MASARYK UNIVERSITY
Faculty of Social Studies

Physical Activity and Menopausal Wellbeing

Habilitation Thesis

Mgr. Steriani Elavsky, Ph.D.

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Abstract

This habilitation thesis presents research on the role that physical activity plays in enhancing psychological wellbeing during the menopausal transition. The work presented is interdisciplinary, intersecting the fields of health psychology, psychology of physical activity, women´s health, and adult development and aging, viewing behavior and the menopausal transition from a lifespan, developmental perspective. The number of women aged 40-60 has been increasing as a result of the aging trends in most Western societies. This period of life brings for women a transition from reproductive to nonreproductive status, which is accompanied by volatile changes in hormonal levels. Changing of the hormonal mileu consequently alters the health risk profiles of women, increasing their risk for cardiovascular disease, osteoporosis, depression, or weight gain. The psychological disturbances that accompany the menopausal transition are often linked to the experience of bothersome menopausal symptoms, which has a negative impact on women´s wellbeing and quality of life. Vasomotor symptoms, in particular, are experienced by the majority of women and often serve as an impetus for women seeking healthcare services at this stage of life. While sociodemographic factors, premenopausal health status, and psychosocial stress act as important determinants of wellbeing as women transition through menopause, lifestyle factors, namely physical activity, also play a vital role. Physical activity brings about numerous health benefits to the menopausal women but its effects on menopausal symptoms and wellbeing have been understudied. In this thesis, seven distinct published studies are presented to unveil how physical activity impacts menopausal symptoms and wellbeing (both long-term as well as acutely in the context of daily life), and to characterize individual differences in how women may benefit from physical activity in terms of symptom and wellbeing outcomes. A variety of methodologies were applied ranging from experimental, intensive longitudinal, ecological momentary assessment, and single case designs to demonstrate that (1) physical activity impacts psychological wellbeing and quality of life indirectly through its effects on more proximal outcomes such as affect; (2) menopausal symptoms can be impacted by physical activity but also have a direct influence on wellbeing; (3) vasomotor symptoms are not triggered by acute exercise in most healthy women but that low-fit women may perceive worsening of symptoms as a result of increased daily physical activity; (4) substantial between- as well as within-person variability exist in both daily physical activity and symptom reporting but enhancing perceived control, positive affect, and coping efficacy may help women cope with symptoms effectively, suggesting a need for intervention approaches that contain multiple components (cognitive, behavioral), are tailored to subgroups of women based on their personality, fitness profiles, and are dynamic, adopting to women´s changing needs and being delivered in the moment when most needed.

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Introduction

Defining menopause, menopausal health and well-being

There are nearly one million women over age 50 living in the Czech Republic, representing one of the fastest growing segments of the population [1]. The United States, Europe, and populations worldwide are experiencing the same aging trends with more and more women reaching menopause each year [2,3] . Menopause refers to cessation of ovarian follicular activity and is manifest by the cessation of menstrual flow lasting at least 12 months. Perimenopause encompasses the time immediately before menopause (i.e., after menstrual cycles become irregular) and the first year after menopause, representing a transitional period when physiological, hormonal, and clinical changes commence, which lasts on average 3.5-4 years [4]. The menopausal transition (MT) is defined as the time before the final menstrual period when variability in menstrual cycle is usually increased [5]; however, the term is often used more broadly to denote the transition from reproductive to non-reproductive years of women's lives (also referred to as such throughout this thesis).

Although the MT is part of a normal aging process, the hormonal changes occurring at this stage of life alter the health-risk profile of women, increasing the risk of cardiovascular disease (CVD) [6], osteopenia and osteoporosis, contributing to weight gain and leading to increases in central adipose tissue [7], risk factors for diabetes. In menopause-related studies health outcomes are generally operationalized along three dimensions: (1) as self-rated or self-defined health; (2) as health status (often assessed as health history, some aggregate measure of different health indicators, or as health-related quality of life); and (3) in terms of specific health/disease end-points (e.g., cardiovascular risk factors). There are also more "acute" manifestations of the MT in the form of different types of symptoms which cluster into three factors: vasomotor, somatic, and psychological [8]. However, only vasomotor symptoms, such as hot flashes and night sweats, and urogenital symptoms, such as vaginal dryness or atrophy, have been linked to the endocrinological changes occurring during menopause [4]. To denote the more positive aspects of health as women transition through menopause the term menopause-related well-being has been used and is most typically operationalized as subjective or psychological well-being [9].

Determinants of health and well-being across the MT

Although some women appear to be more susceptible to the adverse outcomes of menopause [10,11], the idea of a universal menopausal syndrome has been refuted [12], with the majority of women viewing menopause as a neutral event in their lives [13,14]. Several longitudinal studies have identified important determinants of health and well-being across the MT (Health Women's Study [15]; Massachusetts Women's Health Study [16]; Melbourne Women's Health Project [17]; Seattle Midlife Women's Health Study [18]; Penn Ovarian aging Study [19]; Women's Health Australia Study [20]; Study of Women's Health Across the Nation [21]; with several larger studies focusing on postmenopausal and older women only, e.g., Women's Health Initiative), pointing at four inter-related primary factors contributing to health and well-being as women transition through menopause: premenopausal health, menopausal symptoms, psychosocial factors (mainly stress), and lifestyle factors (mainly physical activity) [22,23].

To understand the impact of the MT on health and wellbeing of women, one must view the MT in a broader context with multidimensional causal influences, extending from distal social and built environmental factors to proximate, individual level factors [24,25]. A brief overview of the most relevant covariates of menopausal health and wellbeing follows.

Socio-demographic factors. Chronological age is associated with health status as is age at menopause [26]. Socio-demographic factors such as social class, marital status, parity, and race/ethnicity may impact menopausal health and well-being by modulating age at menopause or by influencing stress exposures, lifestyle behaviors linked to age at menopause or specific health outcomes. For example, lower level of education, single status, not being employed, and African-American [27] and Latina [28] race/ethnicity have been associated with earlier age at menopause [29,30]. Higher parity, especially in women of higher socio-economic status, prior use of contraceptives, and Japanese race/ethnicity have been linked to later menopause [30–32]. More African-American and Latina, but fewer Chinese and Japanese women also report vasomotor symptoms as compared to White women, and fewer women with postgraduate education report vasomotor symptoms [33,34]. Additionally, childless women express more negative attitudes toward menopause compared with parous women but are half as likely to report vasomotor symptoms [35]. Socio-economically disadvantaged women also display more negative health behaviors (e.g., smoking, alcohol consumption, body mass index, stress, diet, physical activity) [36], all of which have been shown to impact age at menopause and/or health outcomes [37–39]. Socio-economic

status and race also contribute to health disparities more generally, resulting in uneven distribution of health [40,41].

Premenopausal health. Premenopausal health is the most important predictor of any health outcome following the final menstrual period. In the Melbourne Women's Health Project, changes in self- rated health have been monitored across a 9-year period in middle-aged women progressing through the MT. In a longitudinal analysis, modeling simultaneously multiple influences on self-rated health and well- being, premenopausal self-rated health emerged as the most potent indicator of any other health and well-being outcome over time [23]. This finding is consistent with other reports suggesting that women with a history of physical or mental health problems are the most likely to have a distressful MT [42].

Menopausal symptoms. Among the most common symptoms reported by menopausal women are hot flashes, night sweats, irritability, moodiness, tension, anxiety, low self-esteem, and emotional instability [4]. However, the term "menopause management" is typically constrained to the management of vasomotor symptoms such as hot flashes and night sweats. These symptoms represent a heavy socioeconomic burden on society [43] and they are the primary reason for middle-aged women visiting a physician [44]. Interestingly, women with menopausal complaints display lower bone mineral density [45] and a less favorable cardiovascular risk profile [46], including higher risk for hypercholesterolemia, hypertension [47], and higher body mass index [48], pointing to a possible overlap in etiology of both CVD and vasomotor symptoms [49,50] and suggesting a potential role of vasomotor symptoms as a sub-clinical marker of health. In the U.S., higher reporting of menopausal symptoms (vasomotor in particular) has been associated with late perimenopausal and early postmenopausal status, specific endocrine changes, African American race, lower educational attainment or socio-economic status, higher body mass index or body fatness, smoking, history of pre- menstrual complaints, stress, anxiety, depression, and sleep problems [34,50–54]. Recently, environmental context has been linked to menopausal symptom reporting but few systematic investigations of the role of context exist. The limited evidence available suggests that social networks, social support, and familial relationships influence how women deal with menopause [55,56], and that women residing in rural environments may be experiencing a more distressful menopause and more frequent or severe vasomotor symptoms, even after controlling for health status and socio-economic factors [57].

Psychosocial stress. The most consistent psychosocial predictor of health and well-being

during the MT is stress. Both acute (e.g., interpersonal relationships or daily hassles) and chronic stressors (e.g., history of child abuse or victimization) have been linked to adverse health outcomes, more menopausal symptoms, and poorer well-being in middle-aged women. There is a reciprocal relationship between stress and the MT as stress may exacerbate menopausal symptoms and menopausal experiences may, in turn, influence the perception, experience of, and coping with stressful life events [58]. Women who experience longer MT and increased symptoms have higher stress, and were found to be at increased risk for depression [59]. Menopause-related distress (i.e., experiencing symptoms) increases levels of inflammatory cytokines [60,61], and psychosocial stress in general has been associated with the development of hypertension, metabolic syndrome, and faster progression of CVD [62]. Interestingly, women in early perimenopause report the highest rate of psychological distress as compared to premenopausal and postmenopausal women [63], and postmenopausal women respond more intensely to stress than premenopausal women [64,65]. Perceived stress has been associated with subsequent dysphoric mood and recently also, stressors such as chronic or childhood stress, abuse, and victimization have been associated with increased reporting of vasomotor symptoms [58,66]. A recent observational study described longitudinal changes in the level of perceived stress in relation to MT and although stress levels tended to decline in postmenopause, factors such as employment, history of sexual abuse, depressed mood, and poor self-perceived health were associated with higher levels of stress. Improvement in role burden, social support, and income adequacy was associated with significantly lower perceived stress [67].

Physical activity. Physical activity is a key lifestyle factor that can influence menopausal wellbeing and women across the menopausal spectrum can derive the numerous health benefits of physical activity [68]. Menopause has been associated with a decrease in energy expenditure and increase in total body fat and visceral adipose tissue [69], and CVD risk factors, but maintaining or increasing participation in regular physical activity may prevent or attenuate any such increases in midlife women . In 2004, the North American Menopause Society (NAMS) recommended lifestyle changes such as regular physical activity as the first line of defense against the adverse consequences of menopause, including the management of mild to moderate menopausal hot flashes [70], although the evidence from quality randomized control trials remains limited, leading NAMS to remove exercise as well as yoga from their list of proven hot flash treatments [71]. Unfortunately, women who experience vasomotor symptoms spend less time on exercise per

week than do those who do not have hot flashes [72], and only approximately half of middle-aged women engage in any leisure-time physical activity on regular basis, with less than 25% meeting the public health recommendations of at least 30 minutes of accumulated moderate physical activity on most days of the week [73]. One 4-year prospective study documented that physical activity decreased significantly two years before menopause and remained low thereafter [69], but other longitudinal studies reported relatively stable physical activity levels on average in middle-aged women across the menopausal stages [22,74], albeit with a significant portion (>50%) of the women reporting insufficient or no regular activity. This is unfortunate given the numerous health benefits of physical activity. Cross-sectionally, physical activity has been associated with less nervousness and fewer menopausal symptoms [75–78], enhanced mood, well-being [9], and quality of life [79], but some experimental [80–82] and population-based prospective studies have provided inconsistent findings when it comes to the relationship of physical activity to vasomotor symptoms in particular [33,36,83,84].

It has been proposed that one of the ways physical activity impacts health and well-being across the menopausal transition is by attenuating the adverse effects of stress on these outcomes. Physical activity has been associated with lower levels of stress generally [85,86] and during ovarian aging [87]. Other literature (animal and human) supports the role of physical activity in attenuating the adverse effects of stress on health [88]. For example, animal studies have supported the physiological effects of exercise on reducing stress through reductions in behavioral depression and immunosuppression brought about by different stressors [89,90]. In human studies, physical activity has been shown to impact health through different pathways depending on the outcomes under study. Physical activity may have a direct impact on health and well-being (i.e., regardless of stress levels) for example by improving cardiovascular and bone health [68] or mood [22]. It may however also affect health and well-being indirectly by either mediating [91,92] or moderating the stress-health relationship [93,94].

The focus, innovation and significance of the present research

My program of research stems from my previous work involving studies examining the effects of physical activity on quality of life (QOL) during the aging process [75,95,96]. Although the menopausal transition is part of a normal aging process, the hormonal changes occurring at this stage of life alter the health-risk profile of women and bring about more “acute” manifestations

of the menopausal transition in the form of vasomotor symptoms such as hot flashes and night sweats. These are perceived as especially bothersome and disruptive and represent the primary reason for women seeking health care services at this stage of life. The menopausal transition may also be a source of psychological distress or instability and there is growing evidence that certain subgroups of women may be more vulnerable to such adverse outcomes than others. For example, overweight and obese women are more likely to experience vasomotor symptoms [54] and consequently may be more vulnerable to experiencing sleep and other health problems. Symptomatic menopausal women in general are also more vulnerable to developing depressive symptoms or clinically defined depression and perimenopause has been identified as a period of transitional vulnerability for depression and other mental health problems [97,98]. Collectively, these adverse physical and mental health changes may negatively impact wellbeing as women transition through menopause.

Although physical activity may attenuate many of the adverse outcomes associated with menopause, including different types of symptoms, few studies have investigated the effects of physical activity on physical and mental health (and subsequent impact on QOL and wellbeing) during menopause. Existing studies have focused either solely on symptom reporting or physiological outcomes primarily in pre- and post-menopausal women and have generally confounded the neuroendocrine, fitness, body composition, and psychological effects of physical activity. Consequently, the psychological and physiological responses to physical activity have not been well characterized in peri-menopausal women, and little is known about how the psychological and physiological systems interact to impact health and wellbeing at this stage of life. Additionally, the majority of existing research has focused on between-group comparisons, providing little understanding of the sources of individual differences in the way women experience menopause and how they may respond to behavioral interventions including physical activity in terms of health and wellbeing endpoints. In this work, I take an interdisciplinary biopsychosocial approach to characterize the role of physical activity in enhancing wellbeing as women transition through menopause by illuminating the mechanisms of the physical activity-wellbeing relationship and identifying relevant individual difference characteristics and other sources of variability in responses to physical activity among middle-aged women.

This work is timely and important given the increasing trend towards using complementary and alternative medicine strategies for menopause management [99], and the fact

that menopause is viewed by many women as a time of life when preventive healthcare and health behavior changes are critical [100]. Additionally, there is a critical need for longitudinal and experimental studies with strong measurement and innovative designs, given the inherent methodological challenges in research on menopause-related outcomes which to date has been dominated by epidemiological approaches [101]. Although such studies are useful in providing information about prevalence and incidence rates, trends, and trajectories, they are limited in their ability to unveil the processes that underlie the effects of various behavioral modalities on menopause-related outcomes. The majority of existing studies have typically relied on subjective and mostly retrospective assessments of vasomotor symptoms and physical activity (known to be subject to recall and social desirability biases), lacked detailed physiological and psychological assessments, and focused on between-person comparisons, ignoring intra-individual variability and within-subject associations among physical activity and wellbeing outcomes.

Recently, ecological momentary assessment methods (EMA) have been gaining popularity and have been advocated for the assessment of momentary psychological processes in the context of daily experiences [102,103]. Studies applying these methods conduct frequent "in-real-time" measurements and provide rich data for the study of patterns in intra-individual variability in outcomes of interest. The inclusion of objective measures and within-person replicated time-series design may also enhance our understanding of individual differences in physical activity behavior, menopausal symptoms, and wellbeing outcomes. For example, sternal skin-conductance monitoring is considered the gold standard in objective ambulatory assessment of hot flashes [4]. This technique has been shown to have high agreement (95-100%) with self-report data in laboratory settings. However, substantial under-reporting rates (43-65%) have been found in ambulatory assessment studies. It is unclear what contributes to these discrepancies with possible explanations ranging from different symptom interpretations or perceptions (potentially driven by aspects of introspective personality), affective, contextual, or lifestyle influences. Adopting a within-person methodology along with EMA allows for the characterization of the patterns of subject responses over "time" while allowing for investigation of the effects of important covariates (non-time or time-varying) on these patterns. The ultimate goal of employing these novel methodological approaches is to form person-specific recommendations regarding avoidance of behaviors and contexts that trigger symptoms and developing effective coping strategies to minimize the impact of bothersome symptoms on normal daily functioning.

Findings from such studies also help inform the design of interventions by allowing for individualization of treatment options or program design, ultimately optimizing their effectiveness.

Consequently, this habilitation thesis presents work that could be characterized as interdisciplinary, and it terms of classification of study fileds, lies at the intersection of health psychology, psychology of physical activity, women´s health, and adult development and aging. Research questions regarding psychosocial outcomes, symptom reporting and health behavior fall within psychology of health and physical activity. The study of physiological and psychosocial outcomes during reproductive transitions such as menopause also fall witin the realm of women´s health. Understanding and approaching menopause as a developmental, transitional period with important consequences for the aging process, also reflects a lifespan perspective, a cornerstone of adult development and aging fields [104,105]. Notwithstanding the interdisciplinary, biopschosocial nature of this work, standard (and novel) methodology from within general and developmental psychology form the basis of this research, thus, general or developmental psychology should be used as the interpretation framework of the whole thesis.

List of Original Publications

This habilitation thesis presents a series of original publications investigating the role that physical activity plays in enhancing menopausal wellbeing. The publications are ordered chronologically but the order is also consistent with the conceptual underpinnings of the studied theme, starting with the results of a large-scale randomized controlled trial that demonstrated individual differences in response to physical activity, followed by an examination of long-term effects of physical activity on quality of life in middle-aged women, and culminating in a series of studies aiming to unveil the individual characteristics and within-person variability in physical activity and menopause-outcomes using intensive longitudinal designs and EMA methodology. The presented studies do not represent the entire body of work on the subject, rather they have been selected to provide a meaningful glimpse into the topic and types of methodologies utilized in my work.

Study I
Elavsky, S., & McAuley, E. (2007). Physical activity and mental health outcomes during menopause: A Randomized controlled trial. *Annals of Behavioral Medicine, 33*(2), 132-142.

Study II

Elavsky, S. (2009). Physical activity, menopause, and quality of life: the role of affect and self-worth across time. *Menopause, 16*(2), 265-271.

Study III

Elavsky, S., McAuley, E. (2009). Personality, menopausal symptoms, and physical activity outcomes in middle-aged women. *Personality and Individual Differences, 46*(2), 123-128.

Study IV

Elavsky, S., Gonzales, J.U., Proctor, D.N., Williams, N.I., & Henderson, V.W. (2012). Effects of physical activity on vasomotor symptoms: Examination using objective and subjective measures. *Menopause, 19*(10), 1095-1103.

Study V

Elavsky, S., Molenaar, P., Gold, C.H., Williams, N.I., Aronson, K.R. (2012). Daily physical activity and menopausal hot flashes: Applying a novel within-person approach to demonstrate individual differences. *Maturitas, 71*(3):287-93.

Study VI

Elavsky, S., Kishida, M., & Mogle, J. (2016). Concurrent and lagged relations between momentary affect and sedentary behavior in middle-aged women. *Menopause, 23*(8), 919-923.

Study VII

Kishida, M., & **Elavsky, S**. (2015). Daily physical activity enhances resilient resources for symptom management in middle-aged women. *Health Psychology*, *34*(7), 456-64.

Author's contribution

Study I-VI: The author conceptualized, designed and directed the studies and data collection and processing, wrote 100% of the first drafts of the papers, collaborated on data analyses (studies IV-VI) and on paper revisions (studies I-VI).

Study VII: The author helped conceptualize the study and supervised the study design and conduct, wrote 10% of the first draft of the paper and collaborated on data analyses, paper

revisions. This study was conceptualized to fit thematically with other presented work but also represents an example of mentored doctoral research.

Summary of Research Questions

Research aims of presented studies

The overall theme of presented studies is to characterize how physical activity impacts wellbeing across the menopausal transition. In **Study I**, a large-scale randomized controlled trial (the second largest trial in existence at the time) was conducted to test the effects of physical activity on mental health, symptom, and wellbeing outcomes in middle-aged women. Community-dwelling women across the menopause spectrum were recruited for a study (LifePAQ) comparing the effects of aerobic exercise (supervised walking program), yoga, and a control group. Additionally, differences in response to the interventions were probed to identify possible moderators of treatment response. In **Study II**, women previously enrolled in the LifePAQ study were followed two years after the trial end to evaluate the long-term effects of physical activity on QOL and the underlying mechanisms of these effects. In **Study III**, individual differences in menopausal symptom reporting were evaluated in the context of the LifePAQ trial to identify personality characteristics that explain these differences. As part of **Study IV**, a 15-day daily diary study with ecological momentary assessment (EMA) methods was conducted to examine the relationship between chronic (habitual) physical activity and acute exercise and vasomotor symptoms. This study utilized both subjective and objective measures of physical activity and vasomotor symptoms (the first study at the time to do so). **Study V** applied a novel approach, a single case longitudinal time-series analysis to demonstrate individual differences in the relationship between physical activity and menopausal symptom reporting. In this study within-person associations between physical activity and symptoms were analyzed over time across one menstrual cycle or a period of 30 days if postmenopausal. **Study VI** examined the role of inactivity (sedentary behavior) on affect in middle aged women. On data obtained from Study III, associations between inactivity and affect were analyzed at the momentary level to unveil both concurrent and lagged effects. **Study VII** used a 21-day daily diary design to evaluate the direct and indirect associations between physical activity and

menopausal symptoms and test mediational pathways involving sources of resilience such as positive affect and coping efficacy.

Methods

Data sources

A range of different methodological approaches were used to address the questions under study, all however involved quantitative data analyses. **Study I** was a 4-month randomized control trial (LifePAQ) with 3 (group) by 2 (time) design involving 164 community-dwelling middle-aged women. **Study II** was a 2-year prospective examination of participants enrolled in the LifePAQ study. **Study III** examined the contribution of personality characteristics to the reporting of menopausal symptoms in the context of the LifePAQ randomized controlled trial. **Study IV** was a 15-day daily diary study with ecological momentary assessment of 121 community-dwelling women reporting menopausal symptoms upon enrollment into the study. Additionally, the women completed an acute bout of aerobic exercise in the lab to investigate acute effects of exercise on the reporting of vasomotor symptoms which were assessed subjectively as well as objectively through sternal skin conductance monitoring. **Study V** used a novel single subject design with person-specific time series analyses to identify individual differences in the relationship between daily physical activity and symptom reporting in 24 middle-aged women followed intensively across an entire menstrual cycle or a 30-day period. **Study VI** used data from the 15-day daily diary study (Study IV) to examine how inactivity (sedentary behavior) influences momentary affect in middle-aged women. **Study VII** utilized a daily diary study design with 21 daily online assessments of 103 community-dwelling middle-aged women to investigate sources of resiliency in the relationship between physical activity and menopausal symptoms. A brief overview of the specific methodologies and statistical approaches used in these studies follows.

Study I

This study investigated the effects of a 4-month randomized controlled exercise trial on mental health and wellbeing outcomes in 164 previously low-active middle-aged women (*M* age = 49.9; *SD* = 3.6). Participants completed body composition (DXA) and fitness assessment (VO2 max test) and a battery of psychological measures at the beginning and end of a 4-month

randomized controlled exercise trial with three arms: walking, yoga, control. A series of mixed model) repeated measures Univariate and Multivariate Analyses of Variance (ANOVAs and MANOVAs) and Covariance (ANCOVAs and MANCOVAs) were conducted to evaluate the effects of the intervention on outcomes of interest.

Study II

This study examined the long-term effects of physical activity on menopause-related quality of life (QOL) and tested the mediating effects of physical self-worth and positive affect in this relationship. Middle-aged women previously enrolled in a 4-month randomized controlled trial involving walking, yoga, and a control group completed a follow-up mail-in survey two years following the end of the trial. The survey included a battery of psychological and physical activity measures, including measures of menopausal symptoms and menopause-related quality of life. Longitudinal linear panel analysis was conducted within a covariance modeling framework to test whether physical self-worth and positive affect mediated the physical activity - quality of life relationship over time.

Study III

This study examined the contribution of personality factors to the reporting of menopausal symptoms in the context of a 4-month randomized controlled exercise trial. Symptomatic middle-aged women (N = 164 M age = 49.9, SD = 3.6) completed measures of menopausal symptoms, personality, physical activity, fitness and body composition assessment at the beginning and end of a 4-month randomized controlled trial involving walking and yoga.

Study IV

The purpose of this study was to assess the effects of acute aerobic exercise and daily PA on menopausal vasomotor symptoms. Community-dwelling midlife women (N=121; age range 40-60 years) not on hormone therapy were recruited for a 15-day daily diary study with ecological momentary assessment. Women completed psychological, cardiorespiratory fitness (VO2 max test), body composition (DXA), and hormonal status screening (urine and blood samples), followed by a 15-day prospective assessment in a "real-life" setting using a personal digital assistant device. Participants also completed a 30-minute moderate-intensity aerobic exercise bout on a treadmill between days 5-8. Daily PA was assessed objectively through accelerometry and all symptomatic women (n=92) completed two 24-hour Biolog sternal skin conductance recordings of hot flashes (HFs), one at baseline and one immediately following

treadmill exercise.

Study V

This study applied a longitudinal within-person design through a prospective daily diary study which applied experience sampling methods. Time series modeling techniques investigated, at the within-person level, the relationship between objectively measured daily physical activty of varying intensities and self-reported menopausal hot flashes (HFs) in 24 symptomatic middle-aged women (*M* age = 50.4; *SD* = 4.9). All women completed fitness, body composition and hormonal status screening, and reported on daily HFs using an electronic personal digital assistant (PDA) device across one menstrual cycle or for 30 days (if postmenopausal). Daily physical activity and physical activity intensity was measured using accelerometry and subjects completed a battery of psychological measures.

Study VI

The purpose of this study was to investigate the reciprocal relationship between sedentary behavior (SB) and momentary affect in the context of daily experiences in a sample of community-dwelling midlife women (*N* = 121; age range 40-60 years) recruited for a 15-day daily diary study. The women rated their positive and negative affect when prompted on a PDA device four times per day and wore an accelerometer for objective assessment of SB. Multilevel models were estimated to test concurrent and lagged associations between momentary estimates of SB and affect.

Study VII

The aim of this study was to evaluate the direct and indirect associations between physical activity and menopausal symptoms in 103 community-dwelling middle-aged women (age range 40-60 years) who completed daily Internet surveys at the end of the day and wore an accelerometer for the objective assessment of physical activity for 21-days. 1-1-1 multilevel meditational models were estimated to test whether resilient resources (i.e., positive affect and coping efficacy) mediated the association between physical activity and symptom burden at both the between- and within-person level.

General Discussion

My scholarship focuses on accumulating scientific evidence that a physically active lifestyle is central to successful and healthy aging, and that physical inactivity presents one of the most prominent public health challenges of our time. As a scholar I aim to engage in, and foster greater awareness of, physical activity research from the public health perspective, while investigating and integrating scientifically relevant issues to the concrete concerns of real people in terms they can make sense of and benefit from. The overarching long-term goal of my research is to understand how best to harness the power of physical activity to enhance health and wellbeing as we age. Specifically, I have made substantive contributions in three areas: (1) understanding the role that physical activity plays in improving quality of life (QOL) across populations (with a particular focus on the wellbeing of the menopausal woman); (2) integrating objective and subjective methods to study clinical issues; and (3) using within-person methodology to reveal the intra-individual dynamics of motivational processes linked to physical activity and its psychological consequences. The work is interdisciplinary in nature drawing on the knowledge framework across different fields including psychology of health and physical activity, women´s health, and adult development and aging. The methods and theories applied however stem from mainstream psychology, resulting in largely psychological research with potential public health relevance.

Specifically, my work on wellbeing helped establish psychosocial influences such as self-efficacy, social support, affect, and self-worth as important determinants of physical activity behavior and as mediators of physical activity effects on quality of life in young, middle-aged, and older populations. One of the main thrusts of my research focuses on women in midlife and menopause, as a transitional period with important implications for successful aging. Fourteen publications have specifically aimed to illuminate the mechanisms of physical activity effects on wellbeing in women as they transition through menopause.

These studies advanced the field by addressing notable shortcomings of previous research which relied on self-reported measures and failed to adequately account for between-person differences in physiological and psychological factors linked to menopausal symptom reporting. Specifically, these were the first studies to: (1) incorporate both objective and subjective measures of physical activity (accelerometry) AND vasomotor symptoms (sternal skin conductance); (2) carefully characterize fitness levels, body composition, hormonal status, and psychological profiles of women to take into account these important correlates of

menopausal symptom experiences; and (3) employ longitudinal within-person designs to examine how changes in physical activity impact menopausal outcomes while ruling out the potential influence of established (and unknown) individual difference variables.

Parts of this research, also recognized by the biomedical menopause community (2011 New Investigator Award from the North American Menopause Society), are presented in this habilitation thesis. Across seven different studies, this thesis attempts to address some of the major issues in the study of physical activity behavior and its effects on mental health and psychological outcomes in women as they transition through menopause. This work also reflects a variety of different methodologies in an effort to address some of the shortcomings of previous research. As a matter of summarizing these findings and general discussion, I would like to emphasize several key themes or messages of this work.

1. **The menopausal experience is idiosyncratic and individual differences exist in how women benefit from behavioral modalities such as physical activity during menopause.**

Although from a public health perspective, one might desire to draw a simple message regarding health behaviors and their positive effects on health and wellbeing, that would also apply to populations broadly, the message regarding physical activity during menopause must be nuanced. From the standpoint of physical and mental health status, women can derive the same health benefits from physical activity as the population at large, nonetheless for menopause management, which is usually akin to management of symptoms, some women stand to benefit more than others. In Study I [81], it was demonstrated that walking and yoga were effective in enhancing positive affect and menopause-related QOL and reducing negative affect. Nonetheless, the treatment response varied significantly based on changes in menopausal symptoms across the trial. Women who experienced decreases in menopausal symptoms across the trial benefited more from the interventions, experiencing more pronounced improvements in all positive mental health and QOL outcomes and greater reductions in negative mental health outcomes. Whether menopausal symptoms increased or decreased across the trial appeared to be determined in part by whether there were increases or decreases in cardiorespiratory fitness, suggesting that cardiorespiratory fitness may represent a factor modifiable by interventions.

In Study III [106], additional individual difference variables were identified as contributors to the differential responses in menopausal symptoms. Specifically, after controlling for baseline values, psychological symptoms at the end of the 4-month trial were associated with

trait anxiety (β = .47, $p < .001$) and changes in fitness (β = -.20, $p < .01$); vasomotor symptoms with optimism (β = -.18, $p < .05$) and changes in fitness (β = -.15, $p = .053$); and sexual symptoms were associated with changes in fitness (β = -.16, $p < .05$). These findings support previous suggestions that aspects of personality play a role in the experience of menopausal symptoms [42,107]. This individual variability also predisposes women to benefit differently from physical activity, suggesting that personalized multimodal intervention strategies may be required to minimize the impact of bothersome symptoms in women.

Other research also indicates that different women experience different clusters of symptoms and that symptom experiences are dynamic and change over time, only further underscoring the need for personalized and adaptive interventions. For example, in the Seattle Midlife Women's Health Study, three latent classes representing broad categories of symptoms were identified: Class 1 with observations of low severity levels for all symptoms (e.g., vasomotor, psychological, somatic), class 2 with low-severity hot flashes and moderate-severity levels for all other symptom factors, and class 3 with high severity hot flashes with lower severity levels of all other symptom factors [108]. While profiling women from the late postmenopausal stage only, more specific profiles were also identified: group 1 experiencing low severity for all symptoms except for joint ache (65%); group 2 high severity for all symptoms except for hot flashes (13%); group 3 with high severity for hot flashes, joint ache, and awakening at night (12%); and group with high severity for problem concentrating and joint ache (10%) [109]. Although symptom clusters changed somewhat across the different stages of the menopausal transition, they were best predicted by symptom clusters from a previous stage, suggesting some consistency in the types of symptoms women exhibit as they transitions from early perimenopause to late postmenopause [110]. From a clinical translational perspective, identifying subgroups of women with different symptom clusters and personality dispositions that may make them more vulnerable would allow for tailoring of intervention approaches to maximize their effectiveness.

It should also be noted that different types and intensity of physical activity are likely to affect women differently and that individual differences exist in how women may respond to different physical activity modalities. In Study I [81], there were differences in the effects of walking versus yoga on different types of symptoms and mental health outcomes with walking having largely stronger effects than yoga. Although yoga impacted the sexual QOL domain more and had different pattern of impact on psychological outcomes such as self-esteem (shown in a separate study [111]). Study IV [112] demonstrated that acute aerobic exercise may have different effects on vasomotor symptoms than habitual physical activity and that

personal characteristics such as fitness level moderate this relationship. Study V [113] delineated in greater detail the person specific effects of daily physical activity of different intensities, pointing to affect and perceived control as factors modifying this relationship. Consequently, when it comes to optimizing management of menopausal symptoms, physical activity recommendations should be tailored and combined with other behavioral and cognitive strategies for most effective symptom management.

2. **Physical activity enhances wellbeing and quality of life during menopause, both directly and indirectly through its effects on more proximal outcomes such as affect, self-worth, or coping resources.**

Study II [114] tested whether physical activity enhanced menopause-related quality of life (QOL) across a 2-year period in middle-aged women previously enrolled in a 4-month randomized trial involving walking and yoga. There was an indirect relationship between physical activity and QOL such that increases in physical activity and decreases in menopausal symptoms over the 2-year period were related to increases in physical self-worth (βs = .23 and -.52) and for symptoms also to decreased positive affect (β = -.47), and both physical self-worth (β = .34) and affect (β = .43) directly influenced enhancements in QOL (R^2 = .775). The findings support the position that physical activity effects on QOL are in part mediated by intermediate psychological outcomes and that physical activity can have long-term benefits for women undergoing the menopausal transition.

From a theoretical perspective, influences on wellbeing/QOL could be divided into two general categories of top-down and bottom-up influences [115]. Top-down influences can be seen as time-invariant or slow-changing phenomena such as individual difference characteristics (demographics, personality factors, or health status). Bottom-up influences can be viewed as different contextual or process variables that change over time and in shorter timescales such as daily affect, symptoms or stress. Data from the studies presented here support the position that physical activity can operate both as a top-down and bottom-up influence on wellbeing/QOL in menopausal women whereby changes in physical activity have been linked to changes in menopause-related QOL over time, albeit indirectly. The more immediate effects of daily physical activity on outcomes such as symptoms, affect, and coping resources (in Studies IV-VII [112,113,116,117]) at the daily and momentary levels would support effects of physical activity on important bottom-up influences on wellbeing of menopausal women. In other words, one would expect fluctuations in physical activity (i.e.,

deviations from usual activity) to be reflected in changes in different physical, self-related, and cognitive functional outcomes which are likely to impact domain-specific or global wellbeing/QOL. The strength of the effects would then be expected to be greater at the level of the intermediate (more proximal) outcomes than the more distal outcomes such as life satisfaction, just as shown in my other work [96,118,119] and in Study II [114]. To maximize the impact of physical activity on QOL/wellbeing, interventions should thus target activities that are personally meaningful and that demonstrate measureable improvements in proximal outcomes such as affect, self-efficacy and self-worth, enhancing sense of personal control, competency and enjoyment.

3. **Physical activity effects on menopausal symptoms, vasomotor in particular, warrant further study, but acute exercise is unlikely to exacerbate hot flashes in most healthy women.**

There has been controversy regarding the role that physical activity plays with respect to vasomotor symptoms such as hot flashes and night sweats. This controversy stems from inconsistent and generally low quality research. Cross-sectional studies typically report positive effects of physical activity on vasomotor symptoms and QOL [72,77,78], while prospective studies provide contradictory results [33,36,120]. Only few randomized controlled trials evaluating physical activity effects on symptoms and QOL during menopause exist, and these have provided inconsistent results and are often underpowered [121–123]. Aiello et al. [80] reported an increase in vasomotor symptoms in some women following a 12-month moderate intensity exercise program and at least one study suggests that lifetime exercisers may report more frequent or severe vasomotor symptoms during menopause [124]. Hot flashes are believed to be caused by altered neurotransmitter release in the hypothalamus leading to altered regulation of the thermoregulatory centre [125] and are triggered by small elevations in core body temperature acting within a reduced thermoneutral zone (mainly due to a lowering of the core body temperature threshold for sweating). It has been suggested that exercise may acutely exacerbate or trigger hot flashes by increasing core body temperature [126,127]. A recent Cochrane review of studies on the topic have failed to find sufficient evidence for physical activity alleviating vasomotor symptoms [128] and the North American Menopause Society has recently removed exercise from their list of recommended treatements for lack of evidence [71].

In Study IV [112] both objective and subjective methods of assessment were applied to study the effects of acute exercise and habitual physical activity on vasomotor symptoms.

The results have shown that a single bout of acute exercise does not increase *objectively* or *subjectively* assessed hot flashes (contrary to a pre-existing view, from a single study [126], that has influenced clinical recommendations for menopausal women), but that at the within-person level, increasing levels of moderate-intensity physical activity performed on a daily basis may be associated with increased reporting of vasomotor symptoms, particularly in women with low levels of cardiorespiratory fitness. Previously inactive low-fit women may thus be at risk of perceiving their symptoms as intensifying when first initiating behavior changes. For these women, increasing physical activity levels gradually is essential along with other (behavioral, cognitive) strategies to help ease symptom burden. These results along with demonstrated person-specific effects in Study V [113] may help explain why demonstrating consistent effects of physical aktivity is difficult.

Clearly, more quality research is needed to further investigate the mechanisms of the relationship between physical activity and vasomotor symptoms. Especially needed are sufficiently powered randomized controlled trials as well as experimental studies to shed light on the causal mechanisms involved in hot flashes, and also to increase our understanding of *when, why, and for whom* there is a relationship between physical activity and vasomotor symptoms [129]. Along with these efforts, there should be a greater acknowledgement of the other effects regular physical activity may have on psychological outcomes that may help build resiliency in the face of bothersome symptoms. The work of my doctoral student in Study VII [117] has demonstrated that daily physical activity generates positive affect and coping efficacy which may help women cope better with symptoms. Specifically, using daily diary data from 21 days of reporting, multi-level mediational analyses demonstrated that on days when a woman engaged in more physical activity than was typical for her, she also reported more positive affect and higher coping efficacy both of which were assocated with lower symptom burden. Importantly, these effects were non-significant at the between-person level suggesting one way in which physical activity may help a woman to cope with her symptoms is through the enhancement of positive affect and coping efficacy in the context of daily experiences.

Finally, it should be noted that not all physical activity is created equal and that different modalities may exert different effects. A recent review of mind-body intervention studies indicated that different intervention approaches (which included physical activity and yoga) impact different types of symptoms differentially. For example, physical activity was found to reduce hot flashes and mood symptoms (though results were mixed), whereas relaxation therapy with mindfulness-based stress reduction training was shown to reduce sleep and

mood symptoms, and yoga to reduce hot flashes and improve cognitive, sleep, and pain symptoms [130]. In Study I [81], we also observed effects of differenct magnitude by exercise modality on different types of symptoms. From a clinical translational perspective this means that women with different symptom clusters would be expected to benefit differentially from different interventions, highlighting a need for multi-component approaches that could be tailored to subgoups of women with specific characteristics. Nonetheless, regardless of vasomotor symptoms, given the well-demonstrated physical and mental health benefits of physical activity, sustained physical activity participation through young adulthood into midlife will remain key to optimizing health through the menopausal transition.

4. **The use of within-person methodologies can meaningfully contribute to increasing our understanding of physical activity behavior and its effects on wellbeing outcomes.**

The use of within-person methodologies in my work has provided additional meaningful insights into individual differences in responses to physical activity in middle-aged women as well as into the within-person dynamics in motivation linked to physical activity participation and wellbeing outcomes in younger populations of adolescents and emerging adults (six manuscripts to date). These studies have demonstrated that daily physical activity is regulated by both automatic and controlled motivational processes and that it influences QOL at the within-person level.

There are great individual differences in the way women experience menopause but little is known about what underlies this variation. In Studies IV-VII [112,113,116,117]intensive longitudinal designs were employed to unveil the dynamics of the physical activity – symptom relationship at the within-person levels. Study V [113] specifically applied a person-specific time series model to best describe the dynamic patterns underlying each individual time series. Within-person analysis identified significant relations between physical activity (PA) and hot flashes (HFs) in 50% of subjects, although the specific PA indicators that predicted HFs varied, both in terms of direction and magnitude. Perceived control over HFs was the variable that most consistently differentiated between women for whom more PA was associated with fewer HFs as compared to those for whom more PA was associated with more HFs, but other individual difference characteristics such as affect, depressive symptoms, and anxiety were identified. In recent years, this methodology as well as analytical approaches accomodating this methodology have gone through substantial

development, allowing for sophisticated sub-group analyses of commonalities between elements of sets of subject-specific state-space models, potentially helping to identify distinct subtypes of symptom and physical activity experiences (e.g., for women with personality profiles indicative of increased somatization or by residential/occupational status). Ultimately, such analyses can be done dynamically in real time through data collected in real life settings on an ongoing basis (e.g., through smartphones or wearable sensors). The promise of combining technology with understanding of individual and contextual factors that contribute to health behaviors and health outcomes lies in the possibility of designing effective "just-in-time" or ecological momentary interventions (EMIs) [131] that could help individuals cope "in the moment" with acute symptoms or aid in behavior change.

5. **Inactivity and sedentary behavior deserve attention as intervention targets for optimizing wellbeing during menopause along with the exploration of complementary intervention modalities involving cognitive restructuring, mindfulness or other contemplative practices.**

The results of Study VI [116] demonstrated detrimental effects of inactivity on affect. Specifically, using EMA data across 15 days, in models that controlled for day of week, number of hot flashes, and total minutes of accelerometer wear time, greater concurrent positive affect was associated with fewer minutes spent being sedentary ($\beta = -.31$, $p < .01$). Neither lagged positive nor negative affect predicted later SB, however, more sedentary minutes predicted lower positive affect at the next occasion ($\beta = -.04$, $p < .01$). Affective experiences may also predict future engagement in physical activity (as per hedonic theory of motivaion) [132], pathway which may place sedentary women into a vicious cycle of low positive affect reinforcing inactivity. Additionally, as shown in Study VII [117], positive affect may serve as an important psychological resource when coping with symptoms during menopause and is also related to QOL (Study II) [95,114]. Menopause has also been identified as a window of vulnerability to psychological disturbances including negative mood, depressive symptoms, or even increased risk of first-time onset depression [97], all of which have been linked to more severe menopausal symptoms. Women leading sedentary lifestyles (also linked to obesity which is another risk factor for menopausal symptoms) may thus be particularly at risk for a problematic menopausal transition. Future intervention efforts should thus focus on reducing or interrupting sedentary behavior to lessen the detrimental effects sedentary behavior appears to have on positive affect, along with efforts to promote physical activity as key to enhancing wellbeing during menopause and successful aging beyond.

Any intervention efforts to modify behavior should be accompanied by intervention strategies for the management of menopausal symptoms, if symptomatic. These strategies may be particularly important for women with high trait anxiety and neuroticism. Cognitive behavioral therapy has been shown effective for the treatment of menopausal symptoms including vasomotor symptoms such as hot flashes and night sweats [133,134] and could be easily incorporated into physical activity programs or with the use of technology [135]. Similarly promising for symptom management (as well as behavior change) have been mindfulness-based practices such as meditation or yoga [71,136].

Future Directions

The findings presented in this thesis provide valueable, novel insights into the dynamics of physical activity and wellbeing relationship in menopausal women, relevant to the fields of health psychology, psychology of physical activity, women´s health, adult development and aging. Most of what is known about the physical activity and menopausal wellbeing relationship stems from studies that have examined between-person differences in physical activity and wellbeing outcomes (e.g., epidemiological studies), whereby a woman´s typical (average) level of physical activity is associated with typical (average) levels of wellbeing (or symptoms). This approach is limited and may not be appropriate as between-person variation does not always reflect individual-level process[137,138]. Investigating intraindividual variability in outcomes of interest, such as through the application of intensive longitudinal designs and EMA methodologies, offers important insights into intraindividual variability in outcomes over time and can also reveal psychological processes at play. Across seven studies (four of which have utilized such methods), the idiosyncratic nature of physical activity effects on menopausal wellbeing has been demonstrated, along with noteable individual difference characteristics and plausible casual pathways for how physical activity could be used or targeted to enhance wellbeing as women transition through menopause.

From a theoretical standpoint, the findings complement other work in the health and physical activity psychology fields on the nature of intraindividual variability in psychosocial outcomes and physical activity behavior. Intensive longitudinal designs and EMA methods have exploded in recent years especially in the areas of affective outcomes, symptom reporting, or cognitive functioning[139–141]. Not only have these investigations helped characterize individual differences in how affect, symptoms, or cognition change over time or

in response to interventions, but they have highlighted the importance that context and the person-by-context interactions play in determining health and wellbeing outcomes. In spite of using EMA methods in studies presented here, the design (with random daily assessments) did not lend itself ideally to more thorough investigation of the role that context plays in the (in)activity-wellbeing relationship. Event- or context-congintent signals (as opposed to random or symptom triggered) should be incorporated in future EMA studies to better evaluate the role of context. Future work should also utilize EMA-derived data to test suppositions of existing theories, most of which have been tested using between-person approaches only. For example, the transactional theory of stress and coping views coping as a process best studied in the moment and as it unfolds over time and across differing situations[142,143]. By applying EMA methods one can accomplish assessment of within-subject factors and the intraindividual variability in experiences and behaviors as they unfold in real-life settings and over time, allowing for testing of casual pathways hypothesizing the links between behaviors, coping, and stress. Similarly, the suppositions of theories of health behavior such as the social cognitive theory or theory of planned behavior could be tested in a more rigorous fashion applying intensive data methods. That is, one could test in a dynamic fashion whether changes in cognitions (e.g., self-efficacy, intentions) drive changes in behaviors and whether the underlying processes operate as hypothesized by these theories. Such testing could lead to refinement of exising theories and their greater practical utility[144].

From a developmemtal, lifespan perspective it will be important to conduct longitudinal studies that could accomodate investigations of both short-term and long-term (between- and within-person) variability in outcomes such as measurement burst designs[145]. Acknowledging that development (and aging) is the result of multiple co-acting influences which are sensitive to context and thus inherently person-specific[138], person-oriented theories and single-subject designs should be incorporated into the study of menopause and wellbeing. In social psychology and behaviroal science more broadly, there is also an increasing awareness of the need to consider systems level approaches such as dynamical systems theories given that behavior and behavior change is nonlinear and involves interaction of multiple levels of influences across different timescales[146]. These trends are partially fueled by advancement in behavior tracking technologies that allow for passive, continuous, and intensive data capture. Approaches utilizing such data will require application of advanced statistical methods that span subject-specific data analysis methods, mixture modeling, multilevel structural equation modeling, or time-varying effect models.

From a practical standpoint, the research presented suggests that „one size fits all“ types of interventions will not be the most effective for enhancing wellbeing during the menopausal transition, especially in women who experience a range of menopausal symptoms. Given that 85% of women will experience symptoms at some point during their menopausal transition[70], intervention strategies that are tailored to the needs of different women are called for. These strategies should also include multiple components to maximize both fitness effects and symptom management. Any such intervention should be based on a good understanding of the factors involved in symptom experiences, the casual pathways linking physical activity behavior, symptoms and wellbeing, as well as the context within which it is to be applied. To this end, future research must incorporate methods of intensive monitoring in everyday life to accurately evaluate symptoms experiences across different contexts and over time, and to allow for intervening in the moment, in the best way possible, and at the right time.

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