Diplomarbeit

Associations of physical activity, nocturnal blood pressure and plasma cortisol in hypertensive patients

eingereicht von

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zur Erlangung des akademischen Grades

Doktorin der gesamten Heilkunde

(Dr.^{in} med. univ.)

an der

Medizinischen Universität Graz

ausgeführt am

Univ. Klinikum für Innere Medizin Graz,
Abteilung für Endokrinologie und Stoffwechsel

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Graz, am 29.07.2015

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Danksagung

Für meine kleine Schwester Astrid Oberreither (19.4.1993 – 6.1.2014).
Ich werde dich nie vergessen.

Danke an Mama, Papa, Margret, Angelika und Martin.

Danke an die Betreuer meiner Diplomarbeit.

Table of contents

Abbreviations

ABPM	ambulatory blood pressure monitoring
ACE	angiotensine converting enzyme
AT1	angiotensine-II-type 1-receptor
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CK	creatine kinase
CRP	C-reactive protein
eGFR	estimated glomerular filtration rate
GGT	gamma-glutamyl transferase
HbA1c	glycosilated haemoglobin A1c
HDL	high density lipoprotein
HPA	hypothalamic pituitary adrenal
HR	heart rate
HRV	heart rate variability
IL	interleukin
LDH	lactate dehydrogenase
LDL	low density lipoprotein
NTproBNP	n-terminale pro-brain-natriuretic-peptide
PAC	plasma aldosterone concentration
PP	pulse pressure
PRC	plasma renin concentration
PTH	parathyroid hormone
PWV	pulse wave velocity
TG	triglycerides

VCAM	vascular cell adhesion protein
WHR	waist to hip ratio
25(OH)D	25-hydroxyvitamin D

Figure legend

List of tables

Zusammenfassung

Hintergrund: Körperliche Aktivität ist einer der wichtigsten modifizierbaren kardiovaskulären Risikofaktoren und hat einen direkten Effekt auf den Blutdruck und das vegetative Nervensystem. Der Zusammenhang zwischen körperlicher Aktivität, nächtlichem Blutdruck – eines besonders aussagekräftigen Wertes für die kardiovaskuläre Gesundheit – sowie Cortisol sind nicht abschließend geklärt und wurden im Rahmen dieser Diplomarbeit untersucht.

Methoden: Wir rekrutierten Patienten mit arterieller Hypertonie von lokalen Ambulanzen. Bei allen Patienten wurde eine 24-Stunden-Blutdruckmessung und eine Blutabnahme durchgeführt. Cortisol im Serum und weitere Laborparameter wurden nach Verfahren in der klinischen Routine bestimmt. Körperliche Aktivität wurde mit Hilfe der langen Form des Fragebogens „International Physical Activity Questionnaire“ erhoben.

Ergebnisse: Es wurden 208 Patienten eingeschlossen (Alter=60.8±10.8 Jahre, 53.8% Frauen) mit einer medianer körperlichen Aktivität von 4800 Metabolische Äquivalent (MET) -Minuten/Woche (median = 1240 Minuten (20.66 Stunden) Aktivität/Woche und median = 3.98 MET Intensität der Aktivität) und mit einem mittleren nächtlichen systolischen Blutdruck von 115±16.8 mmHg und einem mittleren nächtlichen diastolischen Blutdruck von 67±10.0 mmHg. In einer linearen Regression adjustiert für multiple mögliche Confounder zeigt sich eine signifikante Assoziation zwischen MET-Minuten/Woche und nächtlichem systolischen Blutdruck (Beta-Koeffizient= -0.18, P-Wert=0.041) und nächtlichem diastolischen Blutdruck (Beta-Koeffizient= -0.22, P-Wert=0.005) sowie ein Trend für eine Assoziation mit dem Cortisol (Beta-Koeffizient= 0.16, P-Wert=0.096).

Diskussion: Es fand sich in Patienten mit bekannter Hypertonie ein signifikanter Zusammenhang (Assoziation) zwischen MET-Minuten/Woche und nächtlichem systolischen und diastolischen Blutdruck.

Schlagwörter: Hypertonie, Körperliche Aktivität, Sport, Stress

Abstract

Purpose of the study: Physical activity is one of the most important modifiable cardiovascular risk factors and has an effect on blood pressure and the autonomic nervous system. Data on the association between physical activty, nighttime blood pressure – a significant predictor of cardiovascular outcome – and cortisol are however sparse. We therefore aimed to study these associations in this thesis.

Methods: We recruited patients with hypertension from the Division of Endocrinology, Department of Internal Medicine, of the University Hospital Graz. We performed ambulatory blood pressure monitoring (ABPM) measurements and blood collections for measurement of serum cortisol in this cohort. Physical activity was assessed with the long form of the International Physical Activity Questionnaire (IPAQ).

Results: We included 208 patients (age 60.8±10.8 years, 53.8% female) with a median physical activity of 4800 metabolic equivalent (MET) -minutes/week (median = 1240 minutes (20.66h) activity/week und median = 3.98 MET intensity of the activity) and mean nighttime systolic pressure of 115±16.8 mmHg and mean nighttime diastolic blood pressure of 67±10.0 mmHg. In linear regression analysis adjusted for multiple confounders MET-minutes/week (physical activity) was significantly associated with nighttime systolic blood pressure (Beta-coefficient= -0.18, P-value=0.041), and nighttime diastolic blood pressure (Beta-coefficient= -0.22, P-value=0.005) and by trend with cortisol (Beta-coefficient= 0.16, P-value=0.096).

Conclusion: In patients with hypertension we found an association between MET-minutes/week and nighttime systolic and diastolic blood pressure.

Keywords: hypertension, physical activity, exercise, stress

Published articles of the diploma thesis

None.

1 Introduction

Low physical activity is considered to be a key risk factor for the development and progression of cardiovascular diseases, which are the most common cause of death in western countries.[1–3] Physical inactivity is also known to be a major global health problem, particularly in developed countries, causing 9 percent of premature mortality and accounting for 5.3 million deaths worldwide in the year 2008.[4] One out of five adults around the world is physically inactive.[5] In the literature we can see several benefits of physical activity.[6] Physical activity has a beneficial effect in preventing cardiovascular diseases and is known to reduce all-cause and cardiac mortality.[7,8] According to studies of the American Centers for Disease Control and Prevention it is advised for every adult to participate in at least 30 minutes of moderate-intensity physical activity on most or all days of the week to gain beneficial effects.[9] In this context, it has also been shown that a significant reduction in risk of cardiovascular disease and mortality can be achieved with just one hour of moderate or vigorous exercise per week (see Figure 1).[10,11]

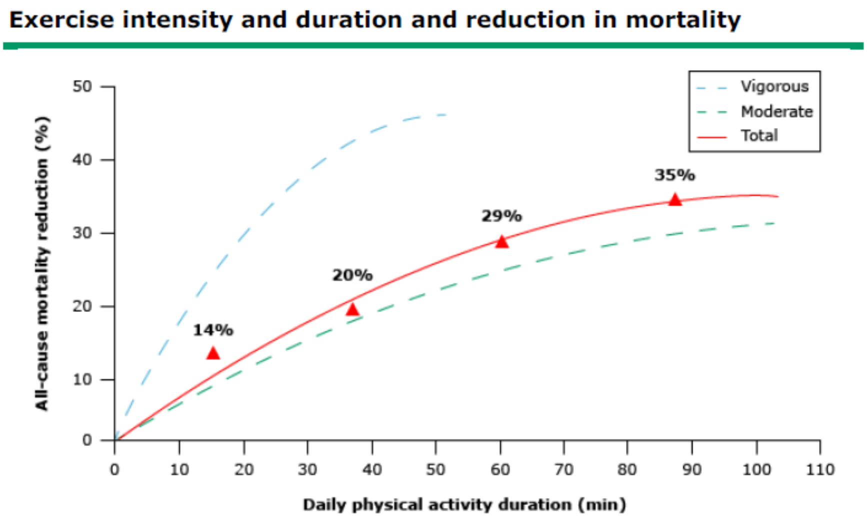

Figure 1. Exercise intensity and duration per day and reduction in mortality[12]

1.1 Definition of physical activity

Physical activity is described as bodily movement due to muscle contraction in one's daily life involving all kinds of activity in work, transportation and leisure time, whereas physical exercise is a subcategory that is planned, structured, and purposed to improve physical skills and fitness.[13] Physical activity requires the coordinated interaction of ventilation, cardiac output, and systemic and pulmonary blood flow to meet the metabolic demands of contracting muscles.[14] It is measured in terms of metabolic equivalents (METs), which are used to estimate the metabolic cost (oxygen consumption) of physical activity.[15,16]

Physical activity contains of three components:[13]

- Intensity (in MET-minutes/week), describing how exhausting the activity is. There are light-, moderate- and vigorous-intensity physical activities. Moderate physical activity includes activity performed at an intensity of 3 to 6 METs and vigorous physical activity includes activity performed at more than 6 METs.[16]
- Frequency (in days), describing how often a person does participate in the activity.
- Duration (in minutes), describing the amount of time a person does participate in the activity in one session.

1.2 Physical activity in the Austrian population

Half of the Austrian population above the age of 15 years does participate in exercise once a week in their leisure time (men: 60%, women: 49%). This is shown in Table 1 with people being considered physically active when participating in jogging, cycling or aerobic exercise for at least three days per week. Due to this criteria only a third of the male and a quarter of the female population are doing exercise (men: 32%, woman: 23%). There is also a difference regarding the age. Men have less physical activity at a higher age, with a decline from 42% being physically active in the group of 15 - to 29 - year olds to 27% in the group of 60 - to 75 - year olds. In women the amount of physically activity is, in most age groups, lower compared to men, with the exception of 45 - to 59 - year olds whom are as active as men in the same group.[17]

Physical activity in the Austrian population in the year 2007						
Physical activity in %	Total (15 years and older)	15 - 29 years	30 - 44 years	45 - 59 years	60 - 74 years	75 years and older
	Men					
active	31,6	42,1	32,7	28,4	27,3	12,0
inactive	68,4	57,9	67,3	71,6	72,7	88,0
	Women					
active	23,3	25,5	26,8	27,7	21,6	5,4
inactive	76,7	74,5	73,2	72,3	78,4	94,6

Table 1. STATISTIK AUSTRIA, Health survey 2006/07. Date: 23.10.2007.

There is an association between the amount of physical activity and the subjective health status. In the group of active people 46% consider their health good, whereas this is only a third in the group of the inactive people. Only 2% of the active people consider their health poor, whereas this percentage is 7 - 8% in the inactive group.[17] Although that might also be related to some form of reverse causality. Despite the widespread prevalence of physical inactivity and its potential health risks, clinicians do not routinely screen patients for physical inactivity or provide adequate counselling.[18]

1.3 Effects of physical activity

Adequate levels of physical activity help to maintain healthy weight and physical strength..[6,9,19,20] The reduction of body fat, the lowering of blood pressure, the improvement of lipoprotein profile and muscle gain itself have been proposed to mediate the beneficial effects of physical activity on health status.[19–21] A growing body of evidence suggests that there are differences in response to physical activity suggesting that not everyone benefits equally.[22] Several studies documented that physical activity reduces serum triglycerides, increases serum high density lipoprotein cholesterol (HDL) and has variable effects on total cholesterol, low-density lipoprotein (LDL) cholesterol, and very low-density lipoprotein (VLDL) cholesterol.[21,23] As a response to physical activity, muscle fibres produce cytokines and other peptides (which are known as myokines), which communicate with the muscle itself, promoting muscle growth and repair, and have anti-inflammatory effects.[19] This is in line with evidence that there are acute and chronic effects on immune functions due to exercise. Acute sessions of exercise cause a temporary depression of various immune functions that last 3-24 hours after the exercise, depending on intensity and duration.[24] After 24 hours there is no difference in athletes and non-athletes regarding such parameters.[24] Swardfager and colleagues described in a meta analysis that physical activity is able to reduce inflammatory activity as indicated by lower CRP, fibrinogen, IL-6, and VCAM-1, which by themselves are biomarkers associated with increased cardiovascular mortality, because of their important role in atherosclerosis.[25] Notable, regular physical activity, particularly exercise, is associated with a reduced incidence of infections.[24] Exercise does also increase the activity of mitochondrial enzymes which leads to improved muscle energetics, decreased insulin resistance and a lower rate of type 2 diabetes.

1.3.1 Neurobiological effects

Physical activity reduces loss of brain tissue, and is therefore considered to have a protective effect against age-related decline in cognitive functions and promotes resistance against neurological disorders.[26] High levels of physical activity are associated with increased gray matter volume in mostly the prefrontal cortex and hippocampus, less in other regions, and thus prevent age-related atrophy, severe memory loss and cognitive impairment.[27] Physical activity is also positively associated with cortisol levels, a glucocorticoid hormone released as a response to stressful stimuli.[28] It’s inappropriate increase, sometimes also referred to as dysfunction of the hypothalamic pituitary adrenal (HPA) axis, might be involved in cardiovascular morbidity and mortality.[29]

1.3.2 Benefits of physical activity on the cardiovascular system

As mentioned before there exists strong evidence linking physical activity to a reduction of cardiovascular risk factors.[30] The benefit of exercise on the risk of myocardial infarction (MI) was demonstrated the INTERHEART study of patients from 52 countries, where regular physical activity was associated with an odds ratio for first MI of 0.86.[31] In line with other observations that higher rates of physical activity were associated with less coronary events.(Figure 4) It has been hypothesized that one of the main mechanisms is the reduction of blood pressure, which is considered to be the most important modifiable cardiovascular risk factor.[20,32,33] Regular exercise can lower the blood pressure (BP) by as much as 5 to 15 mmHg in patients with primary hypertension.[34,35] Optimal BP control with levels less than 130/80 mmHg is recommended to decrease the high cardiovascular morbidity and mortality.[36] Ambulatory blood pressure monitoring (ABPM) is considered to be the gold standard for blood pressure measurement (see Figure 2).[33] The predictive value for cardiovascular risk of nocturnal blood pressure levels as well as the absence of nocturnal dipping has long been established and is superior to daytime BP measurements (see Figure 3).[33,37]

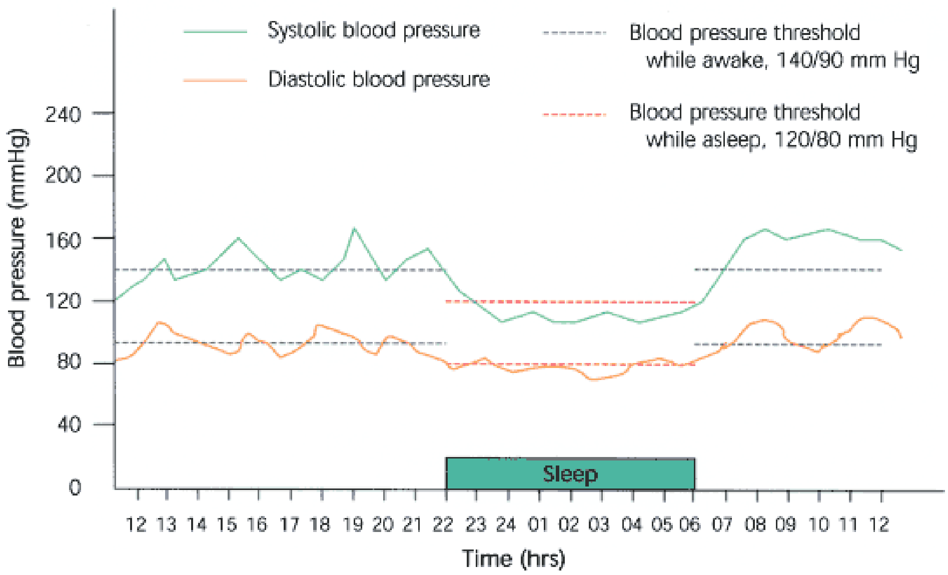

Figure 2. Daytime and nighttime systolic and diastolic blood pressure[38]

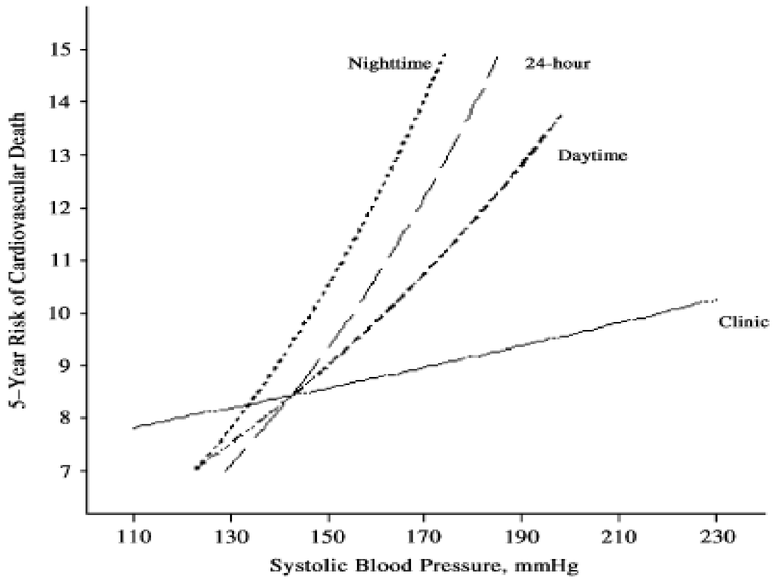

Figure 3. 5-year risk of cardiovascular death[33]

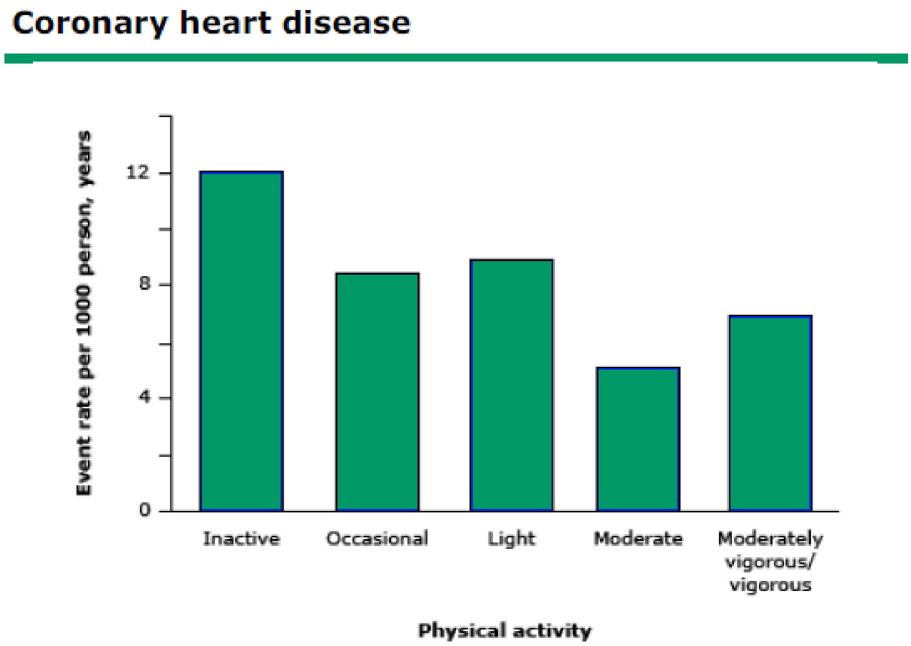

Figure 4. Coronary events among those physically active and inactive.[39]

Nevertheless, there is insufficient evidence about the association of physical activity with blood pressure and neurohumoral activation in patients with arterial hypertension on antihypertensive treatment. This is especially important as those are the type of patients typically encountered in clinical practice.[40] We therefore addressed this issue in the present thesis work.

2 Scientific question

The main question of the present investigation is if there is an association between physical activity (MET-minutes/week) and major cardiovascular risk factors, namely nocturnal systolic and diastolic blood pressure as well as serum cortisol.

2.1.1 Null hypothesis

There is no association between MET-minutes/week, nocturnal systolic blood pressure, nocturnal diastolic blood pressure as well as cortisol.

2.1.2 Aims

A positive association would be hypothesis generating and would provide important information for future interventional studies evaluating the effect of exercise on nocturnal blood pressure and stress hormone levels. Furthermore, it would allow us to estimate effect sizes in a cohort of patients commonly encountered in clinical practice.

3 Methods

3.1 Study population

The Styrian Hypertension Study is a prospective cohort study with the goal to find biomarkers in relation to cardiovascular risk and includes patients of age 18 years and older with a history of arterial hypertension. Study participants were recruited from the Department of Cardiology and Internal Medicine, Division of Endocrinology & Metabolism, at the Medical University of Graz, Austria. Main exclusion criteria were stroke or myocardial infarction in the past four weeks, pregnancy and lactating women, and estimated life expectancy of less than a year. Informed consent was obtained from all participants in a written form. The study was approved by the ethics committee at the Medical University of Graz, Austria, and is compatible with the Declaration of Helsinki.

3.2 Measurements

Details of the methods and study population have been published previously.[41–43] Circumference of the upper arm was measured in all patients to select the appropriate cuff for BP measurements. ABPM was performed with a SPACELABS 90217A device (firmware-version: 03.02.16; Spacelabs Healthcare, Inc, Issaquah, WA) at 15-min intervals during the day (06:00-22:00 a.m.) and every 30 min during the night (22:00–06:00 a.m.).

Figure 5. Spacelabs Healthcare device for ABPM[44]

In parallel, 24-hour urine specimens were obtained from the study participants. 24H-HRV was defined as the standard deviation of 24-hour heart rate obtained by ABPM measurement. QT time was measured on 50 and 100mm/s ECG recordings by a single investigator masked to patient characteristics. An additional sample was recorded randomly by a second investigator independently for validation purposes. The corrected QT time was calculated according to Framingham: QTc = QT + 0,154 * (1-RR).[45] All ECG measurements were performed by adhering to published guidelines.[46]

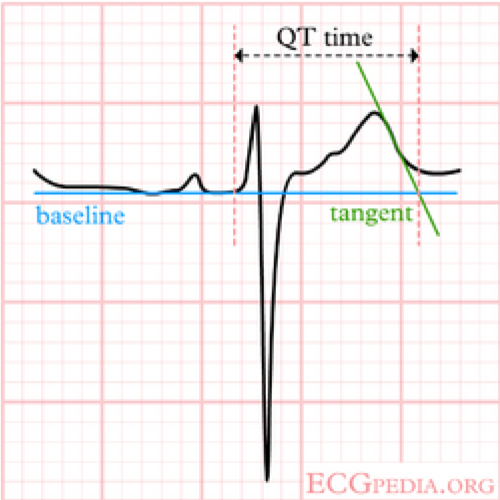

Figure 6. QT time[47]

- **Bazett's formula:** $QT_C = QT / \sqrt{RR}$
- **Fredericia's formula:** $QT_C = QT / RR^{1/3}$
- **Framingham formula:** $QT_C = QT + 0.154\ (1 - RR)$
- **Hodges formula:** $QT_C = QT + 1.75\ (\text{heart rate} - 60)$

3.2.1 Laboratory measurements

Blood samplings were performed in the morning (07:00 to 11:00 a.m.) after an overnight fast and after ten minutes of rest in the seated position. All blood samples were either measured at least within four hours after sampling or were immediately stored at -20° Celsius until analysis. Plasma renin concentrations (PRC) were measured in EDTA plasma by a “RENIN III GENERATION” (GEN. III) radioimmunoassay (RIA) (Renin IRMA RIA-4541, DRG Instruments GmbH, Marburg, Germany). Plasma aldosterone concentrations (PAC) were also determined by means of a RIA (Active Aldosterone RIA DSL-8600, Diagnostic Systems Laboratories, Inc., Webster, Texas, USA). Aldosterone-to-active renin concentration (AARR) was calculated as PAC divided by PRC (ng/dL divided by µU/mL). Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) formula. All other measurements were performed by routine laboratory procedures. Cortisol was measured by an ADVIA Centaur Cortisol-test on a CENTAUR XP (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, U.S.A.). Cross-reactivity with 11-Deoxycortisol was 23.3%, with 21-Deoxycortisol was 8.1%, with 6ß-Hydroxycortisol 6.8%, with allo-Tetrahydrocortisol was 6.5% and with Corticosteron 5.3%. The analytical sensitivity reaches from 0,20 µg/dl (5,5 nmol/l) to 75 µg/dl (2069 nmol/l). Intra-, interassay and total coefficients of variation reach from 2.98 to 3.69%, from 3.99 to 5.45% and from 4.98 to 6.58% for high (37.15 µg/dl) to low (3.88 µg/dl) concentrations (To convert from µg/dl to nmol/l multiply by 27.59).

Quantitative determination of sodium in urine was performed by the ISE (Ion-Selective Electrode) Potentiometry module of a Roche/Hitachi Cobas 8000 analyzer. CV of within-run was 0.6% at maximum, CV of total precision was 1.6 % at maximum, depending on the sodium concentration.

3.2.2 International Physical Activity Questionnaire (IPAQ)

The International Physical Activity Questionnaire (IPAQ) in its long form is used to measure the amount of physical activity. IPAQ is a self-administered questionnaire which has acceptable validity in measuring levels and patterns of physical activity.[48] IPAQ measures physical activity in categories of walking (W), moderate-intensity activities (M), vigorous-intensity activities (V) and a combined total physical activity and expresses them in MET-minutes/week.[49] MET-minutes/week is a value giving information about intensity, duration and frequency of any physical activity done in one week. To measure the intensity of physical activity metabolic equivalent (MET) is used to describe the energy cost. One MET is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 ml O^2 per kg body weight per min, which is the resting metabolic rate.[15] This way it is possible to express physical activity as a multiple of the resting metabolic rate. MET values range from 0.92 MET while sleeping to 23 MET while running at 22.53 km/h[50] are used in the IPAQ in a simplified way as seen in the box below.

Activity	**MET**
Moderate inside chores	3
Walking (at 4.8 km/h)	3,3
Moderate activities in work and leisure time/moderate yard chores	4
Vigorous yard chores	5,5
Cycling	6
Vigorous activities in work and leisure time	8

Table 2. Metabolic equivalent of the activities used in the long form of IPAQ

3.3 Statistical Analyses

The distribution of continuous variables were evaluated by visual inspection of histograms, Q-Q plots, as well as the Mean-Median difference, and tested for differences using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Where appropriate, non-normally distributed variables were log10-transformed and indicated in the text with the prefix “log”. For baseline characteristics we formed three IPAQ categories according to the guidelines from World Health Organisation. Groups were build according to the amount of MET-minutes/week, with 0 – 499 MET-minutes/week as low physical activity group, 500 – 999 MET-minutes/week as moderate physical activity group and above 1000 as high physical activity group. Group comparisons were performed by either Chi-square test for categorical variables, analyses of variance (ANOVA), or Kruskal-Wallis for continuous variables. To test the assumption of a linear regression analysis between the dependent and independent variables of interest we plotted the residuals (observed vs. predicted values) and tested for co-linearity for all included parameters (criteria were variance inflation factor <1.96 equivalent to tolerance >0.51). Further, we compared R^2 values for the plain correlations between independent and dependent variables using linear, quadratic, and cubic terms to estimate whether a linear regression would be appropriate.

A linear regression analysis was then employed to evaluate the association between cortisol, systolic and diastolic nocturnal blood pressure (dependent variables) and MET-minutes/week (independent variable). Cumulative adjustment was performed for various confounders that were selected based on the available literature as well as pathophysiological considerations regarding their interaction with cortisol and nocturnal blood pressure. Three models were built, based on increasing explanatory value. Model 1 included log age (years) and gender. Model 2 additionally included drug intake before blood sampling, statine use, plasma renin and serum homoarginine. In Model 3 we further included for active smoking, estimated glomerula filtration rate [CKD-EPI]. Additionally to all models with plasma cortisol as dependent variable we also included adjustments for triglycerides, intake of loop diuretics, serum albumin and nighttime systolic BP.

3.3.1 Sensitivity check

In sensitivity analysis, further adjustments were performed for: waist, waist to hip ratio, office systolic blood pressure, office diastolic blood pressure, pulse wave velocity, percentage of successful ABPM readings, mean systolic blood pressure in 24h, mean diastolic blood pressure in 24h, mean pulse pressure in 24h, mean heart rate in 24h, mean heart rate variability in 24h, mean heart rate during nighttime in 24h, systolic dipping value, diastolic dipping value, hemoglobin, eGFR, GGT, creatine kinase, LDH, NTproBNP, HbA1c, C-reactive protein, parathyroid hormone, 25-hydroxyvitamin D, aldosterone, rennin, cortisone, homoargenine, HDL, LDL, triglycerides, total 24h urinary sodium, total 24h urinary calcium, ACE inhibitors, AT1-blockers, calcium channel blockers, mineralocorticoid receptor antagonist, beta blockers, statins, loop diuretics and thiazide diuretics.

All statistical analyses were performed with SPSS 22 (SPSS, Inc., Chicago, Illinois) and a two-sided P-value <0.05 was considered statistically significant.

4 Results

	MET-minutes/week															
	low (1-499)					medium (500 - 999)					high (>1000)					
	mean	standard diviation	median	25th percentil	75th percentil	mean	standard diviation	median	25th percentil	75th percentil	mean	standard diviation	median	25th percentil	75th percentil	**P-value**
Number of patients	9					11					188					
Age (years)	62,78	14,31	63,08	52,28	74,43	60,57	13,45	65,75	47,23	70,20	60,71	10,52	62,20	55,79	67,61	.509
Female (%)	56,50					62,70					50,00					.228
Smoking (%)	17,40					11,80					13,40					.806
BMI (kg/m²)	29,25	8,94	28,41	24,71	29,73	30,45	6,67	29,32	24,92	35,61	29,13	5,08	28,28	25,67	31,98	.731
Waist (cm)	101	23	95	88	106	107	17	109	90	119	99	13	98	91	107	.522
Waist to hip ratio	,959	,101	,931	,896	1,040	,985	,087	,989	,951	1,032	,964	,075	,958	,905	1,027	.525
Office systolic blood pressure (mmHg)	147	13	145	141	159	141	13	142	128	148	141	17	140	128	152	.172
Office diastolic blood pressure (mmHg)	87	14	89	80	98	92	11	96	82	100	86	11	85	78	90	.273
Pulse wave velocity (m/sec)	9,49	1,87	8,80	8,00	11,60	8,95	,92	9,00	8,20	9,20	8,88	2,24	8,70	7,70	9,80	.322
Percentage of successful ABPM readings of all readings	63	19	66	53	73	76	15	81	60	89	73	14	77	63	85	.806
Mean systolic blood pressure in 24h RR (mmHg)	126,14	13,86	127,51	118,75	135,41	132,36	9,15	133,31	123,64	141,73	126,52	13,70	124,21	118,25	133,71	.034

Mean diastolic blood pressure in 24h RR (mmHg)	76,50	15,54	74,60	64,52	87,05	82,13	10,11	80,22	73,38	89,70	75,89	9,01	74,75	69,43	82,34	.047
Mean pulse pressure (mmHg)	49,64	10,19	48,71	42,17	53,94	50,24	8,26	48,42	42,01	56,92	50,63	10,22	50,30	42,83	56,65	.970
Mean heart rate in 24h RR (beats per minute)	72,25	9,93	70,80	67,76	79,79	74,65	11,19	71,58	69,09	79,31	71,89	9,08	71,45	65,85	77,97	.148
Mean heart rate variability (beats per minute)	8,53	3,98	9,77	4,88	11,19	10,37	3,64	9,44	7,72	13,47	9,95	3,49	9,45	7,39	12,28	.797
Mean nighttime systolic blood pressure in 24h RR (mmHg)	118,57	16,26	112,00	110,00	124,00	122,91	10,74	122,00	112,00	131,00	114,76	18,68	113,50	105,00	123,00	.072
Mean nighttime diastolic blood pressure in 24h RR (mmHg)	70,43	18,27	66,00	62,00	76,00	74,36	12,27	74,00	62,00	82,00	67,13	9,29	65,50	60,50	73,00	.174
Mean heart rate during nighttime in 24h RR (beats per minute)	65,43	10,80	65,00	59,00	75,00	69,18	12,52	64,00	62,00	74,00	64,48	8,76	64,00	58,00	71,00	.323
Systolic Dipping Value (%)	-5,01	11,64	-5,58	-16,09	9,63	-12,58	7,47	-12,65	-16,21	-10,04	-12,64	8,82	-12,85	-18,51	-7,43	.127
Diastolic Dipping Value (%)	-7,43	9,15	-8,94	-16,11	2,59	-16,49	8,16	-13,09	-21,46	-11,36	-16,27	8,84	-17,13	-22,18	-10,71	.020
Hemoglobin (g/dL)	13,49	2,09	13,55	11,75	14,75	14,23	1,03	14,50	13,50	14,80	14,27	1,24	14,30	13,50	15,10	.767
Estimated glomerular filtration rate (ml/min /1,73m2)	70,24	28,61	61,01	46,03	100,12	84,95	17,85	84,25	74,06	99,85	80,53	17,37	80,60	70,14	91,73	.201
GGT in (U/L)	56,13	54,60	44,00	15,00	75,00	32,91	24,72	20,00	16,00	53,00	37,42	37,65	25,00	17,00	42,00	.360
Creatine kinase (U/L)	105,50	77,09	85,00	58,00	153,50	132,91	89,61	95,00	74,00	192,00	127,97	92,61	105,00	76,00	151,00	.001
LDH (U/L)	171,50	30,38	176,00	155,00	184,50	168,27	37,55	159,00	137,00	185,00	169,89	45,37	164,00	147,00	183,00	.526
NTproBNP (pg/ml)	547,50	586,76	459,00	89,00	724,50	446,09	963,59	109,00	17,00	472,00	135,12	213,57	82,00	40,50	148,00	.053
HbA1c (mmol/mol)	41,25	12,31	38,00	36,50	50,00	41,09	8,22	38,00	36,00	44,00	42,53	10,45	39,00	36,00	44,00	.322

C-reactive protein (mg/L)	2,34	2,14	1,30	,60	4,45	4,30	6,40	1,20	1,00	5,80	2,65	2,82	1,75	,70	3,35	.026
Parathyroid hormone (pg/ml)	58,50	28,72	52,50	44,90	59,05	59,21	24,19	55,70	39,60	71,20	49,67	17,32	47,90	36,75	57,15	.053
25-Hydroxyvitamin D (ng/ml)	27,38	20,30	21,75	13,85	31,05	26,68	8,64	25,60	19,90	33,40	26,27	10,20	25,35	19,10	32,45	.997
Aldosterone (ng/dl)	14,71	5,30	17,70	9,20	19,50	19,47	15,84	15,00	10,60	19,10	15,38	9,16	13,30	9,90	18,60	.960
Renin (µU/ml)	45,23	49,43	30,15	10,10	66,65	23,65	22,28	15,30	8,10	39,00	58,79	273,19	16,40	9,40	41,90	.745
Cortisol (ng/mL)	77	23	88	66	91	91	23	104	87	106	123	48	120	93	143	.021
Homoarginine (µmol/L)	1,73	,60	1,54	1,36	2,17	1,96	,45	1,93	1,59	2,23	1,91	,58	1,84	1,56	2,26	.836
HDL (mg/dl)	53,63	24,47	54,50	35,00	65,50	59,18	13,53	57,00	46,00	70,00	61,43	18,49	58,50	48,00	72,00	.933
LDL (mg/dl)	106,88	41,37	110,00	69,00	144,00	129,73	30,61	135,00	125,00	145,00	111,01	38,40	107,50	82,00	140,00	.741
Triglycerides (mg/dl)	110,38	50,67	92,50	72,50	166,50	109,00	44,80	114,00	65,00	146,00	123,40	87,73	104,00	71,50	141,00	.662
Total 24h urinary sodium (mmol/24h)	134,57	67,29	130,00	81,00	189,00	160,10	62,49	166,50	102,00	202,00	161,46	73,62	150,50	115,00	188,00	.472
Total 24h urinary calcium (mmol/24h)	2,07	1,61	2,20	,40	3,00	5,42	2,15	5,55	3,90	6,30	4,03	2,86	3,40	2,10	5,10	.4127
ACE inhibitor (%)			43,5					25,5					35,8			.252
AT-1 Blocker (%)			34,8					35,3					26,9			.458
Calcium Channel Blocker(%)			21,7					29,4					17,2			.183
Beta Blocker (%)			47,8					43,1					41,8			.863
Statin (%)			34,8					29,4					35,8			.712
Loop Diuretic (%)			13					5,9					2,2			non poss
Thiazide Diuretic (%)			47,8					35,3					31,3			.299

Table 3. Baseline table, comparing physical activity groups built according to CDC guidelines[16]

We included 208 patients (age 60.8±10.8 years, 53.8% female) with a median physical activity of 4800 MET-minutes/week (median = 1240 minutes (20.66h) activity/week und median = 3.98 MET intensity of the activity) and mean night-time systolic pressure of 115±16.8 mmHg and mean nighttime diastolic blood pressure of 67±10.0 mmHg. In linear regression analysis, nocturnal systolic BP was significantly associated with the MET-minutes/week of the IPAQ long form, in the final model adjusted for age, sex, drug intake before blood sampling, statine use, plasma rennin, serum homoargenine, active smoking, estimated glomerula filtration rate [CKD-EPI], triglycerides, intake of loop diuretics, serum albumin and nighttime systolic BP (ß-coefficient for MET-minutes/week as an independent variable: -0.18; P=.041) (Table 4).

	Linear Regression Analysis for log MET-minutes per Week and Nocturnal Blood Pressure, Cortisol								
	Nocturnal Systolic Blood Pressure			Nocturnal Diastolic Blood Pressure			Cortisol§§		
	ß-coefficients	95 % Confidence Interval (CI)	**P-value**	ß-coefficients	95 % CI	**P-value**	ß-coefficients	95 % CI	**P-value**
Model 1	-0.13	-9.3 - 0.25	**0.063**	-0.15	-5.82 - -0.45	**0.022**	0.16	-3.00 - 34.3	**0.099**
Model 2	-0.18	-12.0 - -0.38	**0.037**	-0.22	-7.44 - -1.38	**0.005**	0.18	-1.21 - 36.9	**0.066**
Model 3	-0.18	-12.0 - -0.26	**0.041**	-0.22	-7.41 - -1.34	**0.005**	0.16	-2.80 - 33.6	**0.096**
Model 3 + LDL	-0.18	-12.4 - -0.41	**0.036**	-0.23	-7.77 - -1.65	**0.003**	0.15	-3.47 - 33.4	**0.110**
Model 3 + CRP	-0.18	-12.1 - -0.26	**0.041**	-0.21	-7.36 - -1.23	**0.006**	0.15	-3.55 - 33.3	**0.112**
Model 3 + BMI	-0.15	-10.9 - 0.97	**0.100**	-0.18	-6.43 - -0.48	**0.023**	0.11	-7.00 - 28.9	**0.229**

Model 1 includes age and sex. Model 2 additionally includes drug intake before blood sampling, statine use, plasma renin and serum homoargenine. Model 3 further includes active smoking, estimated glomerula filtration rate [CKD-EPI] §§Additionally to all models with plasma cortisol as dependend variable we included adjustments for triglycerides, intake of loop diuretics, serum albumin, nighttime systolic BP. (*= P<0.050, 95% Confidence Interval refers to regression coefficient B)

Table 4. Linear Regression Analysis for log MET-minutes per Week and Nocturnal Blood Pressure, Cortisol

5 Discussion

We found a significant association between physical activity (MET-minutes/week) and nocturnal systolic and diastolic blood pressure. There was also a borderline significant association with serum cortisol. The results remain significant in different multivariate models (table 4). These findings underline the important relationship physical activity and cardiovascular risk factors. Furthermore it adds to previous studies that higher amounts of physical activity are associated with lower levels of nocturnal blood pressure in treated patients with arterial hypertension. We were unable to demonstrate a clear association between MET-minutes/week and serum cortisol. This might be due to the cross sectional nature of the study, as a single measurement at a given time point might not adequately describe the relationship between physical activity and neurohumoral activation.[28,28,29,51,52] It has previously been described that the normalisation of body weight and lipoprotein profile by physical activity have beneficial effects on health.[19–21] This effects might be based on anti-inflammatory properties[19] and improvement in vascular function.[53–56] Our findings extend these previous studies by demonstrating a linear association between physical activity and nocturnal blood pressure. We did not observe an association between physical activity and serum cortisol, although the confidence interval is borderline significant (-3.47 - 33.4) but might be distorted due to the diurnal variation of the cortisol secretion.[57]

5.1 Limitations and Strengths

Intriguingly we did not see a correlation between physical activity and BMI, waist to hip ratio or lipoprotein status at baseline. This might be due to the fact that the physical activity groups, which are built according to the CDC guidelines[16], are not adequately reflecting physically activeness in the present cohort, as the groups with low- and moderate physical activity are considerably smaller than the high physical activity group (Table 3). Or it might be explained by the fact that patients body weight does not adequately reflect physical activity in our study, likewise because the whole study cohort consisted mainly of elderly and obese (high physical activity median BMI=29.13 kg/m²) hypertensive patients and there was no healthy control group. There is no current method to retrospectively measure the amount of physical activity in an accurate way. IPAQ is considered to be the most precise questionnaire, but it only gives information about physical activity done in the last week. Also it is doubtful that patients are stating the right amount of their physical activity due to problems to remember the exact time and duration of any activity done and due to a different perception of time.[58] The strengths of the present investigation are that we investigated a cohort of patients typically seen in clinical practice, characterized by a broad biochemical work-up, a 24-hour blood pressure monitoring including 24-hour urine samples.

6 Conclusion

We were able to demonstrate that in a group of hypertensive patients under antihypertensive treatment high physical activity is associated with lower nocturnal blood pressure, a strong risk factor for cardiovascular mortality. Further studies are needed to investigate potential treatment options, e.g. supervised exercise therapy, to improve blood pressure control and reduce the burden of cardiovascular disease.

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8 Appendix

8.1 IPAQ:

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

(October 2002)

LONG LAST 7 DAYS SELF-ADMINISTERED FORMAT

9 FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

9.1 Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

9.2 Translation from English and Cultural Adaptation

Translation from English is encouraged to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

10 Further Developments of IPAQ

International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

10.1 More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective.* Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

10.1.1.1.1 PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

☐ 10.1.1.2 Yes

☐ No → ***Skip to PART 2: TRANSPORTATION***

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

_____ **days per week**

☐ No vigorous job-related physical activity → ***Skip to question 4***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

_____ **hours per day**

_____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

_____ **days per week**

☐ No moderate job-related physical activity → ***Skip to question 6***

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day**

_____ **minutes per day**

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ **days per week**

☐ No job-related walking → ***Skip to PART 2: TRANSPORTATION***

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day**

_____ **minutes per day**

10.1.1.2.1.1 PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ **days per week**

☐ No traveling in a motor vehicle → ***Skip to question 10***

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ **hours per day**

_____ **minutes per day**

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No bicycling from place to place → ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**

_____ **minutes per day**

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No walking from place to place → ***Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY***

13. How much time did you usually spend on one of those days *walking* ***from place to place?***

_____ **hours per day**

_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ **days per week**

☐ No vigorous activity in garden or yard → ***Skip to question 16***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ **hours per day**

_____ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

☐ No moderate activity in garden or yard → ***Skip to question 18***

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ **hours per day**

_____ **minutes per day**

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

☐ No moderate activity inside home → ***Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY***

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ **hours per day**

_____ **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ **days per week**

☐ No walking in leisure time → ***Skip to question 22***

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**

_____ **minutes per day**

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

☐ No vigorous activity in leisure time → ***Skip to question 24***

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**

_____ **minutes per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ **days per week**

☐ No moderate activity in leisure time → ***Skip to PART 5: TIME SPENT SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?

_____ **hours per day**

_____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day**

_____ **minutes per day**

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ **hours per day**

_____ **minutes per day**

This is the end of the questionnaire, thank you for participating.