

Cardiovascular mechanisms of the occupational physical activity health paradox: 24-hour physical activity, blood pressure, and heart rate in active workers

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Recent evidence suggests an occupational physical activity (OPA) health paradox where OPA is associated with adverse cardiovascular health. Physiological mechanisms to explain this paradox have not been studied.

METHODS: Nineteen male workers (68% White/Caucasian, age=46.6 years, BMI=27.9 kg/m²) with high reported OPA completed a submaximal exercise test and wore ambulatory activity (ActiGraph and activPAL) and cardiovascular (blood pressure (BP) and heart rate (HR)) monitors for 7days, including at least one workday and non-workday. Individuals recorded work stress levels, work-time, nonwork-time, and sleep times in a diary. Physical activity profiles were described and compared to aerobic physical activity and OPA recommendations. 24-hour cardiovascular load (HR, systolic and diastolic BP) and nocturnal HRV were compared on workdays vs. non-workdays using adjusted linear mixed models. Effect modification by fitness level was explored using interaction models. The effect of work-related stress was analyzed by comparing workdays with low and high stress to non-workdays.

RESULTS: Participants were significantly less sedentary and more active on workdays vs. non-workdays (all $p < 0.05$). While most participants met aerobic activity guidelines, OPA exceeded recommended intensity level and upright time limits. 24-hour HR and diastolic BP were significantly higher on workdays vs. non-workdays ($\beta = 5.4$ beats/min, $p < 0.001$ and $\beta = 2.7$ mmHg, $p = 0.019$, respectively) but systolic BP did not differ ($\beta = 2.0$ mmHg, $p = 0.317$). Nocturnal HRV

(low and high frequency power) was significantly lower on workdays vs. non-workdays ($\beta=-0.27$, $p=0.025$ and $\beta=-0.33$, $p=0.014$, respectively); other parameters (RMSSD, SDNN, LF/HF) were similar. Workday vs. non-workday cardiovascular load was not modified by fitness level (p -for-interactions >0.703). When stratified by stress level and compared to non-workdays, 24-hour HR was elevated on both low- ($\beta=4.7$ beats/min, $p<0.002$) and high-stress workdays ($\beta=5.4$ beats/min, $p<0.001$), 24-hour diastolic BP was only elevated on high-stress workdays ($\beta=4.4$ mmHg, $p=0.023$), and 24-hour systolic BP was never elevated ($p>0.05$).

CONCLUSIONS: Activity was higher and exceeded OPA recommendations on workdays versus non-workdays. Workdays were also associated with elevated 24-hour cardiovascular load and reduced HRV. Fitness did not modify this relationship, but high job stress seemed to exaggerate it. These results suggest high 24-hour cardiovascular load and job stress as potential mechanisms contributing to the OPA health paradox.

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1.0 Introduction

Leisure time physical activity (LTPA) is widely known to have many cardiovascular health promoting effects,³⁻⁶ while occupational physical activity (OPA) has been demonstrated to have opposing health effects.⁷⁻¹⁰ Specifically, moderate and high levels of self-reported OPA are associated with significantly increased risk for cardiovascular disease and all-cause mortality,¹¹ particularly in those with pre-existing hypertension or coronary heart disease¹² or those with low cardiorespiratory fitness.⁸ The conflicting health effects of LTPA and OPA has been labeled the “occupational physical activity health paradox” (OPA health paradox).¹³

A potential explanation for the OPA health paradox is that jobs with high OPA have different occupational responsibilities and activity levels that may adversely affect cardiovascular health. Indeed, occupation is known to explain much of the overall variation in physical activity accumulation.^{14,15} While the population average of the energy expenditure of work activities has decreased over the past 50 years,² Tudor-Locke, et al., reported that approximately 21% of the United States (U.S.) population still remains in occupations requiring moderate or vigorous intensity activities regularly.¹⁶ Steeves, et al., recently used 2005-6 National Health and Nutrition Examination Survey (NHANES) data to report great variation in total uniaxial accelerometry counts per minute (cpm) in high-activity occupations (>400 cpm; e.g., building and grounds maintenance, farming, fishing, forestry, and food preparation) compared to low-activity occupations (<300 cpm; e.g., community and social services, legal, and office administration support).¹⁵ Quinn, et al., also demonstrated similar findings, concluding that occupational classification and employment status is a significant determinant of physical activity and sedentary behavior profile using data from the Coronary Artery Risk Development in Young Adults

(CARDIA) study.¹⁷ Overall, it is known that occupation is a strong determinant of activity patterns across individuals. Although the OPA health paradox has been attributed to these differences in activity patterns, gaps in the literature remain explaining the health implications of OPA specifically.

Epidemiological research suggests the cardiovascular health implications are different across occupational populations with varying amounts and patterns of OPA and LTPA. Specifically, those with high OPA have increased all-cause mortality risk and those with high LTPA have decreased mortality risk.^{7,18} Furthermore, the increased mortality risk associated with high OPA seems to be attenuated by high amounts of LTPA.⁷ While these relationships have been identified, the literature in this field is greatly limited. Almost all studies use self-reported activity data collected at a single time point, are observational and thus likely affected by biases such as uncontrolled confounding (e.g., socioeconomic status) and selection (e.g., the healthy worker effect, i.e., working individuals are healthier than those who cannot work), are restricted to mainly male samples, and do not study direct mechanisms explaining the OPA health paradox. Even still, the consistency of observational findings may justify a re-evaluation of physical activity recommendations in the presence of high-volume OPA accumulation. Moreover, occupational health and safety regulations regarding allowable working times and intensities for highly active occupations may need to consider the potentially detrimental effects of high OPA accumulation on cardiovascular health.

Prior to recommending changes to physical activity recommendations or OPA regulations and standards, better understanding of the mechanisms that explain the OPA health paradox in workers with high accumulated OPA is needed. Holtermann recently proposed six hypotheses to explain this paradox: 1) OPA does not improve cardiorespiratory fitness because it is of too low

intensity or of too long duration;¹⁹ 2) OPA may increase 24-hour heart rate (HR);²⁰ 3) OPA may increase 24-hour blood pressure (BP); 4) OPA does not allow for adequate recovery time;²¹ 5) workers have limited autonomy over the OPA performed; and 6) OPA increases inflammation.^{13,22} While acute bouts of moderate-to-vigorous intensity physical activity (MVPA) increase HR and BP during exercise (i.e., LTPA), the resulting 24-hour cardiovascular load is decreased due to a compensatory hypotensive response.²³ However, when considering the typical pattern of OPA, it is hypothesized that low-intensity activity for a long duration with little recovery results in elevated 24-hour HR and BP, which are known to be positively related to all-cause mortality.²⁰ Furthermore, autonomic dysfunction, which is closely related to poor cardiovascular regulation, has been proposed to occur as a result of high OPA and may be a pathway by which OPA elevates cardiovascular risk.²⁴ Lastly, low task autonomy and high psychological job stress are commonly found in occupational settings and can result in few recovery breaks or days of rest, negatively impacting cardiovascular health.¹³ These effects have also been found to potentially differ across individuals with high versus low fitness levels.⁸ However, these hypothesized deleterious cardiovascular effects of increased 24-hour HR and BP and autonomic dysfunction resulting from high OPA remain speculative. Furthermore, effect modification of these proposed mechanisms by fitness level or job stress are largely unexplored in studies designed for this purpose.

The current study aims to address this knowledge gap using an innovative within-subject design and best practice assessments of objective physical activity, sedentary behavior, and field-based cardiovascular testing of HR, BP, and autonomic function. The intention of this study is to expand understanding of the biological plausibility behind the OPA health paradox with the long-term goal to inform activity guidelines or occupational regulations for individuals achieving high levels of OPA.^{7,8,10,13,24,25}

1.1 Specific Aims

1.1.1 Specific Aim I

To characterize activity patterns in individuals with high reported OPA levels and to describe whether the observed activity levels are consistent with current physical activity and occupational sedentary behavior recommendations on both workdays and non-workdays.

1.1.2 Specific Aim II

To compare within-subject differences in 24-hour ambulatory HR, ambulatory BP, and nocturnal HRV during workdays versus non-workdays among individuals with highly active occupations.

1.1.3 Specific Aim III

To examine potential effect modification of the previous relationships by cardiorespiratory fitness level and subjective perceptions of job stress.

2.0 Review of the Literature

2.1 Current Physical Activity Recommendations and Health

The 2018 Physical Activity Guidelines for Americans recommend that all adults achieve 150 minutes of moderate intensity, 75 minutes of vigorous intensity, or an equivalent combination of aerobic physical activity per week accumulated in any bout duration to obtain substantial health benefits.^{4,26-28} (Table 1) Moderate intensity activity is defined as any activity that requires 3.0 to <6.0 metabolic equivalents (METs) to complete (e.g., walking 2.5 – 4 mph) while vigorous activity is anything of intensity 6.0 METs or higher (e.g., running, jogging).⁴ The physical activity guidelines also recommend that adults perform muscle-strengthening activity on 2 or more days per week.^{4,26}

Table 1. Current physical activity guidelines for adult Americans	
Aerobic	Muscle-strengthening
150-minutes of moderate-intensity, 75minutes of vigorous-intensity, or an equivalent combination per week* 	At least 2 days per week of muscle strengthening activities for all major muscle groups 
*Any bout duration counts towards this goal	

These guidelines are substantiated by a large accumulation of evidence demonstrating the overall and cardiovascular health benefits of acute and regular MVPA. Established benefits of regular aerobic physical activity include lower risk of all-cause mortality,²⁹⁻³² lower risk of cardiovascular mortality,^{29,32,33} lower incidence of hypertension,^{32,34-36} and lower incidence of type 2 diabetes.^{32,37-39} Participation in high amounts of physical activity has also been related to lower

risk of several types of cancer including esophageal, liver, lung, endometrial, myeloma, colon, head and neck, bladder, and breast cancers.^{32,40} Benefits have also been described in terms of brain and emotional health with those who are physically active showing reduced risk for dementia,^{32,41-44} improved cognitive function,^{32,44,45} improved sleep,^{32,46} and improved quality of life.^{32,47,48}

Of particular interest for the current study are the cardiovascular health benefits of physical activity. During the development of the 2008 Physical Activity Guidelines for Americans, a review of the existing literature examined 30 prospective cohort studies for the relationship between self-reported physical activity and coronary heart disease. That review, which included studies from around the world and over 400,000 participants, concluded that the most active men and women had a 30-35% reduction in risk for coronary heart disease compared to the least active individuals.²⁶ A similar magnitude of risk reduction was found in a review of physical activity and cardiovascular disease, including 20 prospective cohort studies, in the same Guidelines report.²⁶ Since that review, studies have continued to demonstrate an inverse, dose-response relationship between physical activity participation and coronary heart disease or cardiovascular disease risk.⁴⁹ Moreover, reduction in cardiovascular health markers with higher objectively-measured physical activity has been observed in large population studies such as the Framingham Heart Study⁵⁰ and NHANES.⁵¹

While the cardiovascular health benefits of physical activity have been well established, explanation of mechanisms driving this relationship become increasingly pertinent to shed light on potential reasons for differential effects by activity domain (i.e., LTPA vs. OPA). In a prospective cohort study consisting of a large sample (n=27,055) of women, the cardiovascular benefits of physical activity were mediated by known risk factors such as inflammatory factors and BP.⁵² Another prospective cohort study of men and women also found that reduced risk for

cardiovascular events in physically active adults was attributed to improved metabolic (e.g., body mass index, cholesterol, diagnosed diabetes) and inflammatory risk factors.⁵³ Furthermore, it has been proposed that improved cardiorespiratory fitness, via increases in physical activity, may contribute significantly to reduction in cardiovascular and all-cause mortality, justifying the recommendation of MVPA participation for cardiovascular health benefits.⁵⁴

Though the cardiovascular health benefits of aerobic physical activity are well researched, much of the research examining associations between physical activity and health outcomes has been limited to self-reported moderate- to vigorous-intensity LTPA.⁵⁵⁻⁵⁷ Recently, however, the use of objective physical activity measurement such as accelerometry has allowed for feasible assessment of activity across the entire day in one's free-living environment. This expanded physical activity assessment includes other types of activity, like OPA, and importantly can capture activity that is difficult to measure by self-report such as sporadic MVPA and light-intensity physical activity. As a result, light physical activity, defined as any activity between 1.5 and <3.0 METs^{4,58}, has been able to be examined in relation to health outcomes. These recent data suggest that even light physical activity may reduce cardiovascular disease risk, independent of MVPA levels.^{32,59} A recent systematic review of literature describing the health benefits of light-intensity activity analyzed 37 cross-sectional and three longitudinal studies to conclude that light-intensity activity is associated with improvements in obesity, lipid and glucose metabolism, and mortality.⁶⁰ In one cross-sectional analysis of 4,832 older women from the Objective Physical Activity and Cardiovascular Health (OPACH) study, higher light physical activity was associated with a lower likelihood of having cardiovascular disease risk factors.⁵⁹ Another study, using 2003-2006 NHANES data and a longitudinal follow-up in 2011 of 5,575 adults, found an inverse association between objectively-measured light-intensity activity and all-cause mortality risk.⁶¹ Yet further

research needs to be conducted to better understand the relationship between light intensity activity and health outcomes, including identifying the optimal pattern or dose as well as the potential mechanisms of light-intensity activity on cardiovascular health.⁵⁹ This is especially relevant in the context of fitness, as previous research has demonstrated that sporadic physical activity is associated with cardiorespiratory fitness only when it is of moderate or vigorous intensity, but not light.⁶²

Despite the well-established and widely publicized health benefits of MVPA, participation in physical activity in the United States remains quite low. Based on the 2016 National Health Interview Survey (NHIS) data, 50.7% of adults in the United States reported meeting the aerobic physical activity guidelines.⁶³ Furthermore, only 23.2% of individuals reported meeting both aerobic and muscle strengthening guidelines.⁶³ When aerobic physical activity was measured objectively using 2005-2006 NHANES accelerometry data rather than self-reported data, the prevalence of U.S. adults meeting aerobic guidelines is estimated to be only 9.6% when using the ≥ 10 minute bout criterion for MVPA accumulation from the 2008 Physical Activity Guidelines.⁶⁴ More recent analyses of the same NHANES data, but allowing for physical activity to be accumulated in 1-minute bouts (consistent with the 2018 Physical Activity Guidelines), suggest a 44.8% of adults meet guidelines.⁶⁵ Regardless of the bout length requirement used, it is also clear that there are significant differences in physical activity levels by age, gender, and race/ethnicity. The 2016 NHIS data demonstrate that men reported more LTPA than women and that activity decreased in both genders with increasing age.⁶⁶ Lastly, non-Hispanic white adults met aerobic physical activity guidelines more often (51.3%) than both non-Hispanic blacks (38.7%) and Hispanic/Latino adults (41.3%).⁶⁶

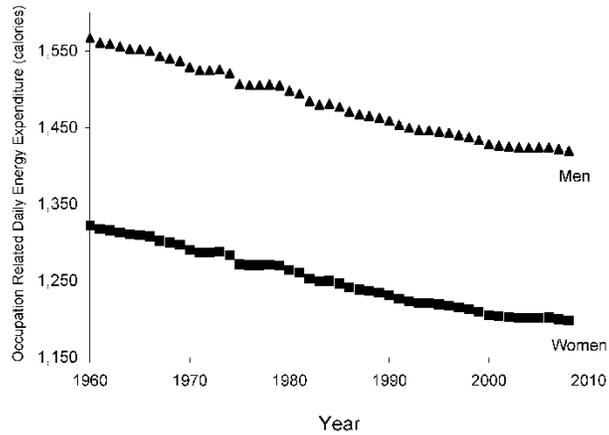


Figure 1. Occupational related energy expenditure in the United States over 5 decades
Figure from Church et al.²

While current estimates show that many Americans do not meet physical activity guidelines, these estimates also suggest that the percentage of Americans meeting aerobic and muscle strengthening guidelines has been increasing gradually since the late 1990s.⁶³ At the same time, from time-use data, daily energy expenditure has decreased by 100 calories per day over the last five decades in both American men and women (Figure 1).² It is hypothesized that this decrease in energy expenditure can be explained primarily by decreases in occupational and travel physical activity in the population.² Collectively, activity patterns seem to be changing in both LTPA and OPA, and more research is warranted to describe and understand the health implications of these changes.

In summary, the U.S. has recommended MVPA for all adult Americans based on an abundance of high-quality evidence that demonstrates the health benefits. Even still, despite the strong evidence of the overall and cardiovascular health benefits of physical activity and the clear recommendations by large governmental organizations, only about one-half of U.S. adults report achieving the recommended levels of physical activity with even fewer reaching the recommendations when measured objectively.^{32,65} Yet, changing trends in physical activity and

the understudied health effects of light-intensity activity highlight the need for more research regarding optimal physical activity patterns for cardiovascular health.

2.2 Current Sedentary Behavior Recommendations and Health

Sedentary behavior has recently been defined as any low-intensity waking behavior with an energy expenditure ≤ 1.5 metabolic equivalents (METs) while in a sitting, reclining, or lying posture.⁶⁷ The 2018 Physical Activity Guidelines for Americans were the first U.S. guidelines to include recommendations regarding sedentary behavior and health. The guidelines state that “Adults should move more and sit less throughout the day.”²⁸ Furthermore, the Physical Activity Guidelines Committee Report concluded that sedentary time seems to be more detrimental to health in those with low levels of aerobic physical activity.³² The Australian physical activity guidelines provide a bit more specificity by stating that adults should “minimize the amount of time spent in prolonged sitting” and “break up long periods of sitting as often as possible.”⁶⁸

Previous literature has suggested that the modern workplace is becoming increasingly sedentary with approximately 20% of Americans holding predominantly sedentary occupations in 2008.^{2,69} In response to this population trend, an international expert panel of researchers recently convened to produce a statement regarding recommendations around workplace sedentary behavior, commissioned by Public Health England.⁵⁸ The expert statement recommended that individuals with predominantly desk-based occupations should complete at least two and up to four hours per day of standing and light activity in an eight hour workday.⁵⁸ In addition, they recommended that seated-based work should be regularly broken up with work in a standing

posture or short activity breaks.⁵⁸ All of these recommendations are substantiated by a growing body of literature regarding the impact of sedentary behavior on health.⁷⁰⁻⁷²

Prolonged sedentary behavior has consistently been found to be related to increased risk for all-cause and cardiovascular disease mortality, with the 2018 Physical Activity Guidelines Committee Report rating both of these conclusions as having a ‘strong’ evidence base with several cohort studies and systematic reviews.³² Biswas, et al., produced an influential systematic review and meta-analysis on this topic in 2015 by analyzing 13 prospective cohort studies to estimate a hazard ratio of 1.24 for all-cause mortality for high compared to low sedentary time and a hazard ratio of 1.18 for cardiovascular disease mortality.⁷⁰ Most recently in 2016, Ekelund, et al., demonstrated a dose-response relationship between sedentary behavior and all-cause and cardiovascular disease mortality risk in a harmonized data analysis of >1 million people.⁷² While this evidence is quite compelling, it is important to understand the limitations of this literature. Most notably, sedentary behavior has been predominantly measured via self-report measures such as reported television viewing time or sedentary behavior recall questionnaires, which are well known to introduce bias.⁷³ However, the introduction of accelerometry measurement to the NHANES surveillance protocol has allowed for objective analysis of sedentary time and mortality rates. Of the 11 studies completed on this topic using NHANES accelerometer data, eight concluded that sedentary behavior and mortality have a significant direct association.^{31,32,74-80} Even still, it is important to note that accelerometer-measured sedentary behavior is not the best practice assessment method for sedentary behavior. Sedentary behavior measured using recently developed posture-based activity monitors, such as the activPAL (PAL Technologies, Glasgow, Scotland), can distinguish between seated and standing postures and therefore can measure sedentary behavior more precisely. However, studies using posture-based monitoring are typically not large

enough or without sufficient follow-up to evaluate the influence of this better measure of sedentary behavior on clinical outcomes, including mortality. Thus, while the available evidence supports an association between sedentary behavior and mortality, caution should still be taken when interpreting these results.⁸¹⁻⁸³

While determining whether excessive sedentary behavior is a risk factor for health outcomes is important for purposes of clinical and population recommendations, it is also important to consider potential physiological mechanisms that could explain these relationships to provide a foundation for intervention strategies and population recommendations. Several physiological mechanisms have been proposed to explain the negative cardiovascular effect of excessive sedentary behavior with varying levels of supporting evidence. The research literature has described deep vein thrombosis resulting from prolonged periods of sitting since the 1950's during activities such as TV viewing, airplane riding, and computer use.⁸⁴⁻⁸⁷ Some information can also be taken from bed rest studies showing decrements in cardiac function, fluid balance, and lipid dysregulation following extended bed rest.^{88,89} However, caution must be taken in translating these results to the effects of sitting because of the differences in posture and duration of time in the postures.^{88,89}

In a 2008 review, Williams, et al., described the potential mechanisms driving the observed relationships between reported TV viewing and several health outcomes.⁹⁰ While no randomized trials were cited to support their conclusions, Williams and colleagues connected TV viewing to decrements in weight, energy intake, and physical activity and concluded that TV viewing may result in poor health outcomes due to increased weight and a positive energy balance.⁹⁰ This notion is consistent with the known downstream effects of body fatness, including vascular and metabolic dysfunction and, long-term, cardiovascular disease.⁹¹ Decreases in cardiac output and stroke

volume as well as increased aortic stiffness resulting from prolonged sedentary time have also been proposed as mechanisms linking prolonged sedentary time and reduced cardiovascular health.^{92,93}

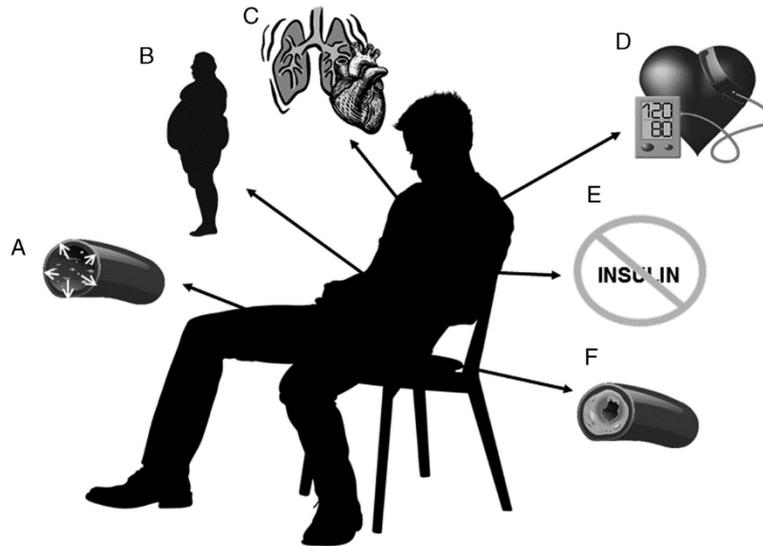


Figure 2. Schematic depicting the effect of sedentary behavior on cardiovascular disease risk factors

A. Vascular structure and function: stiffness and intima-media thickness increase; endothelial function decreases. B. Body mass index increases. C. Cardiorespiratory fitness decreases. D. Blood pressure increases. E. Insulin resistance increases. F. Blood lipids increase.

Figure from Carter, et al., 2017¹

More recent and targeted literature focusing on sedentary behavior has proposed that prolonged sedentary behavior may be related to alterations in lipid metabolism, cardiac function, and glucose homeostasis which could, in turn, be detrimental to cardiovascular health over time (Figure 2).^{89,92} It was also proposed in a recent review that sedentary behavior may result in vascular dysfunction due to downregulation of shear rate and blood flow during sedentary time.¹ Furthermore, a recent review by Dempsey, et al., discussed the effects of sedentary time on BP and the potential mechanisms that may underscore this relationship.⁹⁴ The primary mechanisms driving the relationship between sedentary time and BP are thought to be vascular (via decreased blood flow), autonomic (via increased sympathetic nervous activity), and metabolic (via decreased

muscular activity).⁹⁴ More specifically, Dempsey outlined the vascular mechanisms, describing that during prolonged sedentary time there is low metabolic demand in the muscles which leads to low levels of vasodilator metabolites, constriction of the precapillary arterioles, and precapillary sphincter closure. As a result, blood is shunted through the metarterioles which leads to a reduced pressure gradient between the capillaries and the associated muscular arteries causing lower blood flow, vasoconstriction, and increased peripheral BP.⁹⁴ It is important to note that the acute effects of sedentary time on BP described are preliminarily established; however, the effects of long-term changes in sedentary time on BP are less clear.⁹⁴

Individualized sedentary behavior intervention (1-12 weeks) has been shown effective in reducing sedentary behavior by about 0.4-1.2 hours per day.⁹⁵⁻⁹⁸ However, only a few small sedentary intervention studies have demonstrated reductions in BP^{97,99,100} and postprandial glucose and insulin responses.^{101,102} Additional larger experimental trials must continue to rigorously evaluate the chronic effects of long-term sedentary behavior reduction on health outcomes.

2.3 Occupational Physical Activity and Cardiometabolic Risk and Mortality

While it is known that being physically active and potentially being less sedentary has beneficial cardiovascular health effects, a growing body of literature suggests that this beneficial association may be different for OPA.¹⁸ Although the energy expenditure of work activities has decreased overall in the past 50 years², approximately 21% of the United States population has occupations requiring regular activity.¹⁶ With so many people still accumulating a high amount of OPA, it is important to study whether and how accumulation of OPA may not have the same health-enhancing effects as LTPA; indeed, the existing evidence suggests high levels of OPA may

actually be harmful.^{18,103} This seemingly paradoxical effect is coined the ‘OPA health paradox’.

The OPA health paradox was first described in its current name by Andreas Holtermann in 2012¹⁰ and has since gained attention from occupational health scientists with increasingly supportive evidence from observational studies.⁸ In the 2010 publication from the Copenhagen Male Study with 30-year follow-up examination of 5,249 men, high OPA demands were associated with increased risk for all-cause and cardiovascular mortality while LTPA was associated with reduced risk in the same sample.⁸ The increased risk for high OPA was shown to be especially robust among those with low fitness levels.⁸ Additional support came from the prospective Kuopio Ischemic Heart Disease (KIHD) Risk Factor Study, which assessed 20-year all-cause mortality and coronary heart disease mortality in relation to OPA in a sample of 1,891 Finnish men.¹⁰⁴ The study concluded that a 10% increase in relative aerobic workload of OPA was associated with a 13% increase in risk for all-cause mortality and a 28% increase in risk for coronary heart disease mortality, even after extensive adjustment for 19 confounders.¹⁰⁴ Since that article, several other observational studies, including some with long-term follow-up, have demonstrated similar associations.^{8,10,24} However, several other studies have found opposing results, concluding that OPA reduces the risk for all-cause mortality,^{105,106} cardiovascular mortality,^{9,107} and coronary heart disease.¹⁰⁸ A 2018 meta-analysis and systematic review of 17 studies and 193,696 participants by Coenen, et al., concluded that men with high levels of OPA had an 18% increased risk for early mortality as compared to those with low OPA (HR=1.18; 95% CI 1.05 -1.34).¹⁸ Non-significant but opposing results were found in women (HR=0.90; 95% CI 0.80-1.01) (Figure 3).¹⁸ Though these differing effects reduce coherence of the observed effect, the differential effects found by gender may be explained by differences in perceived physical efforts in OPA across genders as OPA has traditionally been assessed using self-reported measures.¹⁸ Furthermore, men and women

may have differing socioeconomic or lifestyle factors associated with their relative reported OPA levels.¹⁸ Finally, it has been previously shown that men and women respond differently to cardiovascular risk factors¹⁰⁹ and physical activity,¹¹⁰ which could explain the differential effects of OPA and mortality risk.¹⁸

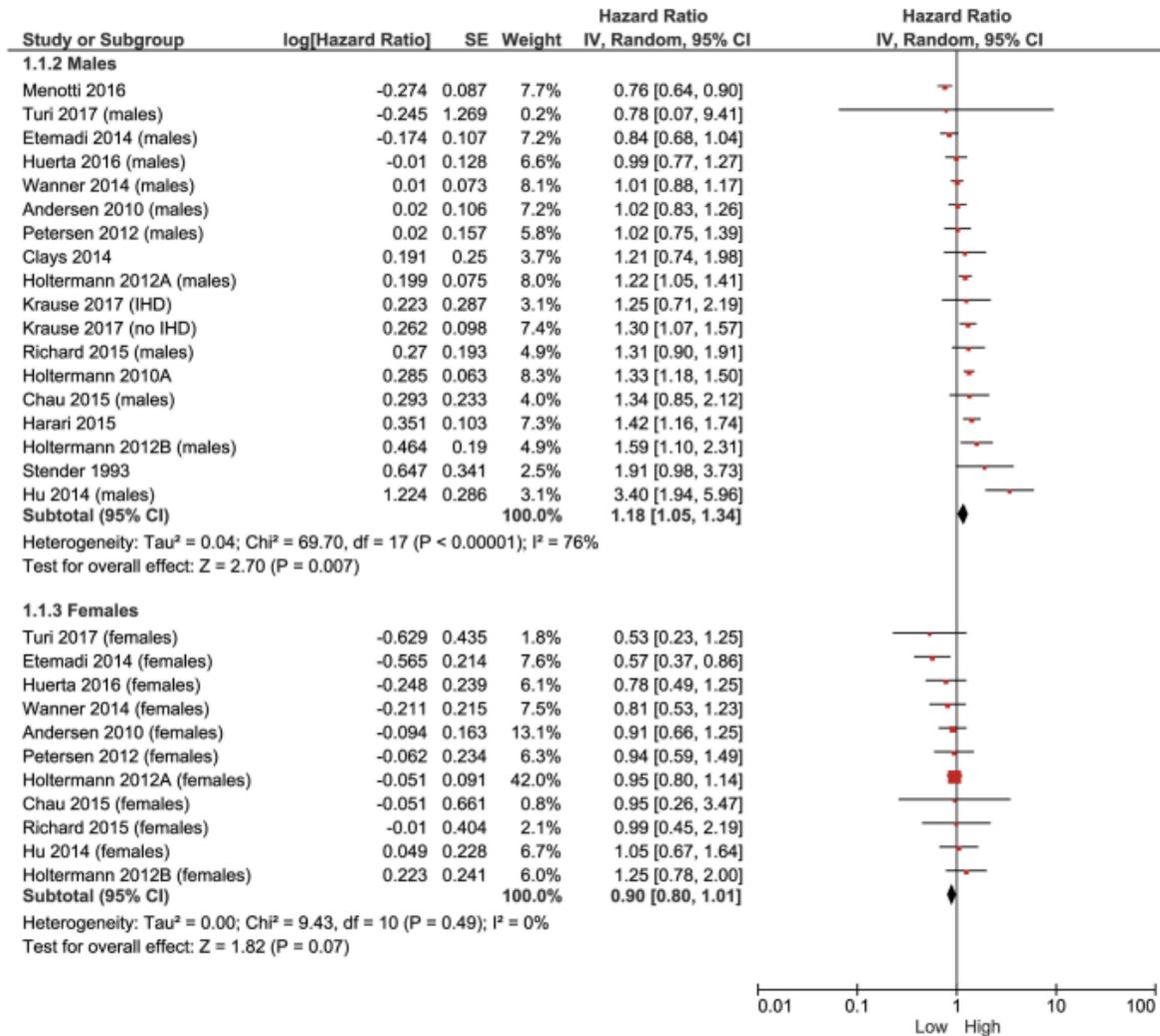


Figure 3. Forest plot of the effect of high compared with low levels of occupational physical activity on all-cause mortality, based on 17 studies with 193,696 participants

Figure from Coenen, et al.¹⁸

Even with the balance of prospective evidence suggesting the presence of the OPA health paradox (that OPA is directly associated with cardiovascular disease and mortality), at least in men, limitations of this literature exist. Most significantly, the measurement of OPA has been

almost exclusively self-reported. While self-report measurement of OPA may provide detailed information regarding specific work tasks, it is likely that reporting is subject to recall or reporting bias.¹¹¹⁻¹¹³ Additionally, it is important to consider that self-reported task intensity is likely to be influenced significantly by the individual's fitness level and familiarization with the task. This potential association between lower fitness/poorer health and increased reporting of task intensity could introduce positive confounding by indication. Measurement of OPA using objective methods such as accelerometry with standard intensity assessment and the ability to distinguish whether activity was accumulated during working or leisure time would greatly improve the quality of the findings previously described. Also, even in prospective studies, measurement of OPA exposure has typically been done only once (i.e., at the beginning of the cohort study), which may introduce exposure measurement error as it does not account for potential changes in occupations or occupational tasks throughout the follow-up periods.

Furthermore, the current literature is limited potentially by the “healthy worker effect,”^{10,18,114} a well-documented finding that individuals who are currently working tend to be healthier, in general, compared to those who are not working.¹¹⁴ This phenomenon is due to the fact that unhealthy people may be unable to work because of their illness or dysfunction.¹¹⁴ However, as opposed to confounding due to self-report that may produce bias in the direction of a positive relationship between OPA and mortality, the healthy worker effect would likely result in more conservative estimates in the OPA health paradox. The healthy worker effect may be especially important for jobs with high levels of OPA and is a salient challenge when designing observational research studies that attempt to compare individuals with high and low OPA.

Lastly, the potential for other uncontrolled confounding may be driving the inverse relationships seen between OPA and health from factors such as socioeconomic status, smoking,

stress, and diet.^{18,115} While most studies statistically account for many potential confounders, it is possible that uncontrolled confounding is still present within the fitted models. This may be due to additional confounders being present in the relationship that are not measured or due to difficulty in measurement (e.g., diet) or inherent measurement error when using discrete classifications (e.g., income level) to statistically model the effects of complex social constructs (e.g., institutionalized inequality). Some creative research has used restriction to control some of this confounding; for example, one study included only blue collar men and demonstrated opposing effects of LTPA and OPA within this more homogenous cohort.²⁴ This suggests that the observed relationships may not be due to uncontrolled confounding alone, though rigorously designed experimental evidence is still needed. It is also worth noting that the strong associations between LTPA and health are not immune to similar uncontrolled confounding from healthy behaviors.¹¹⁶

Thus, while the prospective nature of the current data describing the OPA health paradox is strong, future research in this area must work to address these outlined limitations. Objective measurement must be used in conjunction with self-reported measurement of OPA to account for reporting and recall biases as well as confounding by indication. Future work should also use experimental designs and examine potential mechanisms to substantiate the causal argument that OPA is a risk factor for cardiovascular and all-cause mortality in men.

2.4 Proposed Mechanisms to Explain the Occupational Physical Activity Health Paradox

While high OPA has been related to increased cardiovascular disease and all-cause mortality risk in most studies, mechanisms driving these relationships are still largely unknown. Several physiological mechanisms have been proposed to explain the observational research on

the OPA health paradox. However, these are largely speculative and untested.¹³ In a 2018 editorial, Holtermann outlined several potential mechanisms and argued the need for high-quality research to test these hypotheses.¹³ Such evidence supporting the biological plausibility of this OPA health paradox would strengthen the causal argument and inform potential strategies for prevention or mitigation of the health risks of OPA.

Holtermann proposed six potential mechanisms to explain the OPA health paradox. 1) OPA is too low of intensity or too long of duration to change cardiovascular fitness; 2) OPA elevates 24-hr HR; 3) OPA elevates 24-hr BP; 4) OPA is often performed with insufficient recovery; 5) OPA is often performed with low worker control or autonomy; and 6) OPA increases inflammation. These hypotheses remain largely untested; however, some studies from other fields (e.g., athletic performance, general cardiovascular health, PA and inflammation, job stress) may provide some insight. These proposed mechanisms will be discussed below as four overarching mechanisms: 1) OPA is of too low-intensity to result in increased cardiorespiratory fitness; 2) OPA increases 24-hour cardiovascular load (HR and BP); 3) OPA may cause increased inflammation; and 4) OPA is often performed with low worker autonomy resulting in increased job stress.

The first proposed mechanism to explain the OPA health paradox is that OPA is not intense enough to improve cardiorespiratory fitness.^{13,25} One of the reasons why LTPA improves cardiovascular health is that leisure-time activity is often of moderate to vigorous intensity. This higher intensity exposure induces cardiovascular adaptations that lead to chronic increases in cardiorespiratory fitness and cardiovascular health. However, OPA may not be intense enough to produce these fitness adaptations because it is often of lower intensity. One study previously supported this hypothesis by characterizing the activity levels of hospital cleaners.²⁵ The cleaners had a very high volume of activity ($\geq 20,000$ steps per day on average); however, their fitness levels

were only classified as average to low (34 mlO₂/kg/min).²⁵ Additionally, the same group of cleaners exhibited cardiovascular risk factors despite their high level of activity: >50% had a BMI>25.0 kg/m² and >50% had BP >120 mmHg systolic or >80 mmHg diastolic.²⁵ While this study provides some useful preliminary results, the methods had several limitations that must be addressed. First, physical activity was measured with a pedometer which only counted the total steps throughout the day. This measurement approach prevented the ability to differentiate between OPA and LTPA and, most importantly, classification of different intensities of activity. Furthermore, this analysis was limited by its cross-sectional design and lack of comparison group. Therefore, future investigations should characterize the activity patterns of workers with high OPA using gold standard, objective measurement of sedentary behavior and physical activity.

Second, it has been proposed that the increase in cardiovascular risk from OPA may be due to increases in overall cardiovascular workload throughout the day, typically measured as 24-hour HR and BP^{13,25}. It is well known that higher 24-hour BP and 24-hour HR are associated with increased cardiovascular and all-cause mortality because it is a strong indicator of the stress the cardiovascular system is experiencing on average throughout the whole day.¹¹⁷⁻¹¹⁹ While aerobic LTPA leads to acute increases in HR and BP during the activity, the cardiovascular load then decreases for up to 24 hours following the exercise.¹²⁰ Therefore, participation in LTPA is known to engender a net reduction in 24-hour HR and BP due to a well-established hypotensive response following exercise.¹²⁰ OPA is typically of longer duration and of lower intensity than LTPA. This long duration, low-intensity activity accumulates a lesser but more sustained increase in HR and BP load. However, this exposure is hypothesized to be of insufficient intensity to result in the compensatory, post-exercise hypotensive response. This is further coupled with insufficient recovery time (<24 hours), preventing the body from achieving the same net benefit it does with

acute, shorter bout, and more intense LTPA. As a result, it has been hypothesized that 24-hour BP and 24-hour HR would be increased with high amounts of OPA, thus increasing cardiovascular workload and long-term cardiovascular risk level.¹³ Indeed, 24-hour HR was found to be elevated with greater OPA in one previous study of workers; however, this study was limited by self-reported OPA measurements and lacked a comparison group or condition.²⁵

Table 2. Associations between self-reported occupational/leisure time physical activity and systolic ambulatory blood pressure (mmHg) (N=182)

Physical activity groups	crude mean SBP at work (SD)	<i>P</i> *	crude mean SBP at home (SD)	<i>P</i> *
Summary measure of OPA		0.06		0.11
High	136.4 (13.8)		133.7 (12.3)	
Low	130.0 (11.0)		128.6 (10.1)	
High physical effort at work		0.12		0.17
High	134.4 (14.0)		132.2 (12.6)	
Low	130.2 (10.7)		128.7 (9.8)	
Lifting heavy loads at work		<0.05		<0.05
High	135.6 (14.6)		133.5 (12.6)	
Low	130.3 (10.8)		128.7 (10.0)	
Leisure time physical activity		0.29		0.22
High	130.4 (11.5)		128.4 (11.1)	
Low	131.4 (11.8)		129.8 (10.6)	

* Adjusted for gender, age, BMI, smoking, job stress and usual level of leisure time physical activity.
Table from Clays, et al., 2012¹²¹

In another study, 24-hour BP was found to be higher in those who reported a higher amount of lifting heavy loads at work, though 24-hour BP was not different when compared across objective measures of activity or overall self-reported OPA (Table 2).¹²¹ While these results are suggestive, the lack of a non-work comparison day or group limited the conclusions. Future work should build upon this research by using gold standard measurements of 24-hour workload (BP

and HR), objective physical activity assessment, and comparison of cardiovascular load on workdays versus non-workdays or to workers with low OPA.

Third, lack of job autonomy could result in poor recovery from OPA and increased inflammation, leading to deterioration of cardiovascular health. It has been demonstrated previously that chronic inflammation contributes to increased arterial BP.^{122,123} Acute MVPA results in transient elevations in inflammation, yet training effects of chronic MVPA lower inflammation over time.¹²⁴ This difference between acute and chronic effects is explained by physiological adaptations limited to regular exercise such as decreased fat mass (e.g., decreased release of adipokines), increased production of anti-inflammatory cytokines, and reduced expression of toll-like receptors.¹²⁵ Thus, it is imperative that an individual recovers properly following an acute bout of exercise to allow inflammation to return to normal levels.¹²⁴ Insufficient recovery may result in increased inflammation levels over time.¹²⁴ This notion is especially relevant in the context of OPSA, as proper recovery is not always possible when work is required day after day. It is hypothesized that the lack of self-regulation over occupational tasks may not allow for proper recovery.¹³ Also possible is that light physical activity may not produce chronic, beneficial training adaptations since light physical activity may not acutely increase inflammation to sufficient levels for adaptation as seen following MVPA.¹²⁴ Therefore, future research must examine this hypothesis specifically.

Fourth, and related to the above, it has been proposed that OPA is performed with low worker autonomy resulting in lack of recovery and potentially increased stress levels during work hours, further burdening the cardiovascular system. It is possible that low job autonomy increases worker stress and job stress, potentially increasing cardiovascular strain. Job stress is defined as an imbalance between job demand and reward or high overcommitment.¹²⁶ Previous research has

shown that workplace psychological stress increases 24-hour HR and 24-hour BP.¹²⁶ It is possible that cardiovascular strain from workplace stress could compound the effects on the cardiovascular strain from OPA. This could potentially explain why the context of OPA has a distinct effect of increasing cardiovascular risk while LTPA reduces cardiovascular risk. It is also possible that day-to-day variation in job stress levels or individual job task characteristics could play a role in the cardiovascular load of the worker. Therefore, subjective job stress levels when OPA is performed should be considered when examining cardiovascular mechanisms driving the OPA health paradox for potential effect modification.

The magnitude of cardiovascular risk from OPA is also thought to be different based on specific individual fitness levels. In a large observational study, Holtermann, et al., demonstrated that the cardiovascular and all-cause mortality risks associated with high OPA are stronger in those who have lower fitness levels.⁸ However, this effect modification is poorly understood. Because the same task is relatively easier to complete for a highly fit person as compared to a person with low fitness, it has been further hypothesized that those with higher fitness levels would be working at a lower intensity in the same job and that their 24-hour BP and HR load would be lower as a result. This reduced cardiovascular workload would, in theory, reduce the cardiovascular risk from chronic, high exposure to high OPA. Given the above hypothesis that low-intensity, long duration OPA may not help improve cardiorespiratory fitness levels, this potential phenomenon could inform recommendations for LTPA and developing or maintaining high cardiorespiratory fitness among individuals with high OPA levels.

In summary, accumulating epidemiological literature using prospective cohort designs suggests negative health effects of OPA on mortality outcomes, at least in men. While several mechanisms have been proposed to explain these relationships, few studies have investigated these

proposed mechanisms. Further studies should test the proposed mechanisms using controlled designs to limit bias and support the biological plausibility of the OPA health paradox.

2.5 Current Occupational Physical Activity Guidelines and Recommendations

Guidelines for OPA participation are sparse. Current OPA guidelines around sedentary time come from the previously mentioned consensus statement by Buckley, et al., which was published in 2015.⁵⁸ This statement recommended that people engage in 2-4 hours per day of standing or light activity per 8-hour workday.⁵⁸ That recommendation was built from literature around cardiometabolic disease risk and mortality; however, it was focused on reducing the amount of time spent sedentary in workers with predominantly sedentary jobs.⁵⁸ While this statement recommends an upper limit for light activity of 4 hours per day, this upper limit can be used as a starting point to limit OPA. However, this recommendation is targeted to desk workers so a generalization to non-desk workers should be made with caution, especially when translating the recommendation to those with contrastingly high levels of OPA.

Further research regarding limiting the duration of OPA is sparse. While it appears clear that the type and duration of activity that an individual performs during work is important to cardiovascular and overall health, few recommendations or guidelines address these concerns. Thus far, working time regulations have largely focused on pay, safety, and performance considerations rather than cardiovascular burden or long-term health. The 40-hour work week with increased over-time pay is an example of this. Furthermore, occupations with extreme environmental considerations (e.g., firefighters) or decreased performance over time (e.g., medical

workers) have occupation-specific allowable working time regulations such as 45 minutes allowed in a fire or limiting consecutive hours of work allowed in a hospital.¹²⁷

A few small studies have been conducted to provide a standard for maximal acceptable work time and load for a given number of work hours in a day. A study by Jorgensen, et al., from 1985 is consistently cited for its recommendations regarding maximal allowable working time.¹⁹ This study proposed a maximum workload of 30-35% VO_2max for an 8-hour workday.¹⁹ This was based on an eventual accumulation of lactic acid in the muscles which induces cardiovascular strain and increases HR during steady-state exercise.¹⁹ Therefore, the inflection in HR at the end of a work shift indicated that the work shift was of too high-intensity and should be reduced.¹⁹ Bink, et al., gave a similar recommendation in 1962, giving an upper workload of 33% VO_2max for an 8-hour workday based on the same criteria of HR inflection.¹²⁸ In 2002, Wu and Wang further investigated maximal workload recommendations using different workday durations.¹²⁹ These researchers gave a recommendation for maximum workloads of 28.5%, 31.0%, 34.0%, 43.5% of VO_2max for 12-, 10-, 8-, and 4-hour days, respectively.¹²⁹ Those workloads represent a heart rate reserve (HRR) of 16%, 20%, 24.5%, and 39% for the same respective durations.¹²⁹ All studies, however, noted that consideration must be given to any environmental or equipment factors that contribute to increased workload or cardiovascular stress such as heat, humidity, or use of personal protective equipment. Furthermore, these studies were limited by their small and very specific samples (e.g., Taiwanese young adults). They also were based on acute laboratory studies and did not relate chronic exposure of the recommended intensity of work to long-term outcomes such as cardiovascular or overall mortality as seen in the OPA health paradox literature.

Lastly, recommendations and regulations around object lifting have been implemented in the past. As outlined above, it has been proposed that limitations on lifting throughout a workday

may limit the cardiovascular strain through reduced isometric contractions.¹³ However, the intention of regulations on this type of activity are centered around preserving musculoskeletal health and limiting worker back pain, not reducing cardiovascular health risks.¹³⁰ The International Organization for Standardization (ISO) provides such regulations around occupational safety and health. The ISO standard number 11228 gives recommendations for lifting based on object weight and duration of activity (e.g., for durations of less than 1 hour, you can lift a 10 kg object at a rate of 11 times/min).¹³⁰ Though type and duration of chronic lifting activities have been proposed to affect chronic cardiovascular health through increased BP, this hypothesis has not been tested extensively in research regarding OPA.¹³ Furthermore, no guidelines regarding heavy lifting in relation to cardiovascular health have been established.

To summarize, limited regulations for OPA exist, especially in reference to cardiovascular health. The majority of the literature addressing occupational working time or OPA standards focus on safety and musculoskeletal health. Some research has examined cardiovascular health concerns with OPA; however, the studies are few and were not conducted recently. Further research is certainly warranted to understand the optimal workload of OPA to preserve cardiovascular health of workers with high OPA.

2.6 Summary

Substantial literature demonstrates the health benefits of participating in aerobic LTPA and limiting the accumulation of sedentary time. However, recent evidence suggests that OPA may have an opposing effect on cardiovascular and overall health from LTPA. It seems that those who report high amounts of OPA tend to have increased risk for cardiovascular and all-cause mortality.

This effect is referred to the OPA health paradox. While several mechanisms have been proposed to explain this paradox, few studies have examined its physiological basis. Thus, future research is warranted to expand on the current understanding of mechanisms driving the OPA health paradox. Because current guidelines do not acknowledge this paradox, mechanistic research could establish biological plausibility and inform future guidelines to preserve and improve cardiovascular health in those with high OPA.

3.0 Methods

3.1 Overview

The current study utilized a repeated-measures, within-subject design to address our aims. Nineteen male participants reported to the laboratory to provide written informed consent, complete baseline assessments, and receive ambulatory monitors. Following this session, each participant wore physical activity and ambulatory cardiovascular monitors for 7 days, including at least one non-workday and one workday. Physical activity during work hours and non-work hours was assessed with objective physical activity monitors based upon self-reported time at work (Specific Aim I). The 24-hour cardiovascular load (HR and BP) and nocturnal HRV were compared across workdays and non-workdays (Specific Aim II). Lastly, whether fitness level or daily job stress modified differences in cardiovascular strain between work vs. non-workdays was evaluated (Specific Aim III).

3.2 Sample

This study included 19 middle-aged male workers with high levels of OPA working in the food service, material moving, healthcare, or maintenance industries. These industries were chosen because they have been shown to have high levels of light-intensity activity in published U.S. population research using objective activity monitors and the spectrum of occupational groups.^{15,17} Recruitment of these individuals occurred via flyers, word of mouth, and advertising on the

University of Pittsburgh Clinical and Translational Science Institute's research registry platform (Pitt+Me). Screening was completed by phone or using an online survey (Qualtrics, Inc.; Provo, UT).

To be eligible (Table 3), participants had to self-report working full-time (≥ 30 hours/week), with predominantly light-intensity activity job responsibilities ($\geq 75\%$ work time walking, light movement, or standing), as well as be free from known cardiovascular disease and not currently taking medications known to affect BP or HR (e.g., beta-blockers, ACE inhibitors). As detailed above, the study was limited to male participants because it has been previously shown that the cardiovascular risk associated with high OPA seems to be more apparent in men.⁸ Only men of middle age (35-59 years) were included in the study because cardiovascular disease markers are known to be higher in middle-aged vs. younger adults and the negative effects of high OPA would be more likely observable.¹³¹ Participants were excluded if they reported working overnight shifts (i.e., any time between 10pm and 6am) or a second job to control for known increased cardiovascular risk in shift workers¹³² and to limit non-workday comparison days to non-work activities only, respectively. Additionally, those who reported any mobility limitations (i.e., inability to walk 2 city blocks or climb 2 flights of stairs) or could not complete the submaximal exercise test were excluded. Lastly, anyone whose systolic BP ≥ 150 mmHg or diastolic BP ≥ 95 mmHg was excluded to ensure the safety of all participants during the exercise testing (Table 3).

Participants were required to be classified as 'low risk' based on the Physical Activity Readiness Questionnaire (PAR-Q) at baseline to limit potential risks during the submaximal exercise test as well as to control potential influences on statistical comparisons (e.g., medications, known cardiovascular disease).¹³³ As such, anyone answering yes to any of the following questions were excluded from study participation: 1) Has your doctor ever said that you have a heart

condition and that you should only do physical activity recommended by a doctor? 2) Do you feel pain in your chest when you do physical activity? 3) In the past month, have you had chest pain when you were not doing physical activity? 4) Do you lose your balance because of dizziness or do you ever lose consciousness? 5) Do you have a bone or joint problem that could be made worse by a change in your physical activity? 6) Is your doctor currently prescribing drugs (for example, water pills) for your BP or heart condition? 7) Do you know of any other reason why you should not do physical activity?

Table 3. Study exclusion/inclusion criteria

Inclusion Criteria
<ul style="list-style-type: none"> • middle age (35-59 years) • male • working full-time (≥ 30 hours/week) in the food service, building and grounds maintenance, healthcare support, or material moving and transportation industry • self-report predominantly completing light-intensity activity job responsibilities ($\geq 75\%$ work time walking, in light movement, or standing)
Exclusion Criteria
<ul style="list-style-type: none"> • systolic BP ≥ 150 mmHg or diastolic BP ≥ 95 mmHg • currently taking medication known to affect blood pressure or heart rate (e.g., beta blockers, ACE inhibitors) • greater than low risk to participate in physical activity as determined by the PAR-Q (answer of yes to any of the 7 PAR-Q questions) • report working a second job in addition to their primary full-time job • report working overnight shifts (i.e., any time between 10pm and 6am) • reported mobility limitation (i.e., inability to walk 2 city blocks or climb 2 flights of stairs) • inability to complete the submaximal exercise test

3.3 Baseline Assessment

All participants reported to the Human Energy Laboratory at Trees Hall on the University of Pittsburgh campus to provide informed consent and complete the baseline screening assessment including a submaximal exercise test on a treadmill, prior to beginning the monitor wear protocol. All participants were asked to abstain from food, caffeine, exercise, and nicotine for at least 1 hour prior to the visit; this was verbally confirmed. This was meant to limit variability in resting BP and HR measurements and exceeds the 30-minute abstention period recommended by the American Heart Association.¹³⁴ After providing written informed consent, the following were measured during the baseline screening assessment (in order):

1. PAR-Q questionnaire¹³³
2. Medical history (medications, smoking status, known disease, physical limitations using a standard medical history form)
3. Demographics (age, race/ethnicity, sex, smoking status) and occupational status/history
4. Resting HR and BP were measured on the non-dominant arm, following a ten-minute rest period, using a validated oscillometric device (HEM-705CPN, Omron, Lake Forest, IL), in a chair with feet supported and arms supported at heart level. An appropriately-sized cuff was used so that the bladder encircled $\geq 80\%$ of the arm circumference as measured by a Gulick measuring tape.¹³⁴ Two BP and HR measurements were taken one minute apart and a third measurement was taken if systolic BP differed by ≥ 10 mmHg or diastolic BP differed by ≥ 6 mmHg.¹³⁴ The mean value of all measurements taken was used as the resting HR and BP measurements.
5. Measurements of anthropometry (height and weight) were completed using a calibrated digital scale (WB-110A, Tanita Corporation of America, Arlington Heights, Illinois) to the

nearest 0.1 kg and stadiometer (HM200P, Charder, Taichung City, Taiwan) measured to the nearest 0.1 cm. Each participant was asked to remove their shoes and anything in their pockets prior to the anthropometry measurements. Two measurements of each were taken and averaged. BMI was calculated as kg/m^2 .

6. Each participant completed a submaximal treadmill test using a modified Balke protocol up to 80% age-predicted HR_{max} ($80\% \text{ age-predicted } \text{HR}_{\text{max}} = 0.80 \times (208 - (0.7 \times \text{age}))$)^{27,135} to estimate cardiorespiratory fitness.²⁷ The modified Balke protocol, used previously for fitness estimation in the LOOK AHEAD clinical trial, required participants to walk at 3.0 mph while the incline increased by 1% every minute from an initial incline of 0%.¹³⁶ Ratings of perceived exertion (RPE) were measured using the Borg RPE Scale (6 [no exertion at all] to 20 [maximal exertion]) every two minutes throughout the exercise test and immediately after the last stage of the test to ascertain the perceived effort at test termination.²⁷ BP was measured manually every two minutes throughout the test to monitor the safety of BP response. HR was measured every minute throughout the submaximal exercise test using a Polar HR strap (H10 Bluetooth, Polar). When the participant's HR reached their 80% age-predicted HR_{max} , the test was terminated and the participant was asked to walk slowly on the treadmill (1.0-1.5 mph and 0% grade) until their HR returned to below 100 beats/min. The observed HR trajectory was used to estimate each participant's work rate at their age-predicted HR_{max} using a linear interpolation of a best-fit line, which was then used to predict an estimated maximal oxygen uptake ($\text{VO}_{2\text{max}}$) using an established metabolic equation ($\text{VO}_2 = 0.1(\text{speed}) + 1.8(\text{speed})(\text{fractional grade}) + 3.5$).²⁷ Estimated $\text{VO}_{2\text{max}}$ was used to categorize high and low estimated fitness level in the statistical analyses.²⁷

3.4 Objective Physical Activity Monitoring

Following all baseline measurements, each participant was fitted with physical activity (thigh-mounted inclinometer and waist-worn tri-axial accelerometer) and ambulatory cardiovascular monitors (HR strap and ambulatory BP monitor) to wear for 7 complete days. After 7 days, monitors were dropped off by the participant to the research laboratory. Physical activity was monitored for 7 days using gold standard research-grade methods: 1) thigh-worn inclinometer/accelerometer (activPAL3 micro, PAL Technologies, Glasgow) and 2) waist-worn tri-axial accelerometer (GT3X-BT, ActiGraph, Pensacola, FL). These two measurements have been validated and used extensively to measure physical activity patterns in a free-living environment.^{137,138} In addition to the physical activity monitoring, each participant was asked to complete a paper diary of their working times, sleeping times, monitor wear, and daily job stress. This diary was used to characterize all activity categories into total time, work time, non-work time, or sleep.

The activPAL was affixed to the right thigh using a transparent adhesive dressing (Tegaderm, 3M) for 7 days to measure 24-hour activity, posture (sitting/lying or upright), and stepping throughout the day. Data for each day were considered valid if data were collected for ≥ 10 hours per day. ActivPAL data were exported in 15-second epochs and classified as sedentary behavior (SED), stepping, or standing based on proprietary algorithms using software provided by the manufacturer. All activPAL data were further integrated into 1-minute epochs before analyses to align these data with ActiGraph accelerometry data that were collected in 1-minute epochs. Time spent in SED, standing, and stepping was averaged across all wear days as well as averaged during work time and non-work time. All self-reported nap and sleep periods were coded as sleep after checking for agreement of the body posture with the reported time and were removed from

the calculation of daily sedentary time (total SED). Self-reported non-wear was also removed from the SED calculation. Further data reduction calculated time accumulated in short sedentary bouts (short-bout SED, <30 consecutive minutes), long sedentary bouts (long-bout SED, ≥ 30 consecutive minutes), and long upright bouts (long-bout upright, ≥ 60 continuous minutes) and averaged across all valid wear days. To calculate prolonged bouts of SED and upright time, all adjacent 1-minute epochs that were completely (i.e., 60 seconds) spent in the activity of interest were added together to calculate continuous time spent in that activity. Continuous activity for SED and upright time were then categorized as time spent in bouts less or greater than 30 minutes for sedentary time (short-bout SED and long-bout SED) and greater than 60 minutes for upright time (long-bout upright time). Averages for all variables were also calculated separately within self-reported workdays and non-workdays.

The ActiGraph GT3X-BT was worn over the right hip using an elastic belt to measure pattern and intensity of activity for 24 hours per day for 7 days. Each participant was instructed to only take the monitor off when showering or participating in water activities and to record any non-wear time in their paper diary each day. Data were integrated as 1-minute epochs using ActiLife software (ActiGraph, Pensacola, FL) and considered valid with ≥ 10 hours per day of valid wear time. Wear time was defined using the same intervals from the activPAL monitor (i.e., 24 hours minus self-reported sleep times and non-wear times). Epochs spent in moderate and vigorous physical activity were identified from the triaxial vector magnitude data using Freedson vector magnitude cutpoints.¹³⁹ Duration (minutes/day) of moderate and vigorous activity were averaged across all valid wear days and separately during self-reported work and non-work days and times, based on diary-reported work periods.

Using both activPAL and ActiGraph data, we calculated time spent in total SED, short-bout SED, long-bout SED, upright, long-bout upright, light-intensity activity (light), moderate-intensity activity (moderate), and vigorous-intensity activity (vigorous). Specifically, SED was calculated from the activPAL data, moderate and vigorous activity were calculated from the ActiGraph data, and light activity was calculated as upright time from the activPAL minus moderate and vigorous time from the ActiGraph. Total MVPA was calculated as moderate-equivalent minutes (total MVPA = moderate + (vigorous x 2)) to align with the current 2018 Physical Activity Guidelines for Americans where each minute of vigorous physical activity counts for 2 minutes of moderate activity with respect to meeting recommendations.¹⁴⁰

3.5 Ambulatory Cardiovascular Measurement

3.5.1 24-hour heart rate measurement

A Bluetooth-enabled HR monitor strap (H10 Bluetooth, Polar) continuously measured HR for 7 days to provide average 24-hour HR for every day during the 7-day period. Each participant was instructed to wear the HR strap directly below their nipple line for the duration of the 7-day monitoring period, only removing it during bathing or water activities (e.g., swimming). Any time the monitor was removed, the participant was instructed to record the time in the provided paper diary. The HR monitor was paired via Bluetooth with the ActiGraph accelerometer upon initialization. In this way, the continuously measured HR data at a beat-to-beat resolution of 1 millisecond (ms) was stored on the ActiGraph device throughout the monitoring period. Because Bluetooth activation of the ActiGraph monitor reduced battery life to approximately five days, two

ActiGraph monitors were attached to the elastic belt and worn by the participant for the duration of the monitoring period. The first monitor was programmed to stop approximately four days after the baseline assessment and the second monitor was programmed to start at the same time to ensure no data loss due to insufficient ActiGraph battery life. After downloading of the 1-minute epoch-level data from each of the individual monitors, the data were combined to form a single participant dataset. HR data were downloaded as interbeat R-R intervals using ActiLife software (ActiGraph, Pensacola, FL). All erroneous HR measurements were removed (i.e., HR=0 beats/min). Average 24-hour HR was calculated for all wear days, where the beginning of each 24-hour day was defined as the reported wake-up time for each participant. Thus, as a result of the variation in wake time, the duration of all 24-hour calculations were not necessarily 24 hours in duration (Mean=22.7 hours, SD=3.0 hours, range of 13.4 to 29.5 hours). Average 24-hour HR was then separately calculated for workdays or non-workdays.

Heart rate values for every minute were also calculated as a percentage of heart rate reserve (HRR) for that minute. Percent heart rate reserve was calculated as $\frac{(\text{current HR} - \text{resting HR})}{(\text{age-predicted HR}_{\text{max}} - \text{resting HR})} \times 100$. The average percentage of time spent above and below 30% HRR during work time was then calculated to compare to current OPA intensity guidelines.

3.5.2 Heart rate variability measurement

Nocturnal heart rate variability (HRV) was measured on every night of the 7-day monitoring period using the Bluetooth HR strap described above to examine autonomic function. A previous systematic review concluded that telemetric-derived measures (Polar HR monitor) of HRV provide a valid alternative to electrocardiogram measurement.¹⁴¹ Data collection was performed at a sampling beat-to-beat resolution of 1 ms. Heart rate data were downloaded as

interbeat R-R intervals using ActiLife software (ActiGraph, Pensacola, FL) and then imported into Kubios HRV software (Kubios HRV Premium v.3.2, Kubios, Kuopio, Eastern Finland) for analysis. Two separate processing methods were employed for analysis of nocturnal HRV data. The first method considered the whole sleep bout (whole night), in which every 5-minute period throughout the entire self-reported sleep bout for each night was processed separately to estimate all HRV parameters. Five-minute periods with erroneous HR values of HR=0 beats/min were dropped. Following processing of every 5-minute period, the mean of each HRV parameter was calculated to standardize the values to the duration of the recording, limiting the potential influence of sleep bout duration on HRV parameters. This method for nocturnal HRV measurement has been previously described in the guidelines set by the Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology.¹⁴² The second method averaged HRV variables from only the three 5-minute nocturnal periods with the lowest recorded HR to align with previously described methods used by Hallman, et al., in a study of the OPA health paradox.²⁴ HRV parameters calculated for each night included: mean HR, mean beat-to-beat interval (RR), root mean square successive difference (RMSSD), standard deviation of normal to normal intervals (SDNN), low frequency power (0.04 – 0.15 Hz; LF), high frequency power (0.15 – 0.4 Hz; HF), and low frequency to high frequency ratio (LF/HF).^{143,144} Both time (HR, RR, RMSSD, SDNN) and frequency (LF, HF, LF/HF) HRV domains were used in all statistical comparisons.^{143,144} Log transformed values of LF and HF were used in all analyses as is typically done because they are known to be non-normally distributed. All HRV values were calculated using standard automated protocols from the Kubios software; automatic artifact correction was applied by utilizing a time series consisting of differences between successive RR intervals to separate normal and ectopic beats.^{145,146} Then, for each sleep interval, mean HRV values using

both methods were classified as nights following workdays and nights following non-workdays. The presence of the ambulatory BP monitor was included as a covariate in all HRV statistical models to account to potential disruption in sleep patterns and associated HRV during ambulatory BP monitoring.

3.5.3 Ambulatory blood pressure measurement

Each participant was asked to wear an ambulatory BP monitor (ABPM; Oscar 2, SunTech Medical, Morrisville, NC) on their non-dominant arm for 24 hours on two occasions during the monitoring period (one workday and one non-workday). The participants were only asked to wear the ABPM on two days during the 7-day monitoring period to limit participant burden. These two days were planned by the participant and study staff on the day of the baseline assessment and were adjusted as needed throughout the week if the participant's work schedule changed. The workday monitoring day was chosen with one workday prior, to capture the effects of sustained exposure to OPA, and at least 24 hours after the baseline assessment, to limit any influence from the sub-maximal fitness test (e.g., ABPM wear occurred on a Wednesday when Tuesday was a workday and baseline assessment was on a Monday). Similarly, the non-workday monitoring was ideally conducted with at least one non-workday prior and at least 24 hours after the baseline assessment visit, however this was not always possible as some participants had only one non-workday or no consecutive non-workdays throughout the monitoring period. Ambulatory BP was measured using established protocols including BP measurements every 30 minutes during the day and every 60 minutes during the participant's self-reported typical sleep times.¹⁴⁷ Participants were given the ABPM upon completion of the baseline assessment and shown how to properly wear the monitor. They were also given standardized instructions on monitor wear, how to

activate/deactivate the monitoring, and when to wear the monitor.¹⁴⁸ The participants were instructed to start and stop the monitor on their prescribed ABPM wear days. However, phone call and email reminders additionally encouraged adherence to the prescribed protocol. ABPM data were downloaded using Accuwin Pro software (Suntech Medical, Morrisville, NC) and edited by removing data associated with notable error codes (e.g., artifact or erratic oscillometric signal) in the AccuWin Pro software.¹⁴⁹ All BP measurements were weighted by the amount of time they represent in the day due to variability in the duration between measurements, especially between nighttime and daytime measurements. Daily averages of BP and HR were compared across work and non-workdays and computed as 24-hour time, wake time, nocturnal time, work time, and non-work time based on diary-reported sleep, wake, and work times.

3.6 Job Stress Measurement

Job stress was measured daily on workdays to quantify the level of work-related psychological stress that the participant was burdened with each day across the entire workday. This measurement was used to examine potential differences in cardiovascular responses on days with high versus low job stress (Specific Aim III). Participants were instructed to complete the 8-item Stress in General Scale at the end of each workday in the provided paper dairy; for each item, response options included “yes”, “no”, or “?” associated with the presence or absence of the stressful or non-stressful emotion described by the item (e.g., demanding, pressured). Scores were calculated using standardized methods where “yes” = 3, “no” = 0, and “?”=1.5. All stressful descriptors are positive and non-stressful descriptors (e.g. calm) are coded as negative values. All items were then summed to get a final score ranging from -3 to 21, where higher scores indicate

more stress. This questionnaire has been extensively validated to measure work-related stress.¹⁵⁰ Higher stress measured on this scale has been found to be related to increased BP reactivity from acute psychological stress.¹⁵⁰

3.7 Analytical Approach

Sample size was determined using Stata 14 and with the primary outcome of 24-hour systolic BP. Based upon a previous ambulatory BP study, the standard deviation was 12.4 mmHg in systolic BP.¹²¹ A clinically meaningful difference in systolic BP is 5 mmHg¹⁵¹, resulting in a target effect size of 0.40. Using the effect size of 0.40, with power set at 0.80, an alpha of .05, and a modest within-subject correlation of .50, it was determined that 18 subjects were needed to detect a difference in systolic BP between workdays and non-workdays. To account for potential incomplete data, we recruited 19 subjects for this study.

Descriptive statistics were used to summarize demographic factors, fitness level, job stress, and physical activity levels. Physical activity patterns were operationalized as time spent in total SED, short-bout SED, long-bout SED, upright, long-bout upright, light activity, moderate activity, vigorous activity, and total MVPA during work and non-work hours using combined activPAL and ActiGraph data, as described above.^{137,152} Physical activity was further characterized as the number of participants accumulating daily activity levels consistent with meeting the physical activity recommendations in Table 4 during all days, workdays, non-workdays, and during work time only (Specific Aim I). As day-level averages were used, we converted the weekly recommendation to a daily-level equivalent (150 minutes/week divided by 7 days=21.4 minutes/day). The number of upright minutes per daily work hour was compared to the current

recommended upper limit of 30 minutes per work hour⁵⁸ and the average percentage of work time spent over the currently recommended occupational maximal workload of 30% HRR was summarized for each participant (Table 4).^{19,129}

Table 4. Current leisure-time and occupational activity recommendations

<p>Leisure-Time Physical Activity: ≥ 150 moderate-equivalent minutes per week of aerobic activity^{4,26}</p>
<p>Occupational Activity for Desk Workers: 2-4 hours of upright activity per 8-hour workday (15-30 minutes/hour)⁵⁸</p>
<p>Occupational Activity Upper Limit: Maximal workload of 30% heart rate reserve (HRR) in an 8-hour workday¹⁹</p>

Mixed effects models accounting for within-subject correlations across repeated measures were used to compare all cardiovascular outcomes (e.g., 24-hour, nocturnal, waking, and non-work time HR, BP, and nocturnal HRV) on workdays versus non-workdays (Specific Aim II).

Examination of potential effect modification by fitness level was completed by repeating the same model for 24-hour HR and BP with an added interaction term (workday x fitness) after stratifying fitness as high and low fitness using a median split at $VO_{2max}=42.84$ ml/kg/min⁻¹. This analysis was used to test the hypothesis that lower fitness would result in greater differences in work vs. non-workday 24-hour cardiovascular load (Specific Aim III).

For analyses regarding the impact of job stress, each day was categorized as a non-workday, a high stress workday, or a low stress workday. High and low stress categories were determined using a median split of Stress in General Scale scores (median=0.0). Mixed effects models, similar to those previously described, evaluated 24-hour HR and BP using the workday stress categorical variable (non-workday, high stress workday, low stress workday) as the independent variable with non-workday as the reference. This analysis was used to examine

whether job stress modified the relationship between workdays vs. non-workdays on the cardiovascular load outcomes (Specific Aim III).

All models were adjusted for age, BMI, smoking status, fitness, and the resting value of the outcome of interest (HR, systolic BP, or diastolic BP). All analyses were performed in Stata v.16 (StataCorp, College Station, Texas) with alpha level set at 0.05.

A total of 22 participants were initially deemed eligible to participate. Following initial screening and arrival to the laboratory for baseline assessments, 3 participants were determined as ineligible. Two individuals had exclusionary blood pressure measurements (i.e., systolic BP \geq 150 mmHg or diastolic BP \geq 95 mmHg). Those individuals were given a BP alert form and assessments were discontinued. One individual was unable to complete the submaximal exercise test due to self-reported fatigue and an abnormal heart rate response. None of the data from excluded individuals were included in the current analysis. Non-workday ambulatory BP measurement was missing for one participant; as such, that participant was not included in models assessing BP as the outcome. Similarly, reported job stress was missing for one participant; as a result, that individual was not included in analyses involving job stress.

4.0 Results

4.1 Sample Characteristics

Table 5 presents the relevant sample characteristics. The 19 male participants were, on average, 46.6 (SD=7.9) years old, mostly white (68.4%), and had varied education levels (42.1% high school or less, 21.1% some college or associate degree, 36.8% college graduate or higher). Eight (42.1%) individuals worked in the food service industry, nine (47.3%) in the material moving industry, one (5.3%) in healthcare, and one (5.3%) in the building/grounds maintenance industry. On average, participants reported working 43.3 (SD=7.1) hours per week and estimated that 88% of that time was spent standing, performing light intensity activities, or performing moderate-to-vigorous intensity activities. Eight (42.1%) individuals reported daily smoking and the median number of alcoholic beverages consumed per week was 2. The average body mass index of the participants was 27.9 (SD=5.1) kg/m², resting BP was 122.0 (SD=10.6)/76.4(SD=8.8) mmHg, and resting HR was 68.0 (SD=12.6) beats/minute. The median VO₂max was 42.84 ml/kg/min⁻¹, which is considered to be in the “good” category for men aged between 40 and 49 years.²⁷

Table 5. Sample characteristics (N=19)

Age (years)	46.6 (7.9)
Race/ethnicity	
White/Caucasian	13 (68.4%)
Black/African American	4 (21.1%)
Multi-racial or other	2 (10.5%)
Education	
High School or less	8 (42.1%)
Some College/Associates	4 (21.1%)
College Graduate or higher	7 (36.8%)
Occupational group	
Food service	8 (42.1%)
Material moving	9 (47.3%)
Healthcare	1 (5.3%)
Building/ground maintenance	1 (5.3%)
Number of work hours/week	43.3 (7.1)
Self-reported work time activity	
% Sitting	12.0 (12.7)
% Standing or light physical duties*	56.7 (29.1)
% Moderate/vigorous physical duties	31.3 (27.8)
Job stress	0.0 (-3.0-6.0)
Smoking status	
Daily	8 (42.1%)
Less than daily	1 (5.3%)
Not at all	10 (52.6%)
Alcoholic beverages (number/week)	2.0 (0-5)
Body mass index (BMI)	27.9 (5.1)
Resting systolic BP (mmHg)	122.0 (10.6)
Resting diastolic BP (mmHg)	76.4 (8.8)
Resting HR (beats/min)	68.0 (12.6)
Estimated VO ₂ max (ml/kg/min ⁻¹)	42.8 (35.0-48.2)

All values presented as mean (standard deviation), frequency (percentage), or median (25th-75th percentile), as appropriate. *Measured as standing and light activities separately and added together. Abbreviations: HR=heart rate; BP=blood pressure; VO₂max=maximal rate of oxygen consumption

4.2 Specific Aim I

Table 6 describes the physical activity profile across work and non-workdays as measured by activPAL and ActiGraph monitors. Across all measurement days, participants provided an average of 6.9 (SE=0.7) days of measurement with approximately 955 (SE=13) minutes of waking wear time per day. On average, participants accumulated 533.4 (SE=17.4, 55.9% of total waking time) minutes of total SED each day with just over half of that being short-bout SED (<30 continuous minutes in a bout) and just under half being long-bout SED (≥ 30 continuous minutes). Participants spent approximately 421.5 (SE=17.4, 44.1% of waking time) minutes per day in an upright position with about one-quarter of that (mean 114.6 (SE=22.9) minutes) accumulated in long-bout upright time (≥ 60 minutes). Participants accumulated 359.3 (SE=18.8) minutes of light-, 60.1 (SE=6.8) minutes of moderate-, and 1.6 (SE=0.5) minutes of vigorous-intensity activity per day, resulting in an average of 63.3 (SE=6.9) minutes of moderate-equivalent minutes of MVPA per day. As percentages, participants spent 37.6% of the day in light, 6.2% of the day in moderate, and 0.2% in vigorous intensity activity. Finally, participants accumulated an average of 11,328 (SE=918) steps per day across all days.

Participants were monitored for an average of 4.8 workdays and 2.1 non-workdays. The waking wear time on workdays was 65.7 (SE=22.0) longer than on non-workdays ($p=0.003$). As such, all models were adjusted for wear time and all reported activity variables were standardized to average wear time. In general, participants were significantly more active on workdays versus non-workdays. Participants accumulated approximately 137.1 (SE=20.3) less sedentary minutes on workdays compared to non-workdays ($p<0.001$), most of which (101.2 minutes, SE=21.6) was a reduction in long-bout sedentary time. As the inverse of sedentary time, upright time was 137.1 (SE=20.3) minutes higher on workdays versus non-workdays ($p<0.001$). Long-bout upright time

was significantly higher on workdays versus non-workdays ($\beta=120.1$ minutes, $SE=21.3$, $p<0.001$). Participants had more light- ($\beta=109.9$ minutes, $SE=19.4$, $p<0.001$) and moderate-intensity ($\beta=29.8$ minutes, $SE=8.1$, $p<0.001$) minutes on workdays than non-workdays, but no difference in vigorous minutes between workdays and non-workdays was observed ($\beta=1.0$ minutes, $SE=0.6$, $p=0.126$). Total moderate-equivalent minutes of MVPA was 31.7 ($SE=8.3$) minutes higher on workdays versus non-workdays ($p<0.001$). Finally, participants accumulated 4,848 ($SE=765$) more steps on workdays than non-workdays ($p<0.001$).

Table 6. Physical activity profile across workdays and non-workdays

	All days	Workdays	Non-workdays	β (SE)**	P-value
Number of days	6.9 (0.7)	4.8 (0.8)	2.1 (0.8)	--	--
Wear time (min/day)	954.9 (13.1)	974.5 (14.7)	908.8 (20.3)	65.7 (22.0)	0.003
Total SED (min/day)	533.4 (17.4)	492.5 (18.4)	629.7 (22.5)	-137.1 (20.3)	<0.001
Short-bout SED (min/day)	285.1 (16.3)	274.0 (16.9)	311.1 (19.6)	-37.1 (15.6)	0.017
Long-bout SED (min/day)	248.2 (16.2)	218.1 (17.4)	319.3 (22.2)	-101.2 (21.6)	<0.001
Upright (min/day)	421.5 (17.4)	462.4 (18.4)	325.2 (22.5)	137.1 (20.3)	<0.001
Long-bout upright (min/day)	114.6 (22.9)	150.4 (23.8)	30.3 (27.4)	120.1 (21.3)	<0.001
Light (min/day)	359.3 (18.8)	391.5 (19.9)	285.2 (23.3)	109.9 (19.4)	<0.001
Moderate (min/day)	60.1 (6.8)	68.7 (7.2)	39.7 (8.8)	29.8 (8.1)	<0.001
Vigorous (min/day)	1.6 (0.5)	1.9 (0.6)	0.9 (0.7)	1.0 (0.6)	0.126
Total MVPA* (min/day)	63.3 (6.9)	72.4 (7.2)	41.5 (8.9)	31.7 (8.3)	<0.001
Steps (steps/day)	11,328 (918)	12,772 (945)	7,923 (1,063)	4,848 (765)	<0.001

Outcome data are presented as LS Means (SE)

All models were adjusted for wear time, age, BMI, smoking status, and fitness;

*calculated as moderate intensity equivalent minutes

** β (SE) and P-value represent a comparison between work and non-workdays;

Abbreviations: β (SE)=Beta coefficient (standard error); Short-bout SED=sedentary time accumulated in bouts of <30 continuous minutes; Long-bout SED=sedentary time accumulated in bouts of ≥ 30 continuous minutes; Long-bout upright=upright time accumulated in bouts of ≥ 60 continuous minutes

Figure 4 reports the number of participants who were active at a level consistent with current aerobic physical activity guidelines across all days¹⁴⁰ and specifically on workdays, non-workdays, and during work time. This figure represents whether daily total MVPA accumulated during each of these time periods met minimal thresholds for average minutes per day (21.4 moderate-equivalent minutes) needed to meet weekly aerobic guidelines (150 moderate-equivalent

minutes per week).¹⁴⁰ Thus, individuals were categorized into not meeting guidelines (0-149 moderate-equivalent minutes), meeting guidelines (150-300 moderate-equivalent minutes), and high activity threshold (>300 moderate-equivalent minutes).

All participants were active at guideline levels on workdays, though more than half also achieved these levels on non-workdays. Across all days, 17 of the 19 participants met or exceeded activity levels consistent with the physical activity guidelines. Additionally, 14 of the 17 who met the guidelines also met the high activity threshold. When considering workdays only, all 19 participants achieved activity levels consistent with the aerobic physical activity guidelines with 14 of these meeting the high activity threshold. On non-workdays, 6 participants did not meet the physical activity guidelines, 3 were active at the minimal guidelines level, and 10 were active at the high activity threshold. During work time only, 15 participants met or exceeded physical activity levels consistent with the aerobic guidelines, with 11 of those meeting the high activity threshold (Figure 4).

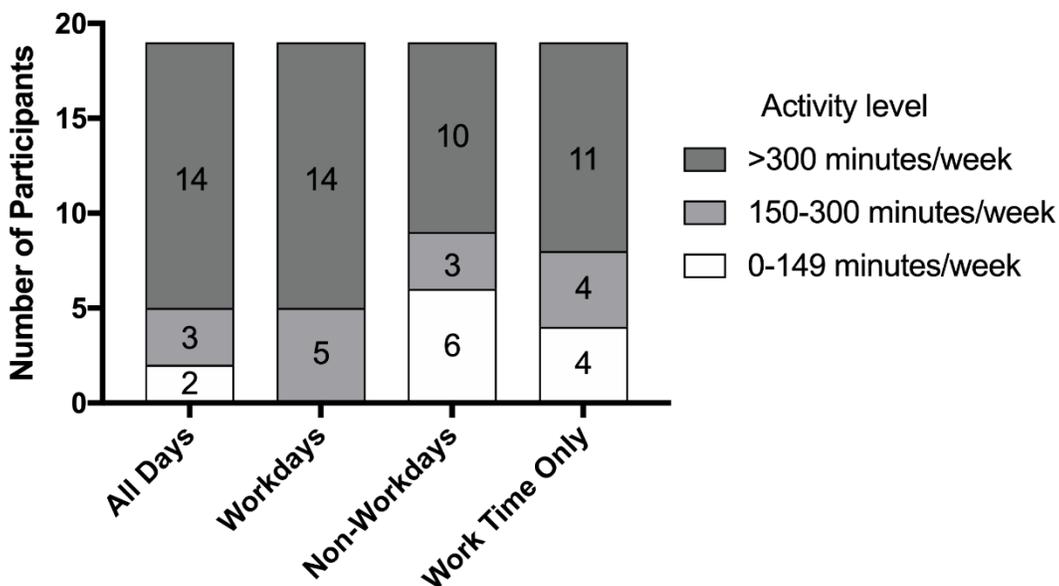


Figure 4. Number of participants meeting physical activity guidelines by day type

Table 7 presents participant physical activity profiles accumulated during work hours only. On average, participants accumulated 489.5 minutes (SD=161.1), or 8.2 hours, of work time per workday. Participants spent about 166.8 minutes (SD=111.3) of work time each day in total SED, which accounted for 34.1% of their work time. On average, participants accumulated 101.4 (SD=80.8) minutes of short-bout SED and 65.4 (SD=49.5) minutes of long-bout SED each day at work. Participants accumulated the other 65.9% of their work time upright, with 143.6 (SD=140.7) minutes accumulated in long-bout upright time (≥ 60 continuous minutes). Figure 5 displays the average upright minutes per hour for each of the participants. Fourteen of the 19 participants exceeded the recommended 30 minutes per hour of upright time,⁵⁸. On average, participants accumulated 54.5% of their time in light-, 11.2% in moderate-, and 0.2% in vigorous-intensity activity per workday. Participants accumulated an average of 57.0 (SD=41.6, 11.6% of their workday) minutes of total MVPA and 9,483 (SD=5,037) steps per workday.

Table 7. Physical activity profiles during work hours

	Mean (SD)	Range	% of workday
Wear time (min/day)	489.5 (116.1)	208.9-637.6	100%
Total SED (min/day)	166.8 (111.3)	1.8-363.2	34.1%
Short-bout SED (min/day)	101.4 (80.8)	1.8-330.2	20.7%
Long-bout SED (min/day)	65.4 (49.5)	0-160.0	13.4%
Total Upright (min/day)	322.7 (117.5)	71.9-533.3	65.9%
Long-bout upright (min/day)	143.6 (140.7)	0-460.0	29.3%
Light PA (min/day)	266.7 (109.5)	56.2-477.1	54.5%
Moderate PA (min/day)	55.0 (42.1)	11.8-143.2	11.2%
Vigorous PA (min/day)	1.0 (1.9)	0-7.8	0.2%
Total MVPA* (min/day)	57.0 (41.6)	12.6-143.2	11.6%
Steps (steps/day)	9,483 (5037)	2,179-21,296	---

*calculated as moderate intensity equivalent minutes

Abbreviations: MVPA=moderate-to-vigorous physical activity; PA=physical activity; SD=standard deviation; Short-bout SED=sedentary time accumulated in bouts of <30 continuous minutes; Long-bout SED=sedentary time accumulated in bouts of ≥ 30 continuous minutes; Long-bout Upright=upright time accumulated in bouts of ≥ 60 continuous minutes

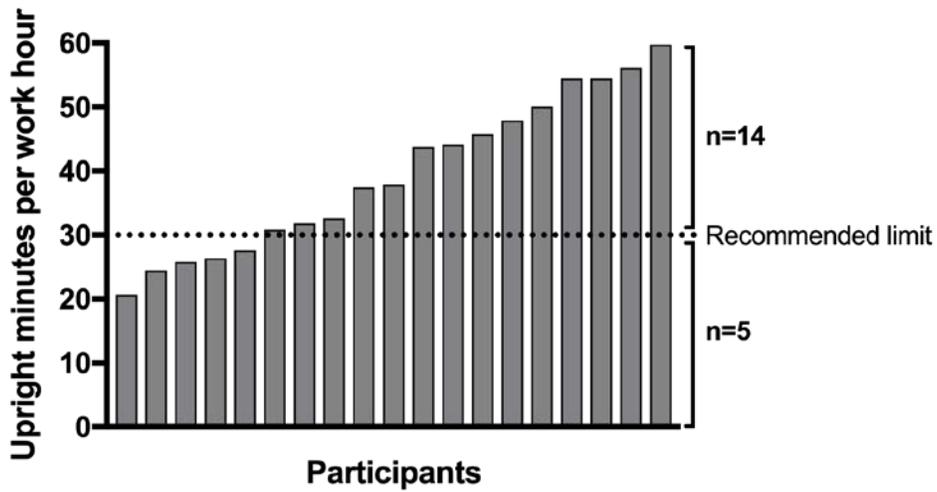


Figure 5. Average upright minutes per hour of work time by participant

Figure 6 presents the percent of time each participant spent above the recommended intensity limit of 30% HRR while at work.¹⁹ Eighteen out of the 19 participants exceeded the limit of 30% HRR during the workday. On average, 30.9% the participants' working time was spent above this threshold with wide variability ranging from 0 – 85.2%.

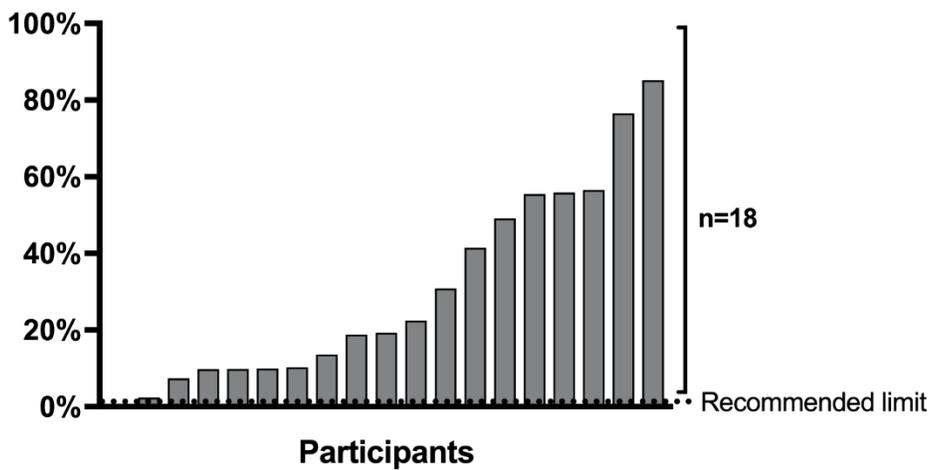


Figure 6. Percent of work time spent above 30% heart rate reserve by participant

4.3 Specific Aim II

Table 8 compares the 24-hour, waking, nocturnal, and non-work cardiovascular load experienced on workdays and non-workdays. Twenty-four-hour HR was significantly higher on workdays versus non-workdays ($\beta=5.4$ beats/min, $SE=1.4$, $p<0.001$). Waking time HR was also significantly higher on workdays than non-workdays ($\beta=6.4$ beats/min, $SE=1.3$, $p<0.001$). Nocturnal HR was not significantly higher on work versus non-workdays ($\beta=2.9$ beats/min, $SE=1.5$, $p=0.056$). Also, there was no significant difference observed in non-work time HR on workdays versus non-workdays ($\beta=1.9$ beats/min, $SE=1.3$, $p=0.162$). Systolic BP did not differ when comparing 24-hour, waking, nocturnal, or non-work time averages between workdays and non-workdays ($\beta=2.0$ mmHg, $SE=2.0$, $p=0.317$; $\beta=2.7$ mmHg, $SE=1.9$, $p=0.157$; $\beta=0.2$ mmHg, $SE=3.5$, $p=0.952$; $\beta=3.8$ mmHg, $SE=2.5$, $p=0.120$; respectively). However, 24-hour, waking time, and non-work time diastolic BP averages were found to be significantly higher on workdays versus non-workdays ($\beta=2.7$ mmHg, $SE=1.1$, $p=0.019$; $\beta=3.9$ mmHg, $SE=1.4$, $p=0.006$; $\beta=3.3$ mmHg, $SE=1.5$, $p=0.023$, respectively). Nocturnal diastolic BP was not different on workdays versus non-workdays ($\beta=0.1$ mmHg, $SE=1.7$, $p=0.940$). Overall, we confirmed the hypothesis that 24-hour and waking time cardiovascular load would be higher on workdays for HR and diastolic BP, while no statistically significant differences were observed in systolic BP. Furthermore, we did not confirm the hypothesis that nocturnal cardiovascular load would be higher on workdays versus non-workdays. Results during non-work time were mixed, as only diastolic BP was found to be significantly different across workdays and non-workdays.

Table 8. Comparison of cardiovascular load on work and non-workdays

	Workdays	Non-workdays	β (SE)	P-value
Heart rate (beats/min)				
24-hour	83.8 (1.2)	78.5 (1.4)	5.4 (1.3)	<0.001
Waking	89.4 (1.3)	83.0 (1.5)	6.4 (1.3)	<0.001
Nocturnal	69.2 (1.0)	66.3 (1.4)	2.9 (1.5)	0.056
Non-work time	84.8 (1.2)	82.9 (1.5)	1.9 (1.3)	0.162
Systolic BP (mmHg)				
24-hour	126.0 (1.7)	124.0 (1.8)	2.0 (2.0)	0.317
Waking	131.7 (1.6)	129.0 (1.8)	2.7 (1.9)	0.157
Nocturnal	113.7 (2.5)	113.5 (3.0)	0.2 (3.5)	0.952
Non-work time	132.5 (1.9)	128.6 (2.1)	3.8 (2.5)	0.120
Diastolic BP (mmHg)				
24-hour	75.2 (1.0)	72.6 (1.1)	2.7 (1.1)	0.019
Waking	80.9 (1.2)	77.0 (1.3)	3.9 (1.4)	0.006
Nocturnal	63.2 (1.4)	63.1 (1.6)	0.1 (1.7)	0.940
Non-work time	80.0 (1.2)	76.7 (1.3)	3.3 (1.5)	0.023

Outcome data are presented as LS Means (SE)

All models were adjusted for age, BMI, smoking status, fitness, and the resting value of the outcome of interest

Abbreviations: BP=blood pressure; β (SE)=beta coefficient (standard error)

Table 9 compares nocturnal HRV parameters on workdays and non-workdays. On average, whole-night nocturnal HR was higher following workdays versus non-workdays ($\beta=2.67$ beats/min, SE=1.31, $p=0.042$); however, no difference was observed between workday and non-workdays when using the average of the three five-minute nocturnal periods with the lowest HR ($\beta=2.24$ beats/min, SE=1.24, $p=0.070$). The average nocturnal RR interval was non-significantly lower on workdays versus non-workdays using both processing methods ($\beta=-26.54$ ms, SE=14.87, $p=0.074$ for whole night and $\beta=-28.93$ ms, SE=16.88, $p=0.087$ for 3x5-minutes). Nocturnal RMSSD did not differ following workdays versus non-workdays ($\beta=-1.17$ ms, SE=2.27, $p=0.607$ for whole night and $\beta=3.85$ ms, SE=4.86, $p=0.428$ for 3x5-minutes). Similarly, nocturnal SDNN did not differ following workdays versus non-workdays ($\beta=-2.29$ ms, SE=1.90, $p=0.230$ for whole night and $\beta=1.37$ ms, SE=3.98, $p=0.730$ for 3x5-minutes). Using the whole-night HRV processing method, nocturnal indices of low-frequency power (LF) and high-frequency power (HF) were both lower following workdays versus non-workdays ($\beta=-0.27$, SE=0.12, $p=0.025$ and $\beta=-0.33$,

SE=0.14, $p=0.014$ respectively). However, using the 3x5-minutes method, no significant differences were found for nocturnal LF or HF following workdays versus non-workdays ($\beta=-0.21$, SE=0.17, $p=0.225$ and $\beta=-0.26$, SE=0.18, $p=0.153$ respectively). The nocturnal LF/HF ratio did not differ following workdays and non-workdays using either HRV processing method ($\beta=0.35$, SE=0.33, $p=0.301$ for whole night and $\beta=0.25$, SE=0.43, $p=0.558$ for 3x5-minutes). Overall, results were mixed relative to the hypotheses that workdays would result in reduced HRV during the subsequent nocturnal period. HR was higher and LF and HF were found to be lower during the nights following workdays versus non-workdays, but no other parameters were significantly different.

Table 9. Nocturnal heart rate variability (HRV) following workdays and non-workdays

	Whole-night*			
	Workdays	Non-workdays	β (SE)	P-value
Average HR (beats/min)	68.31 (1.68)	65.64 (1.90)	2.67 (1.31)	0.042
Average RR interval (ms)	909.75 (19.27)	936.29 (21.73)	-26.54 (14.87)	0.074
RMSSD (ms)	34.17 (4.04)	35.34 (4.32)	-1.17 (2.27)	0.607
SDNN (ms)	39.85 (3.48)	42.14 (3.71)	-2.29 (1.90)	0.230
LF (log)	6.18 (0.20)	6.45 (0.21)	-0.27 (0.12)	0.025
HF (log)	5.22 (0.30)	5.56 (0.31)	-0.33 (0.14)	0.014
LF/HF ratio	4.75 (0.73)	4.41 (0.76)	0.35 (0.33)	0.301
	3x5-minutes**			
	Workdays	Non-workdays	β (SE)	P-value
Average HR (beats/min)	59.88 (1.60)	57.64 (1.80)	2.24 (1.24)	0.070
Average RR interval (ms)	1029.79 (22.82)	1058.73 (25.51)	-28.93 (16.88)	0.087
RMSSD (ms)	50.71 (6.59)	46.86 (7.36)	3.85 (4.86)	0.428
SDNN (ms)	51.60 (4.71)	50.22 (5.42)	1.37 (3.98)	0.730
LF (log)	6.57 (0.21)	6.77 (0.24)	-0.21 (0.17)	0.225
HF (log)	5.94 (0.33)	6.19 (0.35)	-0.26 (0.18)	0.153
LF/HF ratio	3.50 (0.63)	3.25 (0.69)	0.25 (0.43)	0.558

HRV parameters are presented as LS Means (SE)

All models adjusted for the presence or absence of ambulatory blood pressure monitoring, age, BMI, fitness, and smoking status

*values for the whole night were calculated as the mean of each 5-minute period within the self-reported sleep bout

** using the mean of values derived from the three 5-minute periods with the lowest heart rate from the whole-night method

Abbreviations: β (SE)=beta coefficient (standard error); HR=heart rate; RMSSD=root mean square successive difference; SDNN=standard deviation of the normal to normal RR intervals; LF=low frequency power; HF=high frequency power; LF/HF Ratio=low frequency to high frequency ratio; ms=milliseconds

4.4 Specific Aim III

Table 10 presents the 24-hour cardiovascular load across workdays and non-workdays by fitness category. The difference in 24-hour HR between workdays and non-workdays was not significantly different across the high and low categories of fitness (interaction $\beta=0.4$ beats/min, SE=2.6, $p=0.885$). Similarly, the difference of 24-hour systolic BP between workdays and non-workdays was not significantly different across the categories of fitness (interaction $\beta=2.0$ mmHg,

SE=5.4, p=0.703). Lastly, the difference in 24-hour diastolic BP between workdays and non-workdays was not significantly different across the two categories of fitness level (interaction $\beta=0.5$ mmHg, SE=3.8, p=0.889). Overall, these data do not support the hypothesis that differences in 24-hour cardiovascular responses across work and non-workdays are modified by cardiorespiratory fitness levels.

Table 10. 24-hour cardiovascular load on across day type and fitness categories

	Low fitness (n=9)		High fitness (n=10)		Interaction β (SE)*	Interaction p-value
	Workdays	Non-workdays	Workdays	Non-workdays		
24-hour HR	82.8 (1.7)	77.3 (2.1)	84.8 (1.6)	79.6 (2.0)	0.4 (2.6)	0.885
24-hour systolic BP	126.2 (4.0)	128.2 (3.5)	128.4 (3.5)	128.9 (3.8)	2.0 (5.4)	0.703
24-hour diastolic BP	77.6 (2.3)	75.3 (2.8)	78.5 (2.4)	76.6 (2.6)	0.5 (3.8)	0.889

24-hour outcome data are presented as LS Means (SE)

All models were adjusted for age, BMI, smoking status, fitness, and the resting value of the outcome of interest;

Fitness categories were defined as high and low using a median split at $VO_{2max}=42.84$ ml/kg/min⁻¹

Abbreviations: HR=heart rate; BP=blood pressure; β (SE)=beta coefficient (standard error)

* β (SE) and P-value represent the difference in the difference between work and non-workdays comparing low versus high fitness categories

Table 11 presents the 24-hour cardiovascular load on workdays vs. non-workdays stratified across levels of daily job stress. Compared to non-workdays, twenty-four-hour HR was higher on workdays with low stress ($\beta=4.7$ beats/min, SE=1.5, p=0.002) and on workdays with high stress ($\beta=5.4$ beats/min, SE=1.7, p=0.001). 24-hour systolic BP was not statistically different on workdays with low or high stress compared to non-workdays ($\beta=0.2$ mmHg, SE=2.1, p=0.911 and $\beta=4.9$ mmHg, SE=3.0, p=0.106 respectively). 24-hour diastolic BP was not significantly different on workdays with low stress compared to non-workdays ($\beta=1.4$ mmHg, SE=1.4, p=0.263), but 24-hour DBP was higher on workdays with high stress compared to non-workdays ($\beta=4.4$ mmHg, SE=1.9, p=0.023). Overall, high job stress seemed to exaggerate the 24-hour diastolic BP compared to non-workdays, supporting the hypothesis that higher job stress increases

cardiovascular load. While similar significant results were not observed for 24-hour HR or systolic BP, the directions of non-significant effects were consistent with the hypotheses that cardiovascular load is higher on days with higher stress. When 24-hour HR, systolic BP, and diastolic BP on low vs. high stress workdays were compared, no significant differences were observed.

Table 11. 24-hour cardiovascular load across levels of job stress

	LS means (SE)	β (SE)*	P-value
24-hour HR (beats/min)			
Non-workday	78.3 (1.4)	---	---
Low stress workday	83.5 (1.4)	4.7 (1.5)	0.002
High stress workday	84.3 (1.6)	5.4 (1.7)	0.001
24-hour systolic BP (mmHg)			
Non-workday	124.0 (1.8)	---	---
Low stress workday	124.3 (1.9)	0.2 (2.1)	0.911
High stress workday	128.9 (2.9)	4.9 (3.0)	0.106
24-hour diastolic BP (mmHg)			
Non-workday	72.5 (1.1)	---	---
Low stress workday	73.9 (1.2)	1.4 (1.3)	0.263
High stress workday	76.9 (1.9)	4.4 (1.9)	0.023

All models were adjusted for age, BMI, smoking status, fitness, and the resting value of the outcome of interest; Job stress categories were defined as high and low using a median split at job stress=0

* β (SE) and P-value represent a comparison to the reference group of non-workdays

Abbreviations: HR=heart rate; BP= blood pressure; β (SE)=beta coefficient (standard error); LS means (SE)=least square means (standard error)

5.0 Discussion

This study examined 19 men with active jobs in the food service, material moving, healthcare, and maintenance industries. The study quantified the overall activity level of these individuals, as well as their activity during workdays, non-workdays, and during work time, using gold standard measurement techniques to better understand their occupational and non-occupational activity exposure as it relates to current activity recommendations (Specific Aim I). Secondly, this study examined the cardiovascular strain experienced by these workers to more fully understand potential mechanisms through which the proposed OPA health paradox could be occurring (Specific Aim II). Lastly, this study explored whether lower fitness levels or higher daily job stress were associated with greater cardiovascular strain on workdays to further understand the mechanistic pathways and biological plausibility of the OPA health paradox hypothesis (Specific Aim III).

5.1 Specific Aim I

5.1.1 Activity profiles on workdays and non-workdays

This study provides unique descriptive data of objectively-measured activity profiles in a sample of men with highly active jobs. Overall, these individuals were significantly more active on workdays than non-workdays. Specifically, the more active workday profile included less short- and long-bout SED accompanied by more time spent upright, more moderate-intensity activity,

and more steps. Of note, no differences were observed in time spent in vigorous-intensity activity between workdays and non-workdays.

The current analysis estimated that 56% of waking time on all days was spent sedentary. This estimate is somewhat higher than the other studies estimating that men and women in similar occupational classifications spent from 44-54%¹⁵ or 44-52%¹⁷ of their day sedentary. However, it is important to note that waist-worn ActiGraph accelerometry was used in the other available research to quantify sedentary behavior. Though preferable to self-report, waist-worn accelerometers have been known to significantly misclassify sedentary time as compared to the gold standard activPAL used in the current analysis;^{153,154} this difference in measurement methodology could explain the discrepancy. Additionally, the current sample included only men living in Pittsburgh and is not necessarily generalizable to larger and more geographically diverse samples. In contrast, total SED in the current study was lower compared to the previously observed total SED of 66% in a sample of office workers¹⁵⁵ and the estimated 60-66% overall sedentary time in the least active occupations reported by Steeves, et al.¹⁵ Taken together, though the activPAL estimate of SED among the population of workers examined in this study was slightly higher than expected, these individuals still appear to be less sedentary than workers with desk or other sedentary office jobs.

The higher amount of activity observed on workdays as compared to non-workdays was expected in this population. This finding aligns with previous research by Steeves, et al., and Quinn, et al., suggesting that occupation is a strong determinant of one's individual physical activity profile and that those working in industries requiring OPA seem to achieve higher amounts of activity overall.^{15,17} The current study of workers in the food service, material moving, healthcare, and maintenance industries aligned generally with the industry-specific activity

profiles previously reported by Quinn, et al., where workers in the same industries were observed to have high levels of light activity and low levels of total SED.¹⁷

When comparing workdays and non-workdays, participants accumulated 137 fewer minutes of total SED per day on workdays as compared to non-workdays and, importantly, most (101 minutes) of that difference in time was comprised of long-bout SED. One previous finding from the Danish Take-a-Stand study observed higher amounts of sitting during work time compared to non-work time in individuals with sedentary jobs.¹⁵⁶ However, this opposite activity pattern comparing workdays and non-workdays among individuals with active vs. inactive jobs is plausibly explained by compensatory behavior during non-work time. The current study results also align with findings reported by Chastin, et al., who reported that those with sedentary occupations tend to accumulate their sedentary time in long, sustained bouts whereas those with active jobs had shorter average sedentary bout length.¹⁵⁷ Long-bout SED is often accumulated during leisure-time activities such as television viewing and computer use. Our finding that non-workdays had more long-bout SED than workdays likely reflects higher engagement in these behaviors during leisure time.¹⁵⁸ Overall, participants in the current study were observed to have lower accumulation of total SED and long-bout SED on workdays vs. non-workdays.

The current study also estimated that 44% of time across all days was spent upright (standing or moving) and participants achieved 11,328 steps per day. These data also agree with previous research by Steeves, et al., who reported that individuals in food service and material moving occupations accumulated 11,602 and 9,960 steps per day, respectively.¹⁵ Because we are unaware of previous research using inclinometry to measure posture in workers with active jobs, it is difficult to determine whether the upright time observed in the current study is similar to others. However, the percentage of upright time and number of steps is higher than the previously

reported percentage of upright time (33%) and total steps per day (9,737 steps) in office workers,¹⁵⁵ as would be expected. The current study shows that workdays had approximately 137 more minutes of upright time (the inverse of sedentary time) and 4,848 more steps than non-workdays. This is expected, as eligibility criteria for the study required that participants had to report having jobs requiring mostly active duties. Interestingly, the previous study of office workers found no difference in upright time between weekend days (assumed to be non-workdays) and weekdays (assumed to be workdays).¹⁵⁵ However, the same study reported that office workers accumulated approximately 164 more steps each day on weekdays compared to weekend days. This previously reported difference in steps is significantly less than what the current study found between workdays and non-workdays, which suggests greater variability in activity on workdays and non-workdays in men with high OPA.

Overall, the current study observed significantly higher activity levels and significantly less total SED on workdays vs. non-workdays in a sample of men with high OPA. Specifically, more upright, long-bout upright, light, and moderate activity as well as less total SED, short-bout SED, and long-bout SED was observed on workdays compared to non-workdays. The observed activity levels align well with other population-level data using less robust measurement techniques. Workday vs. non-workday variation in activity level seems to be higher than what is observed in other working populations with more sedentary jobs.

5.1.2 Achievement of aerobic physical activity guidelines

To understand whether the men in the current study were accumulating recommended levels of activity during work, non-work time, or both, we estimated daily totals of moderate-equivalent minutes and extrapolated them to weekly guidelines (≥ 150 moderate-equivalent

minutes per week). Discussing the activity profiles observed in the current sample relative to the aerobic physical activity guidelines is important, as physical activity accumulated in any domain (e.g., work or leisure) counts toward these recommendations. Most of the participants (89%) had an overall activity pattern that met the aerobic physical activity guidelines across all days of monitoring. It is important to note that, in comparison, approximately 45% of the general U.S. population meet the aerobic guidelines when measured by accelerometry methods that are similar to those used in the current study.⁶⁵ Even using self-reported physical activity estimates, which are known to be subject to over-estimation, only 50.7% of individuals in the U.S. meet these guidelines.⁶³ Not surprisingly, as we included only men reporting highly active jobs, all 19 participants achieved daily activity levels consistent with aerobic guidelines when considering only workdays. When only considering non-workdays, a majority of participants (n=13, 68%) still had daily activity profiles at or above guideline-level activity thresholds. Given the known cardiometabolic health benefits of regular physical activity, it is vital to note that individuals with active occupations as measured in this study seem to be achieving the aerobic physical activity guidelines at a higher rate than those of the general population, even on non-workdays. Still, as mentioned previously, self-reporting high amounts of OPA has been paradoxically associated with higher risks for cardiovascular and all-cause mortality.¹⁸ Further discussion of the possible effects of habitual OPA on long-term health can be found in Sections 5.2, 5.3, and 5.5.

The assessment of activity in this study, though objective, only measured ambulatory movement rather than lifting, carrying, or other non-ambulatory activities, which could be a substantial part of the occupational duties performed by our study sample. The Physical Activity Guidelines for Americans include not only aerobic activity but also muscular strengthening exercises twice per week to achieve optimal health. While it is possible that the lifting and carrying

activities done at work are intense and build strength, it is not clear from our current data whether the accumulated OPA includes muscular strengthening activities equivalent to those required to meet the associated physical activity guidelines for muscular strength. Future literature should attempt to quantify this aspect of OPA and whether it contributes to achievement of muscular strengthening guidelines and related health outcomes.

Altogether, these conclusions further emphasize the well-established association between occupation and one's activity profile. Those with active occupations are indeed performing physical activity equivalent to or exceeding accepted aerobic physical activity guidelines. However, the effect of OPA on muscular strength and its associated health effects is unclear.

5.1.3 Activity profiles during work time

The few previous studies providing descriptive information regarding activity profiles across occupational categories or specific jobs have been limited by relying on measurement of activity during the entire waking period rather than differentiating work time specifically.^{15,17} Considering this limitation of the previous literature, it is hard to determine in which domain (work, non-work, both, etc.) the measured activity was achieved and therefore difficult to quantify actual OPA exposure.^{15,17} The current study worked to address this limitation by collecting domain-specific activity information by using a study-developed time-use diary. Interestingly, when limiting activity to only that achieved during work time, 79% of participants still accumulated sufficient daily activity to meet aerobic physical activity guidelines. In fact, the overall average was 57.0 moderate-equivalent minutes of activity per workday. These data suggest that, on workdays, individuals with highly active occupations most likely do not need to perform

additional LTPA to achieve the aerobic activity levels recommended in the Physical Activity Guidelines for Americans.

Total SED made up an average of 34% of work time, with the percentage of the workday spent sedentary ranging from 4% to 74% among all participants. Work time in this population was spent mostly upright (66%), with almost half of that being spent in long-bout upright (≥ 60 -minute bouts; 29% of work time). In contrast to overall physical activity guidelines, these activity profiles can be compared to a previous expert statement regarding sedentary behavior at work. In 2015, an international group of scientific experts commissioned by Public Health England recommended that 2-4 hours of an 8-hour workday (i.e., up to 30 minutes/hour) should be spent upright (standing or other activity) and that only 4-6 hours should be spent in sedentary time.⁵⁸ Comparing the upright time observed in this study to these recommendations, we found that 14 out of the 19 participants (74%) exceeded the maximum recommendation of 4 hours per day (or 30 minutes per hour). Notably, upright minutes per work hour ranged from 20.7 minutes to 59.8 minutes across participants. While the adverse health effects of excessive sedentary time throughout the workday have recently become more established,⁵⁸ the inverse of this behavior (excessive occupational standing) has also been associated with negative health outcomes such as an increased risk for incident heart disease.¹⁵⁹ It is clear that the individuals in the current study accumulated a large amount of overall and prolonged upright time throughout the workday. Most of that time was spent performing light activity (83% of upright time) rather than simply standing. While evidence is accumulating that replacing sitting with standing or light-intensity activity is likely beneficial to health in predominantly desk-based (i.e., sedentary) workers,^{58,160,161} the health implications and optimal pattern of standing and light-intensity activity (slow walking, low-intensity occupational tasks, etc.) in highly active workers is unclear and should be explored further in future research.

Holtermann, et. al., hypothesized that the light-intensity nature of OPA is of insufficient intensity to confer cardiorespiratory fitness benefits and the resulting protection against cardiovascular disease.¹³ The current study does suggest that a large majority of OPA was accumulated in light-intensity activity and a very small amount of time (0.2%) was spent in vigorous-intensity activity, which would be most likely to increase cardiorespiratory fitness. Yet, moderate-intensity activity levels were high and aerobic physical activity guidelines were met by most men during the workday. Further, among these same men, fitness levels varied widely. Therefore, it is hard to determine the effect of OPA on fitness in this cross-sectional, observational study. The effect of OPA on fitness and, in turn, future cardiovascular health outcomes should be explored further.

5.1.4 Work-time activity intensity

Lastly, comparing work time activity intensity relative to recommended relative intensity limits for sustaining optimal cardiovascular health could provide insight into the OPA health paradox. Current recommendations endorse that individuals should maintain a relative intensity of less than 30% HRR throughout an 8-hour workday to limit cardiovascular strain and maintain cardiovascular health. In the current sample, 18 out of 19 participants (95%) spent some time above that threshold on an average workday. Specifically, the percent time per working day spent above that 30% HRR threshold ranged from 2% - 85% of the day. The wide range may be due to the wide variety of occupational tasks required for each individual. It could also be due to the variety in fitness levels among the participants. Those with lower fitness would exceed 30% HRR at a lower absolute workload of work tasks and thus may be more susceptible to this exposure. The opposite would also be true among those with higher fitness levels, where the relative intensity of

job tasks would be lower. This concept has been proposed previously as a potential mechanism to explain the OPA health paradox and will be discussed in more detail in the discussion of Specific Aim III.¹³ For some participants, most of their day is spent above the intensity threshold of 30% HRR. This consistently elevated intensity may cause increases in cardiovascular load throughout the day, resulting in cardiovascular strain over time. This concept will be explored in more detail in Specific Aim II.

5.1.5 Conclusions

In conclusion, the current sample of men working in active occupations were observed to have high activity levels, consistent with meeting or exceeding the aerobic Physical Activity Guidelines for Americans. This was especially true during workdays, where the overall activity profile was characterized by higher upright and moderate-intensity physical activity and lower sedentary behavior than on non-workdays. As expected, most work time was spent in upright activity, which resulted in the majority of individuals exceeding previously recommended light activity and working time intensity guidelines on an average workday.^{19,58} However, considering that the current recommendations for OPA were established either many years ago or for a different purpose than to maximize cardiovascular health, caution should be taken when interpreting the currently observed activity levels relative to these recommendations. Future research should work to more fully understand the long-term health implications of exceeding these recommended limits. Such research could inform updated recommendations and policies that lead to optimal cardiovascular health in occupations with high amounts of OPA.

5.2 Specific Aim II

5.2.1 Cardiovascular responses

Specific Aim II focused on comparing the 24-hour cardiovascular load and nocturnal HRV on workdays versus non-workdays to further understand the potential effect that high OPA has on the cardiovascular system. In agreement with the OPA health paradox hypothesis, 24-hour HR, waking time HR, 24-hour diastolic BP, and waking time diastolic BP were found to be significantly higher on workdays versus non-workdays. However, no difference in systolic BP between workdays and non-workdays was observed. HR and BP during the nocturnal period were found to not differ between work and non-workdays. No differences were found in non-work time HR and systolic BP between days, but non-work time diastolic BP was observed to be higher on workdays than non-workdays.

To first understand the comparison between workday and non-workday cardiovascular load, it must be acknowledged that, as demonstrated in Specific Aim I, activity levels on workdays were significantly higher than on non-workdays and generally higher than population averages. Further, this difference in activity was driven by OPA. As discussed above, previous research suggests that high amounts of OPA may be related to adverse cardiovascular risk due to increased 24-hour cardiovascular workload (HR and BP), resulting in chronic cardiovascular strain and, ultimately, cardiovascular damage.^{13,18} However, this proposed mechanism of the OPA health paradox has not been studied with measurement of 24-hour cardiovascular responses across a typical work week for individuals with highly active jobs. The current results provide some initial evidence, using acute OPA exposure, in support of this mechanistic pathway for the OPA health paradox.

It is well established that ambulatory systolic and diastolic BP are expected to increase during a bout of acute aerobic exercise and decrease acutely after the bout as well as chronically in response to aerobic exercise training.^{23,162-165} This hypotensive post-exercise response is consistently observed in waking, nocturnal, and 24-hour time intervals following acute dynamic exercise.¹⁶⁵ This phenomenon has also been shown to be especially true in those with elevated baseline BP.¹⁶⁵ Additionally, the level of reduction has been thought to be directly proportional to the intensity of exercise.^{23,165} Previous research has suggested that the observed post-exercise hypotensive response is a product of decreased cardiac output due to a drop in total and peripheral vascular resistance within the first 30 minutes following an exercise bout.¹⁶⁶ Reductions in 24-hour ambulatory BP following chronic aerobic exercise training are thought to stem from adaptations such as reductions in resting sympathetic activation, increased peripheral blood flow, heightened baroreceptor sensitivity, and improved vasodilatory function.^{23,165,166}

Contrary to the hemodynamic and cardiovascular responses seen in response to acute and chronic aerobic LTPA, the current study's results suggest a different response following a workday with high levels of OPA. Interestingly, we observed that the expected compensatory hypotensive responses following OPA did not occur. This different response is characterized by the non-significant differences in nocturnal systolic or diastolic BP between workdays (following OPA and higher activity levels) and non-workdays (without OPA and lower activity levels). It has been previously suggested that the degree of post-exercise hypotensive response is directly related to exercise intensity, where the greatest hypotensive responses were seen after exercise of vigorous intensity (75% VO_2max).^{23,27} OPA intensity in this study rarely exceeded moderate intensity (<1% of work time) and was mostly light-intensity activity (55% of work time and 83% of the upright time during work). Considering that the magnitude of post-exercise hypotensive response is

directly related to intensity, it is possible that the mostly light-intensity nature of the OPA was insufficient to elicit a hypotensive response following workdays as compared to non-workdays.²³ Additionally, the sustained light activity across the day including non-work times could have also reduced the likelihood of an acute hypotensive response.

Also contrary to previous acute exercise research, a significantly higher diastolic BP was observed during non-work time following OPA on workdays as compared to non-workdays. Similarly, 24-hour and waking HR and diastolic BP were higher on workdays than on non-workdays. These results support the previously stated hypothesis of elevated 24-hour cardiovascular load because BP and HR would be increased during exposure to OPA due to increases in cardiac output to maintain muscle oxygen demand. However, importantly, it seems that a full workday of OPA increases HR and diastolic BP on average throughout the entire 24-hour period on workdays compared to non-workdays. This could reflect the long duration of OPA exposure, with less exposure to subsequent rest, that does not appear to elicit the expected and compensatory post-exercise hypotension seen with LTPA.

Our results can be compared to a previous study of 182 male workers that found a significantly higher 24-hour systolic BP associated with high amounts of self-reported occupational lifting and carrying.¹²¹ However, this study did not find a difference in 24-hour systolic BP when using objective measurement of physical activity, which is consistent with our systolic BP findings and aligns more closely with the measurement technique of the current study.¹²¹ Unfortunately, this previous study did not report ambulatory diastolic BP, limiting this comparison. The reported association between occupational lifting and carrying with higher systolic BP¹²¹ is likely a product of the known phenomenon where isometric contraction greatly increases systolic BP.^{167,168} It is also known that isometric exercise has similar BP reducing effects

as dynamic exercise.¹⁶⁹ Because the current study only used objective measurement of ambulatory activity using inclinometry and accelerometry, we cannot determine how much lifting and carrying the current study population completed nor explore this line of inquiry. Future studies should examine the potentially differential effect of OPA modality (walking, lifting, carrying, etc.) on ambulatory BP and HR response to fully understand this potential connection between OPA and elevated cardiovascular load.

As proposed by Holtermann, the observed heightened diastolic BP and HR responses during the workday coupled with the lack of hypotensive response following OPA could also be a sign of persistent sympathetic activation. This sympathetic activation may be due to occupational psychological stress or the chronic nature of the OPA performed without breaks or adequate recovery.¹³ The sample population of the current study worked, on average, 8.2 hours per day and 4.8 days of a 7-day monitoring period. Paired with the fact that the majority of work time was spent doing physically active tasks, the opportunity for rest and recovery from the OPA load was minimal. Previous literature looking at overtraining syndrome in athletes has suggested that overtraining syndrome can induce increased sympathetic tone due to lack of recovery and result in cardiovascular pathophysiology such as atrial fibrillation.^{21,170-172} The current results provide preliminary data to suggest a similar phenomenon where high levels of OPA could be contributing to increased sympathetic tone and, as a result, increasing 24-hour HR and diastolic BP. More convincingly, the non-work time diastolic BP (not influenced by the acute cardiovascular response of OPA) were observed to remain elevated on workdays compared to non-workdays. Previous research has observed that elevated resting HR is indicative of overtraining syndrome and heightened sympathetic response.¹⁷³ Similarly, elevated BP is known to be associated with increased sympathetic activity and decreased parasympathetic activity due to reduced baroreceptor

sensitivity and increased vasoconstriction.^{174,175} However, inconsistent with this proposed mechanism is our finding that systolic BP was not also significantly elevated on workdays. Previous studies considering sympathetic activation and overtraining responses have shown both diastolic and systolic BP to increase in parallel to acute activity overload.^{173,176} Future research is certainly needed to untangle the effect of acute OPA on ambulatory BP responses, specifically the potential differential responses between diastolic and systolic BP.

Overall, the current study results indicate that 24-hour HR and diastolic BP are higher on workdays than non-workdays. While the current study only measured this acute response over one week and did not consider duration of exposure to OPA, we captured habitual OPA and responses that would likely be similar over a longer period of measurement. It has been previously shown that heightened 24-hour HR and BP is highly associated with all-cause mortality in middle-aged men, likely due to vascular damage sustained from chronic cardiovascular strain.²⁰ Therefore, the results from this study indicate that OPA exposure during a workday may impose a greater average cardiovascular demand and, as such, could lead to compromised cardiovascular health through chronic exposure.²⁰ Prior research has suggested changes in ventricular structure and function as a result of chronic exposure to high levels of aerobic LTPA such as marathon running.²¹ Future research investigating similar effects of chronic OPA exposure on vascular and heart structure and function, and subsequent effects on cardiovascular morbidity and mortality, is warranted.

5.2.2 Heart Rate Variability

The current study compared nocturnal HRV parameters on workdays and non-workdays to further understand the potential autonomic implications of OPA exposure as a mechanism to explain the OPA health paradox. Investigation of HRV parameters resulted in mainly non-

significant differences between workdays and non-workdays across two different processing methods. However, LF and HF were both found to be significantly lower on workdays compared to non-workdays when assessed across the whole night. No significant differences in RMSSD, SDNN, and LF/HF ratio were observed across workdays and non-workdays.

Interestingly, differential HRV results were observed using the two different HRV processing methods. One method considered the whole night's sleep to align with methods for nocturnal HRV measurement from the Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology.¹⁴² The second method considered only the three 5-minute (3x5-minute) periods throughout the night with the lowest recorded HR values to align with previously described methods used by Hallman, et al., when studying the OPA health paradox.²⁴ The whole-night method found significantly lower LF and HF results while the 3x5-minute method did not. This difference may be due to the removal of important variability among the HR samples using the 3x5-minute method. Given the expert recommendation, we concluded that the whole-night method more accurately represents the autonomic activity during the nocturnal period. Thus, we have focused our discussion and interpretations on the whole-night results due to their more valid representation of the whole sleep period. However, further exploration into the difference across these processing methods is warranted.

Our results can be compared with one study by Hallman, et al., who evaluated associations of nocturnal HRV with LTPA and OPA in a group of 514 blue-collar workers.²⁴ Hallman, et. al., concluded that high OPA in the presence of LTPA was associated with lower (i.e., worse) HRV, whereas there was no association when low OPA was paired with LTPA.²⁴ These previous data suggest that the presence of OPA is associated with lower of parasympathetic tone (lower RMSSD, HF, and SDNN). Considering the previous findings of Hallman, et al., our findings specifically,

lower nocturnal HF following workdays compared to non-workdays could indicate that high OPA results in decreased nocturnal parasympathetic activity. However, when using similar HRV processing methods as used in the Hallman analysis, we found no significant differences.

The inconsistent associations we observed between OPA and nocturnal HRV across processing methods and HRV parameters reduce confidence in this proposed mechanism to explain the OPA health paradox. The only significant differences observed between workdays and non-workdays were in whole-night LF and HF; notably, no differences were observed for RMSSD, SDNN, or the LF/HF ratio. While LF is often considered to be a marker of cardiac sympathetic tone, recent evidence has suggested that this is a potential overinterpretation of the measure.¹⁷⁷ Therefore, only limited interpretation will be given to that parameter specifically. SDNN, as a marker of total HRV and not only parasympathetic activity, would not necessarily be expected to respond in parallel with the HF response observed and therefore non-significant SDNN results do not dampen the conclusions made from significant differences in HF.^{177,178} However, it would be expected for RMSSD to change in parallel with our finding of lower HF as another marker of parasympathetic activity.¹⁷⁸ Considering all of this, in addition to our small sample, further research is needed to confirm the conclusion of parasympathetic withdraw as a response to OPA on workdays versus non-workdays.

Notwithstanding the limited associations we observed, several pathways have been proposed to explain impairment of autonomic function with exposure to OPA. The observed decrease in HF, potentially reflecting parasympathetic withdraw, may be due to heightened psychological stress during the workday which persists through the night. Previous literature has shown that periods of high work stress may result in decreased vagal tone and associated decreases in resting HRV due to increased catecholamine release.¹²⁶ Also, high psychological stress while

awake has been shown to impair sleep quality, which could be reflected in compromised HRV.¹⁷⁹ Thus, an effect where psychological stress at work results in lower nocturnal HRV is feasible.

Lower nocturnal LF and HF HRV parameters following workdays compared to non-workdays in the current study could also be a reaction to the prolonged physical stress from OPA. One study measured the effect of acute exercise of various intensities (easy, moderate, hard) and durations (30, 60, and 90 minutes) on nocturnal HRV and HR.¹⁸⁰ Though no differences in response were observed across intensities, lower nocturnal HRV was observed following the longest duration exercise bout (90 minutes), potentially due to delayed recovery of cardiac autonomic modulation during the nocturnal period.¹⁸⁰ These results have been replicated in another study of endurance exercise (marathon training), which suggested a dose-response relationship between exercise duration and the decrement in nocturnal HRV. This study found that the greatest reduction in nocturnal HRV followed the greater duration of exercise (i.e., the marathon run).¹⁸¹ These results align with the current study findings where we observed reduced HF and LF as well as elevated HR on workdays with more physical activity (and specifically OPA) as compared to non-workdays with less physical activity.

It is also possible that the results in the current study are explained somewhat by the direct relationship between nocturnal HRV and sleep. HF power increases with deepening sleep stages, so a greater proportion of deep sleep would result in greater HF HRV.¹⁸² Furthermore, some literature has suggested that OPA may in fact lead to poorer sleep and associated decrements in HRV.¹⁸³ This is in contrast to the known sleep-improving effects of LTPA.¹⁸³ It is, however, still unclear in this study if OPA led to poorer sleep and thus lower HRV, or if HRV was lower despite no change in sleep associated with OPA. Differing sleep durations across work and non-workdays could have also influenced this relationship where non-workdays in the current study had longer

sleep duration compared to workdays. Further research should explore these research questions using measurements of sleep quality to further disentangle the relationships.

Our findings of reduced HRV should be confirmed in future research due to the small sample and the inconsistencies across HRV parameters and data processing methods. However, the results of the current study may provide some initial evidence of acute nocturnal parasympathetic withdrawal associated with high amounts of OPA, potentially due to impaired recovery from the physical and psychological stress of OPA. If that is indeed the case, it would align with the cardiovascular responses discussed previously in Section 5.2.1 since parasympathetic withdrawal can cause a hypertensive response and could be driving associations between OPA and cardiovascular risk.¹⁸⁴

5.2.3 Conclusions

Overall, these data suggest that the hypotensive responses typically seen following acute exercise were not observed following OPA on workdays compared to non-workdays. To the contrary, elevated diastolic BP was observed during non-work time on workdays as compared to non-workdays. Additionally, elevated 24-hour and waking time HR and diastolic BP was observed on workdays compared to non-workdays. Finally, workday nocturnal HF and LF HRV parameters were also lower as compared to non-workdays. Together, these data suggest an overall cardiovascular load on workdays that is significantly higher than non-workdays. This increased cardiovascular load could help explain the seemingly paradoxical association between OPA and adverse cardiovascular health.¹³ Further, reduced nocturnal HRV could suggest that the elevation in cardiovascular load on workdays is associated with nocturnal parasympathetic withdrawal which may inhibit hypotensive responses to physical activity. However, further confirmation of

this pathway should be explored in greater depth as the HRV results were inconsistent across parameters and processing methods.

5.3 Specific Aim III

5.3.1 Effect modification by fitness level

Researchers have proposed that OPA, which is often of low intensity, would not necessarily cause the beneficial cardiorespiratory fitness adaptations observed with habitual LTPA. Therefore, those with high amounts of OPA could still have low fitness and these low fitness individuals could have greater cardiorespiratory responses to the OPA required by their job.^{13,25} The existence of individuals with low fitness levels in the current sample suggests that, indeed, high OPA levels do not necessarily confer high fitness levels. The current study also tested the hypothesis that fitness level would modify the effect of OPA on cardiovascular strain. Specifically, we hypothesized that individuals of lower fitness would have larger increases in cardiovascular strain between workdays and non-workdays as compared to individuals with higher fitness levels. However, our hypothesis was not confirmed in the current data; the difference in cardiovascular strain between work and non-workdays was not different between individuals with high and low fitness.

One possible explanation for these findings is that individuals with lower fitness levels choose, are assigned to, or complete OPA at a lower absolute workload than individuals with higher fitness levels. This would equalize the relative intensity of the OPA across higher and lower fitness categories and could result in the similar workday increases in 24-hour cardiovascular strain

seen among participants with low and high fitness. This is possible with the current observational and cross-sectional study design where jobs and typical OPA tasks were not randomly assigned and the temporality of cardiorespiratory fitness and OPA is not established. Future research using different designs, for example controlling the absolute workload, will be important to further elucidate this proposed mechanism of the OPA health paradox.

Direct comparison of the current study's analyses exploring low fitness as a mechanism explaining the OPA health paradox is difficult because it is the first study to examine this specific interaction. However, a previous study by Korshoj, et al., examined the effect of an aerobic exercise program on fitness in 116 male and female cleaners.¹⁸⁵ This study found that, overall, the cleaners had high levels of OPA and low fitness levels at baseline, which is consistent with our sample where some individuals had low fitness yet high OPA. After completing a 12-week exercise program performed outside of work, the fitness levels of the cleaners increased significantly.¹⁸⁵ Furthermore, following exercise training, the relative intensity of the OPA (as measured by HRR) decreased significantly due to increased fitness.¹⁸⁵ However, contrary to the expected effect where increased fitness would reduce cardiovascular strain with OPA, ambulatory BP increased following exercise training compared to baseline.¹⁸⁵ While both of these studies support the idea that fitness can be low in the presence of an active occupation, the available evidence does not suggest that higher fitness or increasing fitness protects individuals from OPA-related increases in cardiovascular strain.

Additional considerations should be given to other factors that influence the interpretation of the fitness results of this study. The current sample did have a large range of fitness levels (estimated $\text{VO}_{2\text{max}}=35.0 - 48.2 \text{ ml/kg/min}^{-1}$), improving our ability to perform the effect modification analysis adequately. However, the sample was small and the range in fitness levels

observed could have been due to age-related fitness declines rather than as a measurement of training status or activity level. The relatively high VO₂max observed could have been a product of the exclusion of any individuals with known disease or on cardiovascular related medications.²⁷ Furthermore, fitness was estimated using a submaximal (80% predicted HR_{max}) rather than maximal exercise test, which likely introduced inaccuracy in VO₂max estimation. However, this measurement technique provides a superior VO₂max estimation as compared to other studies of the OPA health paradox that have used field-based testing to estimate fitness levels (e.g., step test).²⁵

5.3.2 Effect modification by job stress

Increased cardiovascular load caused or exacerbated by job stress is another potential pathway through which the OPA health paradox may be working.^{13,126} While LTPA has been previously shown to be effective at reducing stress levels,^{186,187} OPA may be stress-inducing due to high job demand and low task control.^{126,150} Cardiovascular responses to this psychological stress could interact with the physical exertion of OPA to exaggerate cardiovascular strain.¹³ Furthermore, chronic high stress has been related to many poor cardiovascular health outcomes such as high BP and incident cardiovascular disease.¹⁸⁶ Though HR was similarly elevated during workdays with high and low stress as compared to non-workdays, the current data suggest that the level of job stress may contribute to the differences in 24-hour diastolic BP across workdays and non-workdays, with a similar but non-significant pattern observed for systolic BP.

These data suggest that the overall result we observed in Specific Aim II, whereby 24-hour diastolic BP was elevated on workdays vs. nonwork days, might be driven by increased diastolic BP specifically on workdays with high work-related stress. Accordingly, an increase in BP was

not observed when comparing low stress workdays to non-workdays. Multiple other studies have found similar results where high work stress levels have been associated with heightened diastolic BP,^{188,189} including ambulatory BP.¹⁹⁰ Yet, the current study is the first to show that a combination of higher work-related stress and OPA may result in higher 24-hour diastolic and potentially systolic BP compared to OPA during a low-stress workday. It is also feasible that OPA could have been higher on high stress workdays, thereby raising diastolic BP on high stress days; however, that question was not specifically explored in these analyses and should be examined in the future.

It is unclear why 24-hour HR would be similar across high and low stress workdays with the presence of the observed differences in diastolic BP. Previous literature suggests that HR would be higher in the presence of high work-related stress.¹²⁶ The current study suggests that the effect of stress on HR is different when stressed in conjunction with OPA. However, considering the limitations of the current study, this concept should be explored further in future research.

Lastly, as described above, the elevated diastolic BP during non-work time and lower nocturnal HRV following workdays compared to non-workdays could signal the withdrawal of parasympathetic activity and increased sympathetic activation on workdays. The finding that higher stress levels are associated with greater 24-hour diastolic BP further supports this autonomic conclusion. Work-related stress associated with OPA could activate the sympathetic nervous response even after work has concluded for the day, therefore explaining the elevated non-work time diastolic BP and lower nocturnal HRV parameters on workdays. This study provides initial evidence that warrants further research to confirm work-related stress as a mechanism to explain the OPA health paradox.

5.4 Study Strengths and Limitations

The current study provides novel examination of the potential mechanistic pathways through which the OPA health paradox could be operating. However, several strengths and weaknesses should be discussed to aid in the interpretation of the results.

First, and most notably, the within-subject design employed in the current study provided the unique ability to control for previously uncontrolled confounding that has been a major limitation of the literature in this topic thus far (e.g., education, socioeconomic status, lifestyle habits such as smoking).¹¹⁵ While the within-subject design limits the influence of the potentially potent sociodemographic confounding by comparing individuals to themselves, this is not a perfect solution as only acute responses across workdays and non-workdays could be examined with this design. This design does not allow comparison of individuals exposed to OPA against individuals not exposed to OPA. The short-term assessment window featured in this research design is a limitation that should be addressed in future research to more effectively explore the potential implications of chronic OPA exposure on cardiovascular health.

Another strength of the current study was the objective physical activity and sedentary behavior measurement using gold standard devices and a diary to determine the activity domain (work, non-work, sleep).¹³⁷ Most previous research on the OPA health paradox employed questionnaires to assess OPA, which are highly subject to reporting and social desirability biases.¹¹¹⁻¹¹³ As evidenced by the current study's self-reported screening tool vs. objective assessment, self-reported OPA seemed to overestimate the amount of higher-intensity job duties. This underscores the need for objective OPA measurement when possible. However, while objective activity monitoring provides valid classification of ambulation, posture, and movement, it does not assess lifting, carrying, and other isometric work activities which may influence BP

differently.¹⁹¹ Since this type of activity may be a prominent component of OPA, future research should work to accurately assess lifting and carrying tasks to better quantify and understand potential differential effects of isometric activities on cardiovascular load.

Additionally, this study was limited to monitoring only volitional activity in free-living environments in which OPA and LTPA were not controlled. Although workdays were significantly more active than non-workdays allowing us to address our hypotheses, the comparison between the two types of days is still influenced by the variability in OPA and LTPA observed across the study population and across days. Future research would benefit from a design with highly controlled activity (e.g., a laboratory protocol with controlled activity exposures).

In addition to the gold standard measurement of activity, this study was strengthened by high-quality and comprehensive measurement of the cardiovascular load (ambulatory BP monitoring, 24-hour HR, and nocturnal HRV). However, as mentioned previously, the cross-sectional design, observational approach, and short-term window of assessment of the current study did not establish temporality or allow for quantification of cardiovascular load or health effects potentially associated with chronic OPA exposure. Study of the chronic effects of long-term exposure to OPA should be considered in the future.

Additionally, measurement of fitness level and job stress provided the ability for novel analyses of these factors as mechanisms explaining the OPA health paradox. While the fitness level measurement utilized in the current study was an improvement from previous studies,²⁵ estimation of fitness level was still made from a submaximal exercise test that relied on the heart rate response, which could have limited the validity of the VO₂max estimation. Job stress was self-reported on the participant diary. Although this measurement of job stress has been associated with acute changes in BP, it is still subject to reporting, recall, and social desirability biases.¹⁵⁰

Nevertheless, the analyses of fitness and job stress provided meaningful data to inform future research into the potential pathways of OPA health paradox.

This study was limited by a small sample size. However, the employment of mixed models and measurement across multiple days allowed for repeated measures comparisons for the primary aims, increasing the power of the analyses. As evidence suggests differential associations of OPA on health outcomes by gender,¹⁸ the sample population of the current study was also limited to males. This limits the external validity of these results; future studies should include females and evaluate the presence of gender differences.¹⁸ Yet, the external validity of the sample was strengthened by the variety in education levels, races, job types, and fitness levels. Previous analyses of the acute effects of OPA on cardiovascular health have examined groups of individuals within the same occupation;^{25,185} however, the inclusion of several different occupations in the current study improves external validity. Ultimately, only four occupational classifications were represented in this analysis and two of those classifications had a single participant. Future research should expand the study population to additional occupations with high levels of OPA in order to improve generalizability. Lastly, the sample population was limited in external validity as we only studied generally healthy participants. Though this design choice was meant to ensure the safety of all participants during the submaximal exercise test and to limit the influence of medications on our outcomes, exclusion of individuals reporting cardiovascular medication use, cardiovascular disease history, or hypertension reduces generalizability. Specifically, we are unable to speculate whether the large proportion of individuals with cardiovascular risk factors would have responded similarly to OPA exposure.

5.5 Future research

While this study provided a novel examination of potential mechanisms to explain the OPA health paradox, it also justifies the need for and informs future directions of more research in this area. The OPA health paradox is difficult to research due to the inherent difficulty in experimentally manipulating long-term OPA exposure (i.e., randomizing individuals to occupations high or low in OPA) and challenges in measuring the complex patterns, modalities, and types of OPA. Thus, a variety of study designs will likely be necessary to elucidate the OPA health paradox.

Future studies should more deeply investigate acute effects of OPA on cardiovascular health. Controlled laboratory studies will be important to understand the acute effects of differing OPA exposures compared to sedentary work without the impact of volitional activity or measurement limitations present in this study. Furthermore, future acute studies should examine the impact of OPA on other proposed mechanisms of the OPA health paradox, such as inflammatory responses. This study provided initial signals of increased sympathetic activity and parasympathetic withdrawal associated with poor recovery and stress from OPA. These signals could be related to inflammatory responses and should be explicitly examined in the future.

In addition to acute measurements of OPA, cardiovascular strain, and other outcomes, longitudinal studies must also examine the long-term effects and potential mechanisms driving the OPA health paradox. Previous longitudinal research provided a basis of understanding for the connection between OPA and all-cause and cardiovascular mortality.^{8,18} However, associations between OPA and more proximal clinical and sub-clinical measures of cardiovascular disease risk are needed to more fully understand the mechanisms underlying the potential OPA health paradox. Statistical modelling methods, such as restriction of important confounding variables or inverse

probability weighting, can address some of limitations of currently available data from observational studies. A growing number of observational cohort studies include objective measurement of activity and these should be used, along with self-reported data, to build latent class profiles of OPA and LTPA patterns in large samples. Lastly, more research is needed in U.S. populations as almost all of the previous studies examining the OPA health paradox have been performed in European or Asian populations. Occupational physical activity exposure and the effect on cardiovascular health may be different among U.S. workers compared to other global populations due to differences in work practices, timing, and culture.

5.6 Considerations for Causal Inference

At this stage, it is reasonable to consider the greater body of the OPA health paradox literature relative to Hill's Criteria for causal inference in observational research. This will determine the strength of the current evidence for the OPA health paradox when adding the results of the current study as well as direct future investigations.¹⁹² Hill's Criteria are a set of nine constructs that can be applied to all existing observational research on a given research topic that is difficult to study using gold standard, experimental approaches (e.g., randomized controlled trials). The strength of inference for determining that an observed association is causal increases as more of these criteria are met. Hill's Criteria include the following: 1) strength of the association, 2) consistency of findings, 3) specificity of the findings, 4) established temporality of the association, 5) evidence of a dose-response relationship, 6) experimental evidence, 7) biological plausibility of the association, 8) coherence of the evidence, and 9) any analogous associations that may exist in parallel to the observed association.¹⁹²

First, the strength of the association observed is low in the current literature. The meta-analytical hazard ratio reported by Coenen, et al., was 1.18 (95% CI = 1.05-1.34) in males and 0.90 (95% CI = 0.80-1.01) in women.¹⁸ Although statistically significant, the magnitude of effect in the males was small while non-significant and in the opposing direction in females. The consistency of observed results is moderate in males and low in females, resulting in low evidence of consistency overall. Again, the meta-analysis by Coenen et al. reported that 14/18 studies found positive associations in males but only 2/11 found positive results in females.¹⁸ Specificity of the available data is low due to notable limitations due to residual confounding from demographic and lifestyle factors that are associated with both OPA and adverse health outcomes. Further, many longitudinal studies report positive associations between OPA and mortality, but OPA exposure is often only measured at one time point, which could result in misclassification of exposure.¹⁸ A dose-response relationship has been demonstrated in several observational studies.^{7,18} However, no experimental evidence is available. While randomization or other experimental manipulation of OPA in longitudinal studies of hard outcomes like cardiovascular events or mortality is likely impossible, manipulation of OPA and acute outcomes like those observed in the current study is a potentially addressable research gap. The current study adds some initial evidence supporting proposed mechanisms for the OPA health paradox and associated biological plausibility of the association, although further research is needed to confirm these results as well as test other potential biological mechanisms. Coherence of the evidence is low due to the lack of available intervention data to support the associations. Lastly, an analogous association that could be used for comparison would be between LTPA and cardiovascular mortality which shows an opposing effect to what is observed in OPA.

In summary, the existing evidence provides some evidence that an OPA health paradox exists. However, the body of currently available literature still has limitations that must be addressed before causal inference for OPA and mortality is considered strong. The available data do suggest that further research is justified to fully understand the observed associations between OPA and long-term health outcomes. Focus should be given to addressing Hill's criteria that cannot be fully evaluated due to limitations of the currently available evidence, such as improving determination of specificity by addressing the limitations of potential residual confounding and misclassification of exposure in the epidemiological literature and further research examining biological plausibility.

6.0 Conclusions

This study provided a novel description of OPA among males with active jobs in comparison to currently recommended LTPA and OPA guidelines. Additionally, it provided an innovative examination of potential mechanisms driving the OPA health paradox.

Overall, the activity levels observed on workdays among the sample was much higher than on non-workdays. This sample achieved daily activity levels consistent with recommendations from the Physical Activity Guidelines for Americans and at a higher rate than the overall U.S population.^{32,140} Furthermore, the majority of the participants achieved this level of activity during worktime alone. However, most also met the guidelines on non-workdays as well. The level of OPA observed often exceeded currently recommended upper limits for accumulated upright activity and relative intensity of activity throughout a workday. While the current recommendations for upright time and guidelines of OPA exist, they were either established many years ago or for a different reason than optimization of worker cardiovascular health. It is therefore worthwhile to pursue future research to understand the health implications of high OPA workloads and make more meaningful recommendations about limitations on OPA based on cardiovascular and overall long-term health.

This study also provides initial evidence that the 24-hour cardiovascular load on workdays is significantly higher than on non-workdays. This increased workload can be most likely attributed to the greater cardiovascular demand required to perform OPA successfully during work time. No compensatory hypotensive response was observed in the non-work or nocturnal periods of workdays as would be expected with acute LTPA. In fact, diastolic BP during non-work time and HR during nocturnal periods remained elevated following workdays compared to non-

workdays, suggesting inadequate recovery or sustained sympathetic activation following OPA. Nocturnal HRV analysis provided limited evidence indicative of lower parasympathetic activity following workdays compared to non-workdays. While these results certainly do not prove the existence of the OPA health paradox, they do provide preliminary evidence that elevated 24-hour cardiovascular load with high amounts of OPA is a potential mechanistic pathway.

This study analyzed effect modification of the relationship between OPA and cardiovascular strain by fitness level and job stress. Though participants had a range of fitness levels, the difference in cardiovascular load between workdays and non-workdays was similar for individuals with higher and lower fitness levels. This result does not support the previously proposed idea that OPA performed in those with low fitness levels may cause increased cardiovascular burden and result in increased cardiovascular risk over time. In contrast, high stress workdays were found to be associated with higher 24-hour diastolic BP compared to non-workdays while low stress workdays were not. A similar but non-significant pattern was observed for systolic BP. These results align with previous literature indicating increased cardiovascular load due to job stress¹²⁶ and provide a potential explanation for the hypothesized elevation in sympathetic activity and decrease in parasympathetic activity following OPA. This research should be repeated in larger and more diverse samples before confirming job stress as a mechanism influencing the cardiovascular load during OPA and contributing to poor cardiovascular health over time.

Caution must be taken when interpreting and translating these results due to the study's limitations, most notably the small sample of men, all with high OPA jobs, and the cross-sectional, observational design. Notwithstanding the limitations, the current results generally support most of our *a priori* hypotheses. Specifically, the results suggest that OPA results in high levels of activity, above OPA recommendations, and that this high OPA is associated with increased 24-

hour cardiovascular load. High job stress experienced concurrently with OPA may exaggerate this cardiovascular load, especially for diastolic BP. That information, combined with the elevated nocturnal HR, a signal of blunted nocturnal HRV, and elevated diastolic BP during non-work time, suggest sustained sympathetic activation and lower parasympathetic activity following workdays with high OPA. These data are in support of an OPA health paradox, however further confirmation is needed before causality can be inferred. Future studies with larger, more diverse samples, using controlled acute laboratory protocols, with better comparison or control groups, and superior longitudinal methods are needed to explore the potential mechanisms explaining the OPA health paradox. However, if the OPA health paradox is indeed true, physical activity recommendations may need to consider OPA as separate from LTPA due to opposing health implications. Furthermore, guidance on OPA time and intensity limits should be reevaluated considering the current literature on OPA and potential negative cardiovascular effects.

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