Merced

-"Buddy" to a prospective graduate student during visitation weekend, ensured the student was able to participate in all visitation weekend activities, provided transportation, and any other support that the prospective student needed.

Research Lab Assistant 2016
University of Southern California

Neuroendocrinology and Social Ties Lab (PI: Dr. Darby Saxbe)

-Recruited study participants from the San Fernando Valley area, ran participants in the study (included saliva collection for cortisol analysis), data entry, and transcribed video and audio interviews.

Research Lab Assistant 2015- 2016

University of Southern California

Family Studies Project (PI: Dr. Gayla Margolin)

-Coded video data of dyads by identifying specific adaptive and maladaptive interpersonal behavioral patterns within the dyad for further quantitative analysis.

Research Lab Assistant 2015- 2016

Pepperdine University

Language and Culture Lab (PI: Dr. Carrie Castañeda-Sound)

-Worked with a team to identify, examine, and interpret patterns and themes from interview transcripts for qualitative analysis.

Research Lab Assistant 2013- 2014

University of California, Los Angeles

Social Environmental Health Experiences Lab (PI: Dr. Constance Hammen)

-Administered informed consent/explained the study, ran baseline measures, and ensured adherence to study protocol for each participant (including daily diary entries, follow-up surveys, and saliva collection for cortisol analysis).

FELLOWSHIPS/AWARDS Amount

Graduate Dean's Relocation Grant (September, 2017)	$500
2018 SSHA Dean's Summer Research Award (April, 2018)	$858
Psychological Sciences Summer Support Award (April, 2018)	$3385
Health Psychology Travel Presentation Award (April, 2019)	$160
Psychological Sciences Summer Support Award (April, 2019)	$4213
Will Shadish Award for Leadership and Service (March, 2020)	$300
Psychological Sciences Summer Support Award (April, 2020)	$3618
Psychological Sciences Research Dissemination Award (April, 2020)	$333
GradEXCEL Peer Mentor Award (December, 2020)	$150
GradSlam Competition Finalist (March, 2021)	$250
GradEXCEL Peer Mentor Award (March, 2021)	$150
Will Shadish Award for Leadership and Service (March, 2021)	$300
Psychological Sciences Summer Support Award (April, 2021)	$3260
Psychological Sciences Development Support Award (April, 2021)	$100
Psychological Sciences Research Dissemination Award (April, 2021)	$250
Outstanding Paper in Health Psychology Award (April, 2021)	$750
Will Shadish Graduate Student Fellowship 2020-2021 Recipient	$1000

Psychological Sciences Outstanding Graduate Student in Health Psychology (2020-2021)

PROFESSIONAL AFFILIATIONS

American Psychological Association
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American College of Sports Medicine
Society for Personality and Social Psychology

Abstract

Dysregulated diurnal secretion patterns of the hormone cortisol are implicated in mediating associations between stress exposure and health outcomes (Chrousos & Gold, 1992; Davis & Sandman, 2010; Lupien et al., 2009), including the onset and progression of mental and physical health disorders (Heim et al., 2008). Physical activity participation has been associated with lower levels of cortisol secretion during times of stress and may contribute to effective regulation of cortisol secretion over time. Adequate HPA-axis regulation is one potential mechanism by which physical activity participation may impact stress-related outcomes and quantifying the effect across studies will demonstrate the degree to which physical activity participation is associated with effective HPA-axis regulation and help to identify the potential conditions or factors that may affect it. We synthesized research examining the association between physical activity participation and two distinct indices of effective HPA-axis regulation; the diurnal cortisol slope and the cortisol awakening response, as well as factors that moderate this relationship across existent literature. The three-level meta-analysis revealed a small, non-zero negative correlation between physical activity and the diurnal cortisol slope with high heterogeneity. Moderator analyses examining effects of sample sociodemographic differences, study design characteristics, cortisol measurement methods, and physical activity-related differences indicated few differences in the averaged physical activity-diurnal cortisol slope relationship across studies at different levels of each moderator. There were observed differences effect in some isolated cases, for example, the correlation was slightly larger and non-zero in experimental studies compared to observational studies in which the correlation was smaller and no different from zero. However, overall, evidence for the effect of moderators on the physical activity-diurnal cortisol slope relationship was weak. For the cortisol awakening response, while the variability estimates about the averaged mean cortisol awakening response were lowest in the moderate physical activity subgroup when compared with the high and low physical activity subgroups, confidence intervals about the variance estimates overlapped considerably across subgroups and did not provide definitive evidence to support lower levels of variability in the mean cortisol awakening response at higher levels of physical activity participation. Moderator analyses did not reduce heterogeneity in the effect in most cases, and confidence intervals indicated no differences in variability estimates for the averaged mean at most levels of the moderator. Overall, findings suggest physical activity participation is associated with an adequately regulated or *steeper* diurnal cortisol slope. However, physical activity level was not associated with an adequately regulated cortisol awakening response as the variability about the mean cortisol awakening response across high, moderate, and low physical activity subgroups did not differ. Based on current findings, studies that test the relationship between physical activity and cortisol regulation relationship should consider using standardized measures of physical activity including frequency, intensity, and duration of physical activity participation, follow consensus guidelines for cortisol sample collection and analysis, and test these relationships in large-scale empirical studies to confirm the direction and causality of the effect.

Supplemental materials submitted with this dissertation include the following:
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Chapter 1

Introduction

Chronic stress has been associated with the development or exacerbation of multiple physical and psychological health conditions including cardiovascular disease, type II diabetes, stroke (Rosmond & Bjorntorp, 2000), cancer (Abercrombie et al., 2004), premature cellular aging (Parks et al., 2009), autoimmune disorders and inflammation (Silverman & Sternberg, 2012), systemic hypertension (Wirtz et al., 2007), depression (Stetler & Miller, 2005), and anxiety (Vedhara et al., 2003). Exposure to stress is ubiquitous, impacting individuals worldwide. For example, in 2018, about one third of the worldwide population and more than half of Americans reported experiencing elevated stress during the day (Gallup, 2019). As a consequence, identifying the correlates of stress and its development, as well as the mechanisms involved, is considered a priority area of research that may inform the development of interventions to minimize the deleterious effects of stress on health (O'Connor et al., 2020).

One factor that has been implicated in the relationship between stress and stress-related health outcomes is the stress hormone cortisol. Physical (e.g., physical activity) and psychological (e.g., work stress) forms of stress can activate stress-related responses, which, in turn, activate cortisol secretion to enable more effective coping with the stressor by increasing arousal (Kirschbaum & Hellhammer, 1989). Although cortisol secretion and associated arousal is an adaptive short-term response to stress, chronic stress-related cortisol secretion can cause the system that produces cortisol, the hypothalamic-pituitary-adrenal axis (HPA-axis), to become *dysregulated*. This means that the diurnal pattern of cortisol secretion does not follow the expected diurnal secretion pattern across the waking day.

HPA-axis dysregulation is typically measured through parameters that capture the circadian diurnal rhythm of cortisol secretion, such as the diurnal cortisol slope and the cortisol awakening response (Chida and Steptoe, 2009; Saxbe, 2008). The diurnal cortisol slope is a measure of the rate of cortisol decline across the day, and the cortisol awakening response is a measure of the increase in cortisol levels during the first 30 minutes to 1 hour after awakening. Deviations from the expected rhythm of the diurnal cortisol slope and the cortisol awakening response suggest HPA-axis dysregulation. Research has demonstrated associations between these measures and increased risk of many chronic physical and mental health conditions such as cardiovascular disease (Whitworth et al., 2005), obesity-related metabolic disorders (Baudrand & Vaidya, 2015), insomnia (Rodenbeck & Hajak, 2001), hypertension (Whitworth et al., 1995), and uni- and bi-polar depression (McIsaac & Young, 2009).

Meta-analytic evidence has shown that deviations from the expected steep daily decline in the diurnal cortisol slope (i.e., a 'flatter' slope), an indicator of a dysregulated HPA-axis, is associated with poorer health in many stress-related mental and physical health outcomes such as depression, fatigue, immune/inflammatory outcomes, obesity and adiposity, cancer, and all-cause mortality (Adam et al., 2017). Stress-related alterations in HPA-axis regulation may, therefore, play a role in mediating associations between stress exposure and health outcomes (Chrousos & Gold, 1992; Davis & Sandman, 2010; Lupien et al., 2009), including both the onset and progression of mental

and physical health disorders (Heim et al., 2008). Based on these data, it is imperative to identify modifiable targets for interventions that promote effective HPA-axis regulation. The purpose of the current study was to examine the association between a candidate target behavior, physical activity participation, and HPA-axis regulation, as well as factors that moderate this relationship across the extant literature. The research will make an important contribution to knowledge by examining the strength of the evidence across studies of physical activity participation as a potential correlate of a key process for stress management, that is, effective cortisol regulation. It will also synthesize evidence on the conditions that affect the relationship between physical activity participation and HPA-axis regulation.

HPA-Axis Regulation

HPA-axis regulation is indicated by daily fluctuations in cortisol secretion across the waking day. Individuals with adequately-regulated HPA-axes produce cortisol levels that are elevated on waking, followed by a rapid increase to 50 to 60% above waking levels within an hour of waking, then a rapid drop in the hours after the awakening surge, and finally a less rapid drop until reaching a baseline around bedtime (Kirschbaum & Hellhammer, 1989; Pruessner et al., 1997). This produces a characteristic steep cortisol slope over the waking day. Individuals with a dysregulated HPA-axis may over- or under-produce cortisol in the morning – known as a 'heightened' or 'blunted' cortisol awakening response, respectively. As a consequence, they will likely exhibit a slower decline or high variability in cortisol patterns over the waking day, producing a 'flatter' overall diurnal cortisol slope from awakening to bedtime (Adam & Kumari, 2009). While genetic factors (Bartels et al., 2003) and circadian rhythms (Van Cauter et al., 1996) influence HPA-axis regulation, it is also influenced by environmental and behavioral factors related to stress (Dickerson & Kemeny, 2004).

Physical Activity and HPA-Axis Regulation

Previous research supports the stress-reducing effects of regular physical activity participation (Nguyen-Michel et al., 2006). Physical activity participation is associated with lower levels of stress reactivity (heart rate, blood pressure; Forcier et al., 2006; Hamer et al., 2006; Wipfli & Ramirez, 2013). While these data provide robust evidence that physical activity participation is related to effective in-the-moment physiological stress management, the underlying mechanisms that mediate this effect are largely unknown. Developing an understanding of *how* physical activity interventions produce these changes and the mechanisms involved may provide targets for future interventions that will reliably produce adaptive changes in stress-related health parameters. HPA-axis regulation is one potential mechanism by which physical activity participation may impact stress-related outcomes (Tsatsoulis & Fountoulakis, 2006).

A proposed mechanism by which physical-activity relates to better stress management implicates HPA-axis regulation (Chen et al., 2017). Chronic physical activity is proposed to have protective effects on the region in the brain responsible for regulating the HPA-axis negative feedback loop, which can be thought of as the 'off-switch' that stops cortisol output after a stressor subsides (Chen et al., 2017; Zschucke et al., 2015). The diurnal cortisol slope has been proposed to represent an intact HPA-axis negative feedback loop as a steep diurnal cortisol slope models an individual's ability to recover and disengage from stressful events over the course of a day (Heim et al., 2000;

Miller et al., 2007). Examining the degree to which physical activity participation is associated with HPA-axis regulation parameters, especially the diurnal cortisol slope, may provide information on the degree to which HPA-axis regulation is a mechanism underlying improved psychological and physiological stress indices from physical activity participation. Physical activity participation may facilitate optimal HPA-axis recovery to disengage from daily stress. Confirming that physical activity participation is associated with indices of adequate HPA-axis regulation may provide important evidence of one mechanism by which physical activity may reduce stress-related health outcomes.

While many studies have found a relationship between physical activity and parameters related to HPA-axis regulation such as the diurnal cortisol slope (Gubelmann et al., 2018; Ho et al., 2020; Vreeburg et al., 2009) and the cortisol awakening response (Calogiuri et al., 2016; Gubelmann et al., 2018; Tortosa-Martìnez et al., 2015), findings across studies have been inconclusive: some studies have reported a statistically non-zero effect (Tortosa-Martìnez et al., 2015; Vreeburg et al., 2009) while others reported an effect that does not differ from the null (Foss et al., 2014; Lederbogen et al., 2010; McHale et al., 2014; Menke et al., 2014). Reviews of research examining the relationship between physical activity on parameters and HPA-axis regulation have suggested an association (Anderson & Wideman, 2017; Pascoe et al., 2017), but, to date, no research synthesis has provided an estimate of the size of the effect of physical activity participation broadly defined and HPA-axis regulation parameters. Quantifying the relationship between physical activity participation and HPA-axis regulation-related parameters across studies may provide important evidence to support the size of the effect and its degree of heterogeneity across studies and may also assist in identifying possible moderators of the effect. Such an analysis is valuable because it will demonstrate the degree to which physical activity participation is associated with HPA-axis regulation and help to identify the potential conditions or factors that may affect it. This is valuable information for those developing future interventions aiming to manage stress by impacting HPA-axis dysregulation and potentially reducing stress and improving health outcomes.

The Present Study

Main Hypothesis

In the present study, we aimed to synthesize research testing the physical activity participation-HPA-axis regulation relationship and examine the effects of candidate moderators on the relationship across studies. Specifically, we aimed to determine the average size and heterogeneity of the relationship between physical activity participation and two independent indices of HPA-axis regulation, the diurnal cortisol slope and the cortisol awakening response, across studies in existing literature using three-level meta-analysis. These indices were selected because they are the most commonly used means to indicate HPA-axis dysregulation in current literature (Adam & Kumari, 2009), provide an estimate of variability in cortisol across key diurnal timepoints of interest, and represent independent aspects of HPA-axis dysregulation (Wilhelm et al., 2007). For each outcome, we aimed to evaluate whether the observed variability in the correlation of the diurnal cortisol slope, or the mean and standard deviation a different levels of physical activity participation for the cortisol awakening response, across studies could be

attributed to methodological artifacts corrected for in meta-analysis (i.e., sampling error), or reflects true variability in the effect across studies and the extent of that variability.

Consistent with prior theory and research (Gubelmann et al., 2018; Ho et al., 2020; Vreeburg et al., 2009), we hypothesized that physical activity participation would be associated with steeper diurnal cortisol slopes across studies. We also hypothesized that physical activity would be related to the cortisol awakening response. Both heightened and blunted cortisol awakening responses are indicative of HPA-axis dysregulation, while a mid-range cortisol awakening response, indicated by rise in cortisol from awakening to peak secretion in the range of 9.3 +/- 3.1 nmol/l, reflects adequate regulation (Clow et al., 2004; Wüst et al., 2000). We therefore hypothesized that the cortisol awakening response would show less variability about the mean from awakening to peak cortisol secretion in those who are more physically active compared to those who are less-active. This is because those who are less physically active may be more likely to exhibit a dysregulated cortisol awakening response, either heightened or blunted, which is expected to be manifested in higher variability about the mean cortisol awakening response across studies. By comparison, those who are active are more likely to exhibit adequate HPA-axis regulation, which is likely to be manifested in less variability in the mean response across studies.

Moderators of the Physical Activity-HPA-Axis Regulation Effect

In addition to quantifying the relation between the physical activity participation and HPA-axis regulation relationship, we aimed to test effects of several key moderators on the relationship for each index: sociodemographic variables (age, sex, BMI, clinical sample), cortisol measurement methods (type of diurnal cortisol slope, number of cortisol samples taken over the relative time period, number of days cortisol was measured, whether samples were taken on a resting day or not reported, cortisol sampling quality), physical activity assessment methods (physical activity intensity, intensity assessment type, physical activity duration, level of physical fitness, fitness assessment type, time of day physical activity was performed, physical activity type, physical activity measurement, and physical activity frequency), and general study design (time lag and study design). These moderators will be assessed using categorical moderator analyses and meta-regression. Next, we outline our predictions for each moderator analysis.

Sociodemographic factors. Consistent with evidence that younger, male participants show more evidence of effective HPA-axis regulation than older, female participants (Therrien et al., 2007; Vreeburg et al., 2009), we predicted a larger averaged association between physical activity and the diurnal cortisol slope in studies on younger participants than studies on older participants. We also predicted that the difference in the variability of the mean cortisol awakening response at high and moderate compared to low levels of physical activity participation would be greater in studies with older participants relative to younger participants. We also expected a larger averaged association between physical activity and the diurnal cortisol slope in studies on male participants relative to female participants. Similarly, we predicted that the difference in the variability of the mean cortisol awakening response at high and moderate, compared to low levels of physical activity be greater in studies with mostly female participants, relative to those with mostly male participants.

In addition, given that high body mass index (BMI) is associated with dysregulation in HPA-axis parameters, we predicted that studies on participants with a BMI classified as under or normal weight (BMI ≤ 25) would exhibit a larger physical activity-diurnal cortisol slope association than studies on participants with a BMI classified as overweight or obese (BMI > 25) (Rodriguez et al., 2015). We also predicted a larger the difference in the variability of the mean cortisol awakening response at high and moderate compared to low levels of physical activity in studies with samples that have a high mean BMI compared to studies with samples with a low mean BMI. Finally, clinical samples (e.g., samples with an elevated risk of depression) show evidence of HPA-axis dysregulation (Adam et al., 2017), so we expected to find a smaller averaged physical activity-diurnal cortisol slope association in studies on clinical samples relative to studies on non-clinical samples. We also expected to find that the difference in the variability about the mean cortisol awakening response at high and moderate compared to low levels of physical activity participation to be greater in studies on clinical samples relative to studies with non-clinical samples.

Cortisol measurement methods. The diurnal cortisol slope can be calculated using a number of methods, and we aimed to examine differences in the calculation method used as a moderator of relations between physical activity and the diurnal cortisol slope. We expected to find that studies using amplitude measures (i.e., many measures of cortisol taken over the course of a day, with the magnitude of the minimum to peak taken as the amplitude of the diurnal rhythm) and wake-bed slopes (e.g., cortisol slopes derived from the difference between waking and bedtime cortisol) would exhibit a greater averaged association between the physical activity and the diurnal cortisol slope effects than studies using other methods to calculate the diurnal cortisol slope (e.g., short daytime slopes or late decline slopes, which measure the slope from several hours after waking to evening or bedtime; Adam et al., 2017). We also expected a larger averaged association between physical activity and the diurnal cortisol slope in studies measuring cortisol on waking compared to studies measuring cortisol at fixed time points. Likewise, we expected the difference in the variability about the average mean of the cortisol awakening response between high and moderate versus low levels of physical activity participation to be smaller in studies measuring cortisol on waking compared to studies measuring cortisol at fixed time points. This is because diurnal rhythms are anchored primarily to person-specific sleep-wake cycles rather than dark/light cycles (Wilhelm et al., 2007).

We also investigated whether the averaged physical activity-HPA axis relationship was moderated by key methodological differences in the measurement of cortisol: number of cortisol samples taken during the first hour of awakening for the cortisol awakening response and number of samples taken over the waking day for the diurnal cortisol slope; number of days cortisol was measured; whether cortisol was sampled on a resting day or not reported; and methodological quality of cortisol sampling rating. We expected to find larger averaged physical activity-diurnal cortisol slope association in studies that took more than two samples in one day to determine the diurnal cortisol slope relative to studies that took only two samples. We also expected the difference in the variability about the mean cortisol awakening response at high and moderate compared to low levels of physical activity to be greater in studies that took

two samples of cortisol to determine the cortisol awakening response than studies that took more than two. This is based on previous research that found non-zero effects of cortisol regulation parameters on health and stress-related outcomes in studies that employed more than three samples to assess the diurnal cortisol slope and the cortisol awakening response (Adam et al., 2017; Chida & Steptoe, 2009). We also expected to find that studies sampling cortisol on one day may exhibit more variability in the physical activity-diurnal cortisol slope effect than studies that sampled cortisol on more than one day. We also expected to find a larger difference in the variability of the mean cortisol awakening response between high and moderate versus low levels of physical activity participation in studies that sampled cortisol on one day only compared to studies that sampled cortisol on more than one day. This prediction is based on research indicating that gathering cortisol samples on multiple days leads to greater reliability in the diurnal cortisol slope and the cortisol awakening response (Adam & Kumari, 2009). In addition, consistent with evidence that physical activity increases cortisol secretion (Viru, 1992) and may influence daily cortisol slope measurements, we predicted that studies advising participants to engage in a period of rest prior to diurnal cortisol measurement may produce a less variable physical activity-diurnal cortisol slope effect than those that do not instruct, or do not report instructing, participants to rest prior to cortisol measurement. Since the cortisol awakening response is measured on awakening and 30-45 minutes after awakening, we assumed that participants would not be likely to engage in physical activity between these times, so we did not test this moderator in the physical activity-cortisol awakening response analysis. We also tested whether the methodological quality of cortisol sampling moderated the physical activity-HPA-axis regulation association in both outcomes.

Physical activity assessment methods. Physical activity intensity, duration, and frequency were also included as candidate moderators of the physical activity-diurnal cortisol slope relationship, but these variables were not assessed in the physical activity-cortisol awakening response effect because intensity, duration, and frequency of physical activity participation are inherent in the classification of study effects into high, moderate, and low physical activity participation subgroups. Consistent with evidence from previous studies suggesting a dose-dependent relationship between physical activity and cortisol secretion, we hypothesized that the averaged physical-activity participation-diurnal cortisol slope association would be larger when bouts of physical activity exceeded an individuals' 50% VO_2 max threshold and were of 30 minutes or greater in duration, a length of time sufficient to stimulate HPA-axis activation and subsequent cortisol secretion (Duclos et al., 2003; Hackney & Viru, 1999; Hill et al., 2008; Viru, 1992). Physical activity frequency was also included as a moderator of the averaged association between physical activity and the diurnal cortisol slope. Previous studies have shown large reductions in overall cortisol concentrations among individuals that engage in physical activity at least five times a week, although reductions have been noted in those participating in physical activity three times a week (Beserra et al., 2018). The averaged physical activity-diurnal cortisol slope association was, therefore, expected to be larger in studies on samples that engaged in three or more physical activity sessions a week compared to studies on samples that engaged in fewer than three sessions per week. We also expected to find a greater averaged physical-activity participation-diurnal

cortisol slope association in studies that measured intensity as relative exercise intensity measures (e.g., expressed as percentage of participants' VO_2 max) than those based on absolute values (e.g., expressed in metabolic equivalents, MET values). We also expected to find smaller difference in the variability of the mean cortisol awakening response in high and moderate versus low levels of physical activity participation in relative exercise intensity measures compared to those based on absolute values.

Fitness level was also assessed as a moderator, as previous evidence suggests that athletes or physically fit individuals are likely to have developed adaptations to their HPA-axis from prior physical activity engagement (Duclos et al., 2003). We expected that athletes and individuals with high levels of physical fitness would have a larger averaged physical activity-diurnal cortisol slope association than those with lower levels of fitness. We also expected to see a smaller difference in the variability about the mean of the cortisol awakening response in high and moderate versus low levels of physical activity, in athletes or participants with a high level of fitness relative to non-athletes or those with lower fitness levels. We also expected that studies utilizing non-self-reported measures of physical fitness are less heterogeneous than studies that utilized self-reported fitness assessment.

We also examined time of day that physical activity was performed, physical activity type, and type of physical activity measurement as moderators. We predicted that the averaged physical activity-diurnal cortisol slope association would be larger across groups of studies on participants performing physical activity in the morning compared to studies on participants performing physical activity in the afternoon or evening. We also expected the difference in the variability of the mean cortisol awakening response between high and moderate versus low levels of physical activity participation to be smaller across groups of studies on participants performing physical activity in the morning compared to studies on participants performing physical activity in the afternoon or evening. This prediction is based on previous research that showed that greater cortisol secretion was reported among participant when physical activity was performed in the morning than in the afternoon or evening (Kanaley et al., 2001). Aerobic physical activity has been shown to induce cortisol secretion more reliably and with less variability than anaerobic types of physical activity (Beserra et al., 2018; Vrinceanu et al., 2019). We therefore expected studies on samples performing aerobic physical activity would exhibit a larger physical activity-diurnal cortisol slope averaged relationship than studies on samples performing anaerobic physical activity. Likewise, we predicted studies on samples performing aerobic physical activity would exhibit a smaller difference in the variability about the mean cortisol awakening response between high and moderate versus low physical activity levels than studies on samples that performed anaerobic forms of physical activity.

We also predicted that studies adopting non-self-report measures of physical activity (e.g., use of accelerometers or pedometers) would exhibit greater precision and less variability in the physical activity-diurnal cortisol slope effect than studies that utilized a self-report measure. We also expected that the difference in the variability of the mean cortisol awakening response in high and moderate versus low levels of physical activity to be smaller in studies with non-self-reported physical activity measures than studies adopting self-reported physical activity measures (e.g., using physical activity

surveys), as self-reported physical activity may be subject to biases attributable to socially desirable responding and limitations of recall (Adams et al., 2005; Sallis & Saelens, 2005). We also accounted for studies that utilized validated versus bespoke self-report measures of physical activity participation, as previously-validated physical activity scales are likely to have better reliability and validity than truncated and bespoke versions (Milton et al., 2011), so we expected to find that studies that utilized validated scales would exhibit greater precision and less variability in the physical activity-diurnal cortisol slope effect than studies that utilized bespoke scales. We also expected that the difference in the variability of the mean cortisol awakening response in high and moderate versus low levels of physical activity would be smaller in studies that utilized a validated self-report physical activity assessment than in studies that utilized a bespoke physical activity assessment.

Study design. We also examined study design as a candidate moderator of the association between physical activity and indices of HPA-axis regulation across studies. We predicted that studies adopting cross-sectional designs would have a larger averaged physical activity participation-diurnal cortisol slope association. We also predicted that the difference in the mean variability of the cortisol awakening response in high and moderate physical activity subgroups, compared with low physical activity subgroups, would be smaller in studies adopting correlation designs compared with studies employing experimental or intervention designs. This is because cross-sectional studies tend to use similar methods and measure constructs in close proximity which may inflate relations due to common method variance and measurement correspondence. We also expected that experimental and intervention studies in which participants were prescribed longer periods of physical activity would exhibit a larger averaged physical activity-diurnal cortisol slope association. We also predicted that there would be a smaller difference in the variability about the mean cortisol awakening response in high and moderate versus low levels of physical activity participation in longer period of prescribed physical activity than those prescribed with shorter periods. This is based on research that suggests studies with a longer duration of assigned physical activity is associated with greater change in morning cortisol levels than those with shorter study durations (Anderson & Wideman, 2017). We also investigated whether interventions with single (physical activity only) or multiple intervention components (physical activity plus one or more intervention components, such as mindfulness), moderate the both the physical activity-diurnal cortisol slope effect and the physical activity-cortisol awakening response effect, and we reserve making a prediction for this moderator, as this comparison has not been made in previous studies and is exploratory. Finally, we expected larger time gaps in longitudinal studies may show greater heterogeneity in the averaged association between physical activity and the diurnal cortisol slope than those with shorter time gaps. We also predicted that the mean cortisol awakening response would show greater heterogeneity in the physical activity-cortisol awakening response effect in studies with longer time gaps relative to studies with shorter time gaps.

Chapter 2

Method

Literature Search

We located studies for inclusion in the current analysis via a search of electronic databases: Web of Science, PsycINFO, EBSCO, PubMed, and ProQuest Dissertations and Theses using the following search string: 'cortisol' AND ('diurnal' OR 'slope' OR 'variability' OR 'awakening response' OR 'drop' OR 'decline' OR 'dys*' OR 'reg*' AND ('physical activity' OR 'exercise' OR 'fitness' OR 'cardio training' OR 'strength training' OR 'resistance training' OR 'endurance training' OR 'weight training' OR 'sport*' OR 'energy expenditure' OR 'caloric expenditure' OR 'cycl*' OR 'jog*' OR 'swim*' OR 'run*' OR 'aerobic' OR 'yoga'). The search was not limited by language or publication year, and included research published on, or prior to, October 31, 2020. We also conducted manual searches of the reference lists of pertinent review and overview articles. In addition, we contacted prominent authors in the field to locate unpublished data. In addition, requests for unpublished data were circulated on the listservs of two relevant organizations: the Society for Behavioral Medicine and the International Society of Psychoneuroendocrinology. The study protocol was pre-registered on the Prospero registry of systematic reviews: https://www.crd.york.ac.uk/prospero/.

Inclusion/Exclusion Criteria

Published research, abstracts, dissertations, and unpublished theses and manuscripts were eligible for inclusion. Studies were included if they fulfilled two main criteria: (1) the study included at least two measures of time-specific cortisol secretion in one day with enough data to assess either the diurnal cortisol slope (i.e., at least one cortisol measurement in the morning between waking and noon and one at night between 4pm-bedtime), or the cortisol awakening response (i.e., at least one cortisol measurement upon awakening and one measurement 30 minutes to 1 hour after awakening); and (2) the study included at least one measure of physical activity participation, defined as participation in exercise, sport, or physical activity as part of daily living, occupation, leisure, and active transportation (Garber et al., 2011). Studies adopting both self-report and non-self-report (e.g., physical activity measured using accelerometers, pedometers, or other devices) measures of physical activity were included. Studies were included if physical activity participation and concurrent or later diurnal cortisol slope and/or cortisol awakening response were measured irrespective of design (e.g., cross-sectional, longitudinal). Case studies, n-of-1 studies, qualitative studies, reviews, and methods articles were excluded. Studies that examined the cortisol awakening response and/or the diurnal cortisol slope as a predictor of subsequent physical activity participation were excluded. Studies that measured the diurnal cortisol slope on a day when physical activity participation was performed were excluded, as this may not reflect HPA-axis regulation, and may reflect diurnal cortisol reactivity to physical activity participation. Studies focusing on daily average cortisol, area under the curve measures of salivary cortisol, or other integrated cortisol measures such as overnight urinary cortisol or hair cortisol were excluded, as these measures do not provide information on daily cortisol variability (Badrick et al., 2017; Fekedulegn et al., 2007). Studies on participants with endocrine

disorders, genetic disorders or polymorphisms, or impaired capacity to provide responses on self-report questionnaires were excluded. Studies with proxy measures (e.g., parent, caregivers) of study variables were excluded.

We located 'fugitive' data (Rosenthal, 1994) by sending email requests for study data to authors of eligible studies that did not report sufficient data to compute an effect size, with authors given a reasonable time frame to respond. This included studies that reported taking measures of physical activity participation and two time-dependent cortisol secretion measurements in the same day, but did not calculate the cortisol awakening response and/or the diurnal cortisol slope (disaggregate values reported only), did not calculate the cortisol awakening response as the raw mean difference (e.g., the peak cortisol value minus the awakening cortisol value), did not report the physical activity participation-HPA-axis regulation relationship, or reported the relationship within a multivariate analysis from which a unique physical activity participation-HPA-axis regulation effect size could not be isolated. Furthermore, authors were contacted if the study only included a statistic reporting the relationship between physical activity participation and either the diurnal cortisol slope or the cortisol awakening response, and sufficient data was gathered to assess the other outcome, but it was not reported. Authors were also contacted if physical activity data were collected as part of a global 'health behavior' measure or as a covariate, but isolated effects of physical activity participation were not reported. In cases where interventions or experimental studies employed a manipulation of physical activity participation and measured changes in HPA-axis regulation parameters, then the effect of the manipulation on the outcome was taken as the estimate of the effect. If the experimental manipulation did not consist of physical activity participation (e.g., pharmacological administration, stress exposure), targeted an outcome other than HPA-axis regulation, or did not specify the target construct, then data at baseline or in the control group were used to estimate the effect where possible, otherwise the authors were contacted to provide the relevant data.

Screening

After removal of duplicate studies, 16,558 studies were identified for inclusion. Titles and abstracts of the articles retrieved in search were screened against inclusion/exclusion criteria. This comprised an initial title screen, followed by abstract and full text screening, conducted by the lead researcher and two trained research assistants. During title and abstract screening, articles were divided into retained, excluded, or potentially eligible categories. Queries raised during screening were discussed between the research team and resolved through mutual agreement, with 250 of the articles screened by all researchers to validate the screening procedure. Of these, 10,270 were excluded after title screening and a further 6,269 studies excluded after abstract screening. Agreement between the three reviewers was calculated for each screening phase using the AC_1 coefficient (Gwet, 2008); with 90.03% average agreement ($AC_1 = .844$, [0.819, 0.909], $p < .001$), during title screening, and with 92.71% average agreement ($AC_1 = .897$, [0.874, 0.941], $p < .001$) during abstract screening, both acceptable. Main reasons for exclusion included: articles were theoretical or conceptual reviews, systematic reviews, and off-topic (not pertaining to any content related to physical activity participation or HPA-axis regulation). The remaining articles ($k = 1,559$) were subjected to full-text analysis for inclusion in the final sample, of these, 1,463 did

not meet criteria for inclusion. Full text screening was conducted by the lead and senior researchers, with 25% of the articles screened by both researchers to validate the screening procedure. Disagreements were also resolved through discussion and inclusion/exclusion criteria were modified and reapplied if necessary. Average inter-rater reliability across raters for inclusion-exclusion decisions during full-text screening was acceptable. Studies were excluded at this stage for the following reasons: cortisol was only measured one time in a day, cortisol was measured twice, but data were insufficient to calculate either the diurnal cortisol slope or the cortisol awakening response; cortisol was measured twice, but physical activity was performed in between sampling times; no measure of physical activity participation was included; study design included physical activity with other stressful components (e.g., hiking in hypoxic conditions, combat military training, overtrained athletic competitors) that may influence the cortisol awakening response and/or the diurnal cortisol slope; or insufficient data were available in the article to compute effect sizes and authors could not be contacted or were unable to supply the required data. Study selection procedures are summarized in the PRISMA (Moher et al., 2009) flow diagram presented in Appendix A (supplemental materials).

Data Extraction

Study characteristics, effect size data, and data for moderator variable coding were extracted from all eligible articles by the lead and senior researchers. The following study characteristics were extracted from each study; author names, publication year, sample size, HPA-axis regulation measure to be included (diurnal cortisol slope/cortisol awakening response). Extracted data for moderator coding were: sociodemographic variables (sex, age, BMI, clinical sample); type of calculation for the diurnal cortisol slope (amplitude vs. wake-bed slope vs. fixed timepoint slope vs. peak and late decline slopes); number of cortisol samples taken to assess the diurnal cortisol slope and/or the cortisol awakening response (2 samples vs. >2 samples); number of days cortisol was sampled (1 day vs. >1 day); cortisol sampling quality rating (score range: 0-9); report of physical activity performed on cortisol sampling day (cortisol was instructed to be sampled on resting day vs. not reported); physical activity measure (self-report measure vs. non-self-report measure); physical activity assessment type (previously-validated physical activity scales vs. bespoke physical activity related questions); physical activity intensity (low intensity vs. moderate-to-vigorous intensity); physical activity intensity assessment type (absolute measure of intensity based on metabolic equivalents vs. relative measure of intensity based on maximal oxygen consumption); duration (more than 30 min per activity bout vs. less than 30 min per activity bout); frequency of activity (<3 times a week vs. 3 or more times a week); time of day physical activity was performed (morning vs. afternoon or evening); physical activity type (aerobic vs. anaerobic) and level of fitness (athlete vs. high fit vs. low fit); fitness assessment type (self-report vs. non-self-report); and study design (correlational vs. longitudinal vs. experimental); intervention components (physical activity intervention only vs. physical activity intervention plus one or more additional intervention component/s); and time lag).

The zero-order correlation coefficient (*r*) was selected as the effect size metric for the diurnal cortisol slope outcome as the majority of the studies were correlational in design and the correlation coefficient was expected to be the most frequently adopted

effect size. Where effect sizes were not expressed as a correlation, an effect size estimate was derived from available data including computed effect sizes (Cohen's *d* or *f*, eta-squared), tests of difference (e.g., *t* and *F*-ratios, chi-square values) and converted to *r* (Borenstein et al., 2009). To assess the relationship between physical activity participation and the cortisol awakening response, the variability of the mean the cortisol awakening response was compared between groups within or between studies with low, moderate, or high levels of physical activity participation. Physical activity level classification was based on the International Physical Activity Questionnaire (IPAQ) categories, representing low, moderate, and high levels of physical activity participation (Sjöström et al., 2002). Activity level was considered moderate if the level of physical activity participation met at least one of the following criteria: (a) 3 or more days of vigorous-intensity physical activity of at least 20 minutes per day; (b) 5 or more days of moderate-intensity and/or walking of at least 30 minutes per day; or (c) 5 or more days of any combination of walking, moderate-intensity, or vigorous-intensity activities achieving a minimum of at least 600 MET-min/week of physical activity. Activity level was considered high if the level of physical activity participation met at least one of the following criteria: (a) Vigorous-intensity physical activity participation on at least 3 days and accumulating at least 1500 MET-min/week; or (b) 7 or more days of any combination of walking, moderate- or vigorous-intensity physical activity accumulating at least 3000 MET-min/week. Activity was considered low if neither of these criteria were met. Where the cortisol awakening response was calculated in a metric other than a raw mean of the cortisol awakening response in different levels of physical activities (e.g., percent increase, slope of the increase), the authors were contacted to provide data. If study authors reported measuring physical activity participation and the cortisol awakening response but did not report the mean and standard deviation of the cortisol awakening response in different levels of physical activity participation (e.g., only provided an overall mean of physical activity participation, without physical activity group separation), the authors were contacted to supply relevant data.

Data for relations between physical activity and HPA-axis regulation were extracted from included studies by two lead researchers. In cases where data for one of the target variables was expressed as a categorical variable (e.g., regular vs. irregular slope), with means and standard deviations for a measure of physical activity participation for each category, we computed a standardized mean difference using the available data and converted to *r*. For experimental or intervention studies with a manipulation of physical activity participation, we computed an effect size using baseline and follow-up data for the dependent variable for either the experimental or control group (controlled designs), or baseline to follow-up (pre-post designs) manipulations of the independent variable (Borenstein et al., 2009). Multiple measures and comparisons between multiple levels of physical activity participation within the same study were utilized, where available, and effects were treated as dependent effects.

Where studies reported multiple effect sizes for the physical activity participation-HPA-axis regulation relationship within each study, we treated each effect size according to a pre-defined protocol. Studies reporting separate effect sizes estimated in two or more independent samples were treated as separate studies (e.g., male/female, low/moderate/high physical activity subgroups). Where multiple effect sizes were

reported in the same study, such as when studies reported correlations between a measure of HPA-axis regulation and two or more levels of physical activity intensity, these data were treated as multiple effects from the same study. However, when studies reported statistics between a measure of physical activity participation and both outcomes of interest, both were included in the separate diurnal cortisol slope and cortisol awakening response analyses. We coded the data according to whether data were from independent samples or multiple effect sizes within a single study, and this coding was used as input for subsequent data analysis. Our protocol outlining how data were treated for each outcome is summarized in Appendix B1 and B2 (supplemental materials), with information on how effects from each study were coded provided in Appendix C for the diurnal cortisol slope and Appendix D for the cortisol awakening response (supplemental materials). The moderator coding protocol is reported in Appendix E (supplemental materials).

Assessment of Quality of Cortisol Sampling Methods

We assessed the quality of the cortisol sampling methods in each study based on criteria from previous meta-analyses and systematic reviews of HPA-axis regulation (Adam et al., 2017; Chida & Steptoe, 2009). The assessment was based on whether studies reported accounting for the following conditions during cortisol sampling: age; gender; smoking status; use of steroid-based medications; wake time; sampling day (weekday or weekend); self-reported adherence with sampling times; objective adherence to sampling times based on electronic monitoring; and clear sampling instructions provided to participants (e.g., to refrain from brushing their teeth, drinking, or eating 15 minutes prior to sampling). Scores were summed and both dichotomous and continuous quality of cortisol sampling methods rating scores were included as a moderator in the final analyses.

Meta-Analytic Methods

The effect sizes of interest were the average sample-weighted correlation (*r*) between the diurnal cortisol slope and physical activity participation, and the average sample-weighted raw mean for the cortisol awakening response in groups of studies at different levels of physical activity participation. Effect sizes from each study were synthesized using multi-level random-effects meta-analysis implemented using the metafor package (Viechtbauer, 2010) in R. Some studies reported data from multiple measures or levels of physical activity participation within the same sample rather than independent samples, so including multiple effects from the same sample in the averaged effect size violates the assumption of independence. To address the dependency issue, we applied a multi-level meta-analytic model in which variation between effect sizes from within the same study were treated as a separate artifact of variance alongside between-study variance and the sampling variance. The multi-level meta-analysis provides averaged sample-weighted effect size estimates and compartmentalizes variance into between-participants (level 1), between-effect sizes (level 2) and between-study (level 3) components separately. It enables estimation of the degree to which each variance component contributes to overall variability across the studies (Assink & Wibbelink, 2016). We coded studies as independent effects or as effects within a single study (see Appendix B, supplemental materials) to designate studies according to the different variance components in the multi-level meta-analytic model. Contribution of the

between-effect size and between-study variance to the total variance in the physical activity participation-HPA-axis regulation relationship across studies, as well the proportion of total variance attributable to sampling error, is provided by Cheung's (2014) formula.

In addition to the averaged sample-weighted correlation corrected for variance components, several tests of the heterogeneity were performed. Specifically, Cochran's Q and I^2 coefficients of the averaged correlations were computed (Higgins & Thompson, 2002). Values for Q and I^2 that were non-zero and exceeded 25%, respectively, were used as indicators of the possible presence of moderators of the effect size (Higgins & Thompson, 2002).

We assessed small-study bias in the effect size using analyses based on 'funnel' plot of effect sizes against their precision estimates. Specifically, this involved plotting the physical activity-HPA-axis effect size from each study against a measure of study precision (e.g., the reciprocal of the study sample size). If the studies tend to deviate from the expected 'funnel' shape, particularly on one or the other side of the averaged effect, it may indicate bias. This can be verified by a formal test provided by Egger and Sterne's (2005) regression test in which the effect size of each study is regressed on the precision estimate. Two versions of the test were computed for each outcome: the precision effect test (PET), in which uses the standard error as the precision estimate, and the precision effect estimate with standard error (PEESE), which uses the square of the standard error as the precision estimate (Stanley & Doucouliagos, 2014). PET and PEESE estimates were computed using the PETPEESE function in R (Carter et al., 2019). Following Stanley and Doucouliagos' (2014) rule, if the PET estimate for the effect size is no different from zero, the PET estimate is used as the corrected value of the effect size, however when the PET estimate is significantly different from zero, the PEESE estimate is used.

We assessed moderator variable effects on the averaged correlation between physical activity participation and the diurnal cortisol slope by conducting separate meta-analyses at each level of the moderator. Effects of moderators on the variability of the cortisol awakening response at each physical activity subgroup was assessed by computing averaged means of the cortisol awakening response in each physical activity subgroup and at each level of the moderator. Moderator group comparisons were made using 95% confidence intervals about the averaged sample-weighted correlations for the physical activity-diurnal cortisol slope analysis, and about the difference in the variability of the averaged sample-weighted mean of the cortisol awakening response between high and moderate physical activity subgroups compared to the low physical activity subgroup between the levels of the moderator (Schenker & Gentleman, 2001). We also conducted multivariate meta-regression analyses to examine the effects of moderators that were continuous in format (e.g., time lag), and also allowed for the examination of unique effects of categorical and continuous moderator variables.

We assessed the presence of outliers by conducting a leave-one-out analysis for each outcome, in which the meta-analysis of the effect of interest is estimated iteratively leaving out exactly one study on each iteration. This provides an estimate of the extent to which each individual study affects the averaged effect size (Iyengar & Greenhouse, 2009).

Chapter 3

Results

Study characteristics

Forty articles were included reporting a total of 50 independent samples testing the relationship between physical activity participation and the diurnal cortisol slope. Some studies also included multiple effect size estimates within studies (e.g., studies reporting correlations between the diurnal cortisol slope and multiple measures of physical activity; see Appendix B, Table B1, supplemental materials), resulting in a final sample of 94 effect sizes available for analysis. For the analysis of the relationship between physical activity and the cortisol awakening response we segregated samples into three physical activity subgroups, low, medium, and high and extracted the mean cortisol awakening response for each study in each subgroup. In the low physical activity subgroup, 29 articles were included reporting a total of 41 independent samples. After including sample dependencies resulting from multiple measures of physical activity and/or multiple timepoints in the same sample (see Appendix B, Table B2, supplemental materials), a final sample of 56 means was available for analysis. In the moderate physical activity subgroup, 25 articles were included reporting a total of 29 samples, and after including dependencies, a final sample of 43 means was available for analysis. In the high physical activity subgroup, 29 articles were included reporting a total of 32 independent samples, and, after adding dependencies, resulted in a final sample of 51 means available for analysis.

In some cases, the samples in each physical activity subgroup (low/moderate/high physical activity) changed within studies across multiple physical activity measures or timepoints, or both. For example, participants in a longitudinal study may have increased their physical activity between baseline and follow up measurement occasions and were therefore classified in different physical activity subgroups within the same study. As a consequence, modeling all sampling dependencies in each study for each physical activity subgroup was not possible, as it was unclear which participants changed physical activity level, and therefore subgroup, between measures or timepoints. For this reason, model comparisons of different sampling dependencies were analyzed for the cortisol awakening response outcome (see Appendix F for sampling dependency coding in each tested model and Appendix G for model comparison results, supplemental materials). There were no differences between models with the different sampling dependencies, so the most conservative sampling dependency modeling scheme was selected, wherein dependencies in samples under the same physical activity subgroup were accounted for, whenever possible. Study characteristics, details of the outcome measures, moderator coding, and raw effect sizes in each study are provided in Appendix C and D (supplemental materials), a full list of studies included in each meta-analysis is presented in Appendix H and I (supplemental materials), and a PRISMA checklist (Moher et al., 2009) is provided in Appendix J (supplemental materials).[1]

[1]The data file used in the meta-analysis including effect sizes and moderator coding is available online: https://osf.io/ebpy2/

Overall meta-analytic effects

Results of the three-level meta-analysis of the relationship between physical activity participation and the diurnal cortisol slope are reported in Table 1. Results indicated that both within- (level 2) and between- (level 3) study variance components accounted for a significant proportion of the total variance in the correlation across studies. This was confirmed by performing separate meta-analyses and comparing the variance accounted for each variance component (Table 1). We therefore took the estimate and heterogeneity statistics from the overall analysis that included both within- and between-study variance. The analysis revealed a negative, small non-zero overall sample-weighted average correlation between physical activity participation and the diurnal cortisol slope (r = -0.047, 95% CI [-0.090, -0.006]). The proportion of the total variance in the correlation across studies attributable to within-study (33.44%) and between-study (44.23%) variance components was larger than the proportion attributable to between-participant variance (22.32%). Heterogeneity statistics indicated high medium-to-high heterogeneity in the effect size and suggested the presence of moderators of the effect size.

Turning to the physical activity and cortisol awakening response analysis, results of the three-level meta-analysis of the mean cortisol awakening response at each level of physical activity participation are reported in Table 2. In the analyses for all physical activity subgroups (low, moderate and high), we selected the relevant model based on whether the within- or between-study sampling variance components, or both, accounted for a significant proportion of the total variance in the mean across studies. Although the variance estimate associated with the mean cortisol awakening response was observed to be smaller in the moderate physical activity group compared to the low and high physical activity subgroups, confidence intervals about the variance estimates overlapped considerably across subgroups. These data therefore do not provide definitive evidence to support lower levels of variability in the mean cortisol awakening response at higher levels of physical activity. Heterogeneity statistics indicated substantive heterogeneity in the averaged cortisol awakening response mean across studies in each activity subgroup.

Moderator analyses

Results of the categorical moderator variable analysis for the association between physical activity and the diurnal cortisol slope are presented in Table 3. Despite observed differences in the averaged effect sizes across moderator groups, there was substantive overlap in the confidence intervals about the correlation at each level of the moderator in most of the analyses. This was mirrored in the heterogeneity statistics for the effect sizes in each moderator group, which indicated that considerable heterogeneity remained in the majority of cases and suggested that most of the moderators did not reduce the variability nor lead to the narrowing of the confidence intervals about the effect size, with a few exceptions. Nevertheless, difference tests in the effect sizes across moderator categories using the confidence intervals about the mean difference revealed some noteworthy differences: the physical activity-diurnal cortisol slope size was larger in mixed age groups relative to older age groups ($t(68) = -2.04$, $p < .05$); larger in the general population than in populations with a physical health condition, ($t(76) = 2.03$, $p < .05$); smaller in studies with a longitudinal design compared to studies with cross-sectional ($t(66) = 2.84$, $p < .01$) and experimental studies ($t(63) = 2.67$, $p < .01$); larger in studies

that either assigned physical activity as an intervention or studies that grouped participants based on physical activity level than a self-reported physical activity measure; validated self-report measure; ($t(56) = 2.72$, $p < .01$), bespoke self-report measure; ($t(53) = 2.80$, $p < .01$). Importantly, the effect was non-zero in experimental studies that assigned physical activity interventions or manipulations, and this provides some evidence to suggest a causal effect, whereas changing physical activity participation behavior produced changes in the diurnal cortisol slope. However, in each of the cases above, heterogeneity statistics remained non-zero and the confidence interval about the mean differences in the effect were wide. These findings suggest that although there was some evidence of moderation, the differences did not lead to homogenous cases, nor did they lead to a narrowing of the confidence interval about each correlation in each moderator group.

It should also be noted that the effect size for studies with mixed age groups, younger participants, mean BMI of the sample classified as under- or normal-weight, a general population sample, studies utilizing previously-validated physical activity scales and bespoke physical activity measures, studies measuring the diurnal cortisol slope as a peak-to-bed or late decline slope have a relatively large number of studies and represent homogeneous cases, although comparisons with other moderator groups were not different from zero. The effect size in each of these homogenous cases was also no different from zero based on confidence intervals. Effect sizes for studies with mostly male participants, studies utilizing physical activity only as the intervention design, vigorous-intensity physical activity, and studies that took only two samples of cortisol in one day to determine the diurnal cortisol slope were also homogenous, with the correlation in studies using physical activity only as the intervention the only non-zero effect size. It must be stressed that the number of studies in each of these variables was small, and may not provide a precise estimate of the heterogeneity in these levels of the moderator variables.[2]

Turning next to the cortisol awakening response analysis, moderator analyses for each physical activity subgroup are reported in Table 4. Numbers of effect sizes at each level of the moderator groups comparing averaged cortisol awakening response values across the physical activity subgroups numbered few (typically $k < 10$) in most cases precluding a meaningful comparison of the levels of each moderator between physical activity subgroups for many of the planned moderator variables: clinical status, intervention components, study design, physical activity type, cortisol awakening response measurement type. However, there were some analyses for which there were sufficient numbers of effect sizes to make comparisons. Large absolute differences in the variability about the mean cortisol awakening response between physical activity subgroups were observed between some levels of the moderator in some analyses. For example, the comparison between low and moderate, and between low and high, physical activity subgroups in studies with samples with low and high BMI; the comparison between low and moderate physical activity subgroups in studies with validated and non-self-report physical activity measures; the comparison between low and moderate

[2] Meta-regressions were conducted to examine the effects of categorical and continuous moderators simultaneously and mirrored the above results (reported in Appendix K).

physical activity subgroups in studies using bespoke and non-self-report physical activity measures; the comparison between low and moderate physical activity subgroups in studies that sampled cortisol on one day only and studies that sampled cortisol on more than one day; and the comparison between low and moderate physical activity subgroups in studies adopting non-self-report and experimental assignment or longitudinal grouped physical activity measures. However, in all instances, the confidence intervals about the variance estimates of the effect size at each level of the moderator were wide and overlapped substantially, so moderation was not supported.

Also, it should be noted that moderator analyses for the mean cortisol awakening response significantly reduced the heterogeneity of the effect in some instances. For example, the effect was homogenous in the analysis of male participants in the low and moderate physical activity subgroups. This was also the case in some other moderator analyses, but the number of studies in the level of each of these moderators were small, and the confidence intervals largely overlapped across subgroups.

Small study bias

'Funnel' plots of the corrected effect size against its standard error in the sample of studies for each analysis are presented in Appendix K. Regression tests based on the funnel plot for the diurnal cortisol slope analysis revealed non-zero effects of the precision estimate on the effect size for the PET ($B_0 = 0.342$, 95% CI [0.007, 0.062], $p = 0.015$) and PEESE ($B_1 = -0.011$, 95% CI [-.029, .006], $p = 0.006$) tests. The intercept provides an estimate of the effect size under conditions of no bias. As the PET estimate for the effect size was non-zero, the PEESE estimate was taken as the corrected estimate for the physical activity participation-diurnal cortisol slope effect size ($B_1 = -0.011$, 95% CI [-.029, .006], $p = 0.006$). These findings provided some evidence of small study bias for this effect in the sample of studies. Although there was an observed difference in the corrected estimate from the PEESE analysis from the uncorrected estimate, the difference was modest, although the corrected estimate did not differ from zero.

Regression tests based on the funnel plot revealed non-zero effects for the precision estimate on the cortisol awakening response mean for the PET and PEESE versions of the test in all physical activity subgroups (see Appendix L). These analyses suggested the presence of small study bias in each subgroup, however, observed differences in the corrected effect size estimates from the tests did not differ substantially from the original estimates in each subgroup and did not lead us to alter our overall conclusions on the size and variability of mean cortisol awakening response in each physical activity subgroup.

Sensitivity analyses

The leave-one-out analysis for the physical activity-diurnal cortisol slope analysis revealed two effect sizes that may have affected the overall effect size. Omitting each study from the analysis did not substantively change the overall estimate of the effect and its variability (see Appendix M). The leave-one-out analysis for the mean cortisol awakening response in each physical activity subgroup identified a few influential studies in each physical activity subgroup, but in all cases, omission of those studies did not change the overall estimate of the mean effect.

Chapter 4

Discussion

The aim of the present study was to determine the average size and degree of heterogeneity of the relationship between physical activity participation and two independent indices of HPA-axis regulation, the diurnal cortisol slope and the cortisol awakening response, across studies using three-level meta-analysis. In line with our hypothesis, findings revealed a negative, non-zero averaged correlation between physical activity and the diurnal cortisol slope across studies, suggesting that the diurnal cortisol slope is steeper at higher levels of physical activity participation. However, contrary to our hypotheses, confidence intervals about the average mean variance estimates for the cortisol awakening response overlapped considerably across physical activity subgroups and did not provide definitive evidence supporting lower levels of variability in the mean cortisol awakening response at higher levels of physical activity participation. Significant heterogeneity in the averaged correlation between physical activity and diurnal cortisol slope suggested the presence of moderators. Tests of moderators revealed some differences in the effect in some age, clinical status, study design, and physical activity measure moderator subgroups, but no clear pattern emerged and significant heterogeneity in the effect sizes in each moderator group remained. Significant heterogeneity in the averaged mean estimate of the cortisol awakening response in each physical activity subgroup also suggested the presence of moderators. However, the small number of studies in each subgroup precluded a meaningful comparison for many planned moderators, although, in some cases, there were sufficient studies at each level of the moderator across subgroups to examine moderator effects.

Physical activity and the diurnal cortisol slope

Current findings provide evidence supporting a small, non-zero negative correlation between physical activity participation and the diurnal cortisol slope, suggesting better HPA-axis regulation among those participating in physical activity, a finding that corroborates findings elsewhere (e.g., Gubelmann et al., 2018; Ho et al., 2020; Vreeburg et al., 2009). Overall, a significant degree of heterogeneity was present in the effect, signaling the presence of moderators, although the effect size did not significantly differ across levels of our candidate moderator variables and moderator analyses did not resolve the high degree of observed between-study heterogeneity.

Although the candidate moderators of the physical activity-diurnal cortisol slope relationship tested in the current analysis did not confirm the presence of moderators of the effect, some of the correlations for specific moderator groups were non-zero and worth noting. For example, the averaged correlation in the following moderator groups was non-zero with sufficient numbers of studies for the effect to be considered reliable: experimental studies; studies that either assigned physical activity participation as a part of an intervention or studies that grouped participants based on previous physical activity history; moderate intensity physical activity; and physical activity performed three or more days a week. In line with our hypotheses on the dose response effect of physical activity on the diurnal cortisol slope, the correlation between physical activity and the diurnal cortisol slope was larger studies in which participants engaged in physical activity over three times a week and performed physical activity of at least moderate intensity.

However, physical activity duration was not. While intensity and frequency of physical activity participation signal moderation in this analysis, these moderator effects were unclear given the lack of differences in the overall mean effect. Moving forward, there is a need for more precision in measurement and reporting of dose-response physical activity factors such as intensity, duration, and frequency so that continuous and more fine-grained categorical analyses of intensity and frequency can be tested in future studies to determine the whether the dose of physical activity moderates the association with the diurnal cortisol slope. Also, future research should systematically vary intensity and frequency of physical activity participation and examine the effect on the diurnal cortisol slope. This may provide more robust data on the dose response hypothesis and may inform the development of physical activity interventions.

Another important finding was that the averaged correlation between physical activity and the diurnal cortisol slope was non-zero in experimental studies and studies that measured physical activity by experimental or longitudinal group assignment moderator groups. This suggests that physical activity interventions are significantly related to change in the diurnal cortisol slope. This supports the prediction that increasing physical activity participation through intervention may result in changes in the diurnal cortisol slope, specifically to become more steep, and suggests interventions promoting physical activity participation may lead to better HPA-axis regulation. This finding implies the need for large-sample longitudinal, panel design studies to evaluate directionality and change over time, as well as large-sample experimental studies to establish more reliable evidence of the causality of the effect.

Physical activity and the cortisol awakening response

Findings from the current analysis did not support the hypothesized relationship between physical activity participation and the cortisol awakening response. Although there were some observed differences in the variability estimates for the mean cortisol awakening response in the different physical activity subgroups, there were no clear differences. For example, the moderate physical activity subgroup had the lowest absolute degree of variability in the mean cortisol awakening response relative to the low physical activity subgroup, which was expected, however, the high physical activity subgroup exhibited higher absolute variability than the moderate physical activity subgroup. This may have been due to the inclusion of athlete samples in the high physical activity subgroup, as athletes have been shown to exhibit blunted cortisol awakening responses after periods of intense physical training and competition (Filaire et al., 2013). Although we excluded studies that measured the cortisol awakening response within two days before or after competition, athlete samples may be contributing to the high degree of heterogeneity and more variability about the mean cortisol awakening response in the high physical activity subgroup. Importantly, the mean estimate for the cortisol awakening response at each level of physical activity participation was outside of the range of cortisol awakening response values that are considered adequately regulated based on population norms (i.e., a rise in cortisol from awakening to peak secretion of 9.3 nmol/l plus or minus 3.1). Findings suggest that, on average, each subgroup displayed somewhat blunted cortisol awakening response (Clow et al., 2004; Wüst et al., 2000). In addition, the observed mean cortisol awakening response was higher in the low physical activity subgroups compared to the moderate or high level subgroups. These findings

suggest that the cortisol awakening response is not substantially different at levels of physical activity participation.

The high variability in the observed mean at each physical activity level suggests the presence of moderators, and we conducted some moderator analyses although many analyses were contraindicated due to small numbers of studies in many of the moderator groups. Large absolute differences in the variability about the mean cortisol awakening response between physical activity subgroups were observed between some levels of the moderator, such as the comparison between low and moderate, and between low and high, physical activity subgroups in studies with samples with low and high BMI. However, in all instances, confidence intervals about the variance estimates at each level of the moderator were wide and overlapped substantially, so moderation was not supported. Moderator analyses for the mean cortisol awakening response also resulted in homogeneous effects in some instances. For example, the effect for male participants in the low and moderate physical activity subgroups was homogeneous, although in all of the cases where moderator effects were homogeneous, the number of studies in the level of these moderator were small, and the confidence intervals largely overlap across subgroups providing little definitive evidence of moderation.

To speculate, a number of additional factors may have contributed to the high degree of heterogeneity in both the physical activity-diurnal cortisol slope effect and the physical activity-cortisol awakening response effect in the present analysis that were not accounted for in moderator analyses. For example, various environmental and contextual factors have been shown to influence cortisol awakening response, such as the time of awakening, ambient light exposure, prior day experiences, anticipation of the day ahead, ovulation, jet lag, and alcohol consumption (Adam et al., 2006; Doane et al., 2010; Edwards et al., 2001; Stalder et al., 2009, 2010; Wolfram et al., 2011). These factors were not controlled for in the current analysis and may have contributed to high heterogeneity in the means estimates of the cortisol awakening response in each subgroup. Furthermore, recent evidence has shown that sleep moderates the relationship between prior-day physical activity and the cortisol awakening response the next morning (Anderson et al., 2021). Sleep may, therefore, have been an important factor that could be contributing to the heterogeneity in the effect. Another example is that a wide range of immunoassay methods were utilized to determine cortisol values for the cortisol awakening response. Different methods have different sensitivities and have weak comparability, which may have contributed to the observed variability in effects (Kirschbaum & Hellhammer, 1989; Miller et al., 2013). Taken together, deviations from recommended awakening times and sampling, and the methods used to measure cortisol may have introduced additional error variance to the mean cortisol awakening response in each physical activity subgroup. Although speculative, results should be interpreted with this in mind. Future studies testing the physical activity-cortisol regulation relationship should account for and examine the potential impact of these variables on the effect.

Key contributions and implications

This is the first meta-analysis to examine the association between physical activity participation and indices of cortisol regulation. A key contribution of the current research is that it provides initial empirical support of the link between physical activity participation and the diurnal cortisol slope across multiple studies, an association which

is proposed to underlie a variety of health conditions and disease processes (Adam et al., 2017; Heim et al., 2008). This implies a link between adequate diurnal cortisol regulation and physical activity participation and may be one possible mechanism by which physical activity leads to reduced risk of chronic illness and health conditions (Pedersen & Saltin, 2015; Warburton & Bredin, 2017; Warburton et al., 2006) and better mental health (Biddle et al., 2019; Dunn, Trivedi, & O'Neal, 2001).

Although the effect size between physical activity participation and the diurnal cortisol slope was non-zero, the small magnitude raises considerations for the clinical significance of the effect. Two important additional questions arise from the current findings, which have relevance to the clinical impact: (1) can physical activity participation change the trajectory of the diurnal cortisol slope; and (2) are changes in the degree of the decline in the slope sufficient to produce clinically meaningful changes in the stress-related health outcomes that have been associated with 'flatter' diurnal cortisol slopes? Since the effect size for the physical activity-diurnal cortisol slope relationship is non-zero across multiple studies, it implies that physical activity participation is an important correlate of the diurnal cortisol slope. Most important in this regard, our analysis of experimental studies employing physical activity interventions and testing their effects on the diurnal cortisol slope also revealed a non-zero averaged effect. Although the difference in the diurnal cortisol slope effect sizes between correlational and experimental design studies was not significant, the analysis provides additional meta-analytic data to support the prediction that increasing physical activity participation through intervention may result in changes in the diurnal cortisol slope and suggests interventions promoting physical activity participation may lead to better HPA-axis regulation.

In order to confirm the clinical impact of physical activity on stress-related health outcomes, studies should test whether changes in physical activity participation not only produces change in the diurnal cortisol slope, but also evaluate whether those changes are associated with clinically meaningful changes in stress-related health outcomes related to cortisol dysregulation. Meta-analytic evidence supports an association between the diurnal cortisol slope and health outcomes (Adam et al., 2017), but evidence is needed to evaluate the mediating role of the diurnal cortisol slope in the physical activity-health outcome association. Based on current evidence, we cannot unequivocally conclude that the small relationship between physical activity and the diurnal cortisol slope is of practical or clinical significance, but the initial evidence provided in this analysis justifies future investigations that aim to quantify what constitutes a clinically significant effect in this context and employ appropriate research designs with optimal sampling to evaluate whether effect sizes of this magnitude will lead to clinically significant effects in physiological stress regulation.

By comparison, findings for the relationship between physical activity and cortisol awakening response was weaker. Although we observed lower variability estimates for the mean cortisol awakening response at moderate activity levels compared with low and high levels of physical activity participation, confidence intervals about the variance estimates overlapped considerably. While this was somewhat surprising considering we hypothesized lower variability in the averaged mean cortisol awakening response at higher levels of physical activity participation, the high heterogeneity in the

samples and the methods used in the studies included in our analysis (e.g., participants with physical and mental health conditions, utilization of various immunoassay types with varying sensitivities in detecting cortisol concentrations) is likely to have impacted the cortisol awakening response data, as discussed elsewhere (Miller et al., 2013). These factors may have masked any differences as they are likely to have contributed substantially to the observed variability in the cortisol awakening response.

Key considerations for future research

The substantive heterogeneity observed in the relationship between physical activity and indices of cortisol regulation highlights some imperatives for future research. Specifically, the current analysis highlighted the need for more precise measures of the indices of cortisol regulation – only about a third of the studies in the current sample were classified as having high methodological quality in cortisol sampling. There is also a need for uniformity in the collection, calculation, immunoassay type, analysis, and reporting of cortisol regulation indices to allow uniform comparisons in findings across studies. Following consensus guidelines for cortisol regulation measurement and reporting, and advocacy of adherence to these standards in peer review is also important to ensure greater precision in effects of physical activity on indices of the cortisol awakening response (Stadler et al., 2016). Most important, given the high variability in the methods used to measure cortisol regulation across studies, there is also a need for systematic, large-sample tests of how key measurement components might affect estimates of the physical activity-cortisol regulation relationship. For example, utilizing various immunoassay methods across studies limits effect size comparison across studies in a meta-analysis. Standardization of immunoassay methods across studies would allow for more precise comparisons, and there is a need to determine what may be the most precise immunoassay to use while also accounting for cost of the assay and skill level of the assayist across studies. Another example is the way in which HPA-axis indices are calculated and operationalized. In the current sample of studies, researchers calculated the diurnal cortisol slope in three ways and reported data for the slope in four ways (i.e., wake-to-bed, peak-to-bed, late decline, fixed timepoint). Future research should systematically evaluate the effect of standardizing calculations and slope type on the relationship between physical activity and the diurnal cortisol slope.

Current findings also suggest there may be value in adopting better measurement and reporting of physical activity participation in studies testing the relationship between physical activity and cortisol regulation. While we were able to code for a large number of candidate measurement-related moderators of the effect, in many cases the moderators lacked precision due to insufficient information or data available to develop precise, fine-grained moderator groups, limiting the ability to detect moderation effects overall. For example, physical activity intensity was predicted to be a key moderator of the physical activity-diurnal cortisol slope correlation, but 39 studies utilized a physical activity measure that included all intensities together, precluding a meaningful interpretation of how intensity may have impacted the correlation in these studies, and they had to be omitted from the moderator analysis. Furthermore, in cases where researchers used self-report measures of physical activity, there is a need for clear reporting of the items used unless a freely-available standardized measure (e.g., the IPAQ) was used. This will assist with greater accuracy in moderator coding. Also, researchers should consider reporting

physical activity participation using a standardized metric that includes an overall estimate of the intensity, frequency, and duration of physical activity participation over a specific amount of time, such as METs-min/week. While some studies did report physical activity in this metric in the current study, there was considerable variability, requiring estimates to be made based on close-as-possible conversions (e.g., using the Adult Compendium of Physical Activities to estimate the intensity of a certain type of physical activity that was mentioned in a study, such as cycling), or by requesting the data from authors. Standardized reporting would allow for more precision in comparing the effects across studies.

Strengths and limitations

The current study had numerous strengths: (a) Use of data from multiple studies and populations to provide a meta-analytic estimate of the size and variability of the relationship between physical activity participation and two indices of cortisol regulation: the diurnal cortisol slope and the cortisol awakening response; (b) Use of three-level random-effects meta-analytic methods to correct effect sizes for the physical activity-cortisol regulation relationship for variability attributable to within- and between-effect size variance components; and (c) Testing the effects of, key moderator variables of the relationship. Overall, current findings provide a comprehensive assessment of the association between physical activity participation and cortisol regulation indices in the extant research literature, and is expected to guide future research by estimating the strength of the evidence for physical activity as a key correlate of cortisol regulation and the extraneous variables that may affect it, and identifying the gaps in current evidence and avenues for future research.

However, a number of limitations should be highlighted. For the analysis of the correlation between physical activity and the diurnal cortisol slope, while we found no moderator effects in the current set of studies, this should not be taken as definitive evidence for the null effects of these moderators. A number of caveats to the current analysis and the available data should be considered when interpreting these findings. First, imprecision in moderator coding may have impacted the results. Many of the moderators were based on self-report (e.g., physical activity scales, BMI), which may have introduced error in classification of studies due to imprecision (e.g., affirmation bias and socially desirable responding). Bias due to self-report may have introduced considerable error variance in the physical activity-diurnal cortisol slope relationship itself given that many studies used self-report measures of physical activity, which may have had the effect of inflating or attenuating effect. Second, moderator categories were produced to ensure that moderator analyses were feasible (e.g., sufficient numbers of studies within moderator groups). This may have resulted in some loss of fidelity in the moderator variables. For example, the BMI moderator variable was coded as high ($\geq$ 25 kg/m^2) or low (<25 kg/ m^2). As these classifications were made at the study level, some participants in the samples of these studies may have been on the border of the cutoff values. These classifications may have resulted in a reduced ability to detect moderator effects. As the research in this domain expands, future analyses in which moderator groups with greater precision may be enabled, and may provide more rigorous tests of moderator effects in future meta-analyses.

Another consideration is that while we had planned to assess moderation of fitness level and fitness assessment type, intensity assessment type, and physical activity time of day, these variables were not measured with sufficient frequency in the current set of studies to conduct these analyses. While research suggests that physical fitness is related to the diurnal cortisol slope (Lucertini et al., 2015), future studies should consider assessment of fitness, as well as current levels of physical activity participation in relation to the diurnal cortisol slope to enable future moderator analyses to be conducted. In terms of fitness assessment type, when fitness was measured, in most cases it reflected self-reported fitness level, and non-self-reported fitness assessments (e.g., VO_2 max in a controlled lab setting) were used less often. Future research in this domain should determine how non-self-reported fitness impacts this relationship. In cases where physical activity intensity was measured and reported, it was usually in terms of absolute intensity (e.g., METs), and absolute intensity assessments are less precise than relative intensity assessments. It is also important to assess whether relative physical activity intensity based on individual factors moderates this relationship in future research. Finally, the time of day that physical activity was performed was only reported in one study (Küüsmaa et al., 2016). Future studies should include a measure of the time of day that participants engaged in physical activity, and consider examining whether the time of day that physical activity is performed moderates the physical activity-diurnal cortisol slope relationship.

With respect to the cortisol awakening response, we needed to divide effect sizes from the included studies into physical activity subgroups based on physical activity level in order to provide a fit-for-purpose test of the physical activity-cortisol awakening response relationship. However, this classification limited the numbers of studies in each activity subgroup, reducing the scope for conducting moderator analyses due to small numbers of studies in moderator groups. Like the moderator analyses for the physical activity-diurnal cortisol slope relationship, there were also studies with participants on the boundaries of the cut-off for certain moderator variables (e.g., age) and participants who changed physical activity subgroup classification over the course of the study. Second, while physical activity subgroup classification was based on the IPAQ classification scheme, physical activity measurements were highly variable, and some studies did not provide enough information to classify the sample into the defined activity subgroups with a high precision, so results should be interpreted with this caveat in mind. Considering the above limitations, caution should be exercised in interpreting current results. Future studies examining the physical activity-cortisol awakening response relationship should evaluate the cortisol awakening response using standardized measures that adequately capture the response (Stalder et al., 2016) and measure physical activity using measures with appropriate precision, and adequately report the contextual factors that likely moderate the effect.

Conclusion

This study aimed to determine the average size and degree of heterogeneity of the relationship between physical activity participation and two indices of cortisol regulation, the diurnal cortisol slope and the cortisol awakening response, across available studies using three-level meta-analysis. Consistent with theory and research, findings revealed a non-zero negative effect between physical activity and the diurnal cortisol slope across

studies, supporting the hypothesis that the diurnal cortisol slope is correlated with physical activity participation. For the cortisol awakening response, while the observed variability estimates about the averaged mean cortisol awakening response were the lowest in the moderate physical activity subgroup when compared with both the high and low physical activity subgroups, confidence intervals about the variance estimates overlapped considerably across subgroups. Results therefore do not support lower levels of variability in the mean cortisol awakening response at higher levels of physical activity participation. Heterogeneity statistics in each analysis signaled the presence of moderators for both analyses. Moderator analyses did not provide clear evidence of moderation, although there were some noteworthy findings, such as the non-zero, negative effect of physical activity on the diurnal cortisol slope in experimental or intervention studies, providing initial evidence that physical activity interventions may have efficacy in promoting adequate cortisol regulation.

Results also serve to highlight some important gaps in the current literature, such as the need for more precision in physical activity participation assessment (e.g., including the time of day, current fitness level of participants, intensity, duration, and frequency of participation); more precise cortisol data collection and analysis (e.g., based on consensus guidelines, Stalder et al., 2016); and reporting of univariate statistics among all included variables including covariates and cortisol regulation parameters. Findings also suggest the importance of more research examining the mediating effect of the diurnal cortisol slope between physical activity participation and the subsequent impacts on health outcomes. There is also a need for review studies to examine how other health behaviors relate to cortisol regulation. Studies with factorial designs are also advocated to determine how multiple health behaviors may relate to the diurnal cortisol slope. This research is expected to provide valuable data on the relative contribution of health behaviors in cortisol regulation, which may be utilized to intervene to improve cortisol regulation, and, indirectly, health conditions associated with cortisol dysregulation.

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