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Inverse Relationship Between Physical Activity, Adiposity and Arterial Stiffness in Healthy Middle-aged Subjects

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Abstract

Background: Several obesity related factors are reported to exacerbate premature arterial stiffening, including inactivity and metabolic disarray. The aim of the present study was to investigate the relationship between physical activity, arterial stiffness and adiposity using objective methods. To further explore the role of adiposity in this complex process, obesity associated anthropometric and humoral biomarkers were measured.

Methods: Seventy-nine healthy, lifelong non-smoking, subjects were recruited. Habitual physical activity was measured using accelerometry. Arterial stiffness (augmentation index; AIx & pulse wave velocity; PWV), was measured using tonometry. Body composition was estimated using bioimpedence. Adipose associated biomarkers, leptin and adiponectin, were also measured.

Results: Sedentary time was significantly associated with AIx (r=0.38, *P*<0.001), PWV (r=0.33, *P*<0.01), body fat composition (r=0.40, *P*<0.001) and age (r=0.30, *P*<0.01). Moderate + vigorous activity was inversely correlated with AIx (r= -0.28, *P*<0.05) body fat composition (r=-0.30, *P*<0.01), postprandial insulin (r=-0.35, *P*<0.01) and leptin/adiponectin ratio (r=-0.28, *P*<0.05). Moderate + Vigorous activity, body fat composition and post prandial insulin remained independent predictors of AIx but not PWV.

Conclusion: The more time healthy individuals spend being sedentary, the greater their body fat and arterial stiffness. Conversely higher activity levels are associated with reduced body fat and less arterial stiffness.

Arterial stiffening is an independent predictor of cardiovascular risk and target organ damage such as left ventricular hypertrophy, myocardial infarction, renal failure, retinopathy and vascular dementia.[1] Several factors, such as smoking, metabolic disease, adiposity and physical inactivity, are reported to accelerate vascular stiffening.[2,3,4,5,6,7] Many of these factors are inter-related with inactivity predisposing to adiposity, low-grade inflammation, metabolic disarray and arterial damage.[3,7,8,9,10] In contrast, when subjects spend more time being vigorously active during adolescence they have less arterial stiffness in adulthood and the observed benefits are related to changes in blood pressure, body composition, cardiorespiratory fitness and their metabolic profile.[6] Consequently activity levels are considered of key importance in maintaining metabolic and arterial health.

However, many studies examining the impact of physical activity on arterial stiffness have used subjective questionnaires to quantify activity patterns with few studies adopting more objective methods such as accelerometry.[2,3,5,6,10,11,12] In addition many of these studies have focused on subjects in different age/gender groups and in patients with established metabolic risk factors.[10,11,13]

Therefore, the aim of the present experiment was to simultaneously evaluate the association between activity levels and arterial wall changes in clinically healthy, middle-aged subjects, using objective methods. In order to further explore the complex relationship between physical activity, arterial wall properties and obesity, we investigated if the interrelationship of activity levels and arterial changes were correlated with adiposity associated anthropometric, metabolic, hormonal and inflammatory markers.

Methods

Seventy-nine (51 male & 28 female) subjects were recruited from the general population via poster advertisements in the local community within a 5 km radius of the hospital where all the study protocols were performed. The study was approved by Trinity College Dublin Ethics Committee. Written informed consent was obtained from all subjects prior to testing protocols. Subjects were included if they were lifelong never-smokers, free from cardiovascular disease, normotensive (<140/90 mmHg), had normal lipid profile (LDLc <4.0 mmol.L^{-1}), normal oral glucose tolerance test responses (fasting & post prandial glucose <7 & <11 mmol.L^{-1}) and moderate alcohol intake (male <21 units per week; female <14 units per week). Subjects were excluded if they were receiving treatment for or had a history of hypertension, hyperlipidaemia, diabetes or were taking any medications that affected haemodynamic and/or metabolic responses.

Following a 12-hour overnight fast, enrolled subjects attended the Cardiovascular Research Unit at Tallaght hospital. Various anthropometrical measurements were recorded, including height (Seca 202, SECA, UK), weight (Avery E101, Avery, UK) and waist circumference (Creative Health Products, USA). Body fat composition was estimated using whole-body bioimpedance (TBF 410 GS, Tanita, UK).

Subjects completed a 2-hour oral glucose tolerance test (OGTT). Blood glucose and insulin values were measured from venous blood samples before and after a 75g oral glucose challenge. Homeostasis model assessment (HOMA), a measure of glycaemic homeostasis, was calculated from fasting glucose and fasting insulin values (fasting glucose × fasting insulin / 22.1). In addition, for each subject, glycosylated haemoglobin (HbA$_{1c}$), full fasting lipid profile and the adipose associated blood markers, adiponectin and leptin were measured. Nonspecific markers of systemic inflammation such as white cell count (WCC) and high sensitivity c-reactive protein (hsCRP) were also measured to determine the potential impact of adipose associated inflammation.

Pulse wave analysis

The aortic augmentation index (AIx), a measure of wave reflection and surrogate marker of arterial stiffness, was calculated from pressure waveform measurements recorded from the radial artery using a previously validated method (Sphygmacor, AtCor Medical, Australia).[4,14] Central aortic systolic and diastolic blood pressure was calculated from the radial artery waveform using a previously validated transfer function (Sphygmacor, AtCor Medical, Australia).[14] The sphygmacor software automatically generates an “operator index” as an indication of quality control. The operator index is based on the pulse wave height/shape variation over ten successive cardiac cycles. In the present experiment, the mean of three values with an operator index ≥90% were used.

Pulse wave velocity

Pulse wave velocity, a direct measure of carotid-femoral arterial stiffness, was calculated from simultaneous recordings of the carotid and femoral pressure waveform using a previously validated semi-automated method (Vicorder, Skidmore Medical, U.K.).[15] Briefly, two pressure sensitive transducer cuffs were fixed to the subject’s neck and leg, recording the time delay (Td; ms^{-1}) between the carotid and femoral pulse waveforms using the foot-to-foot method.[15] The distance between the two sites was measured using a tape-measure (Dist; m). PWV was calculated by the "in-built" software (Td/Dist; $m.s^{-1}$).[14]

Physical activity

A triaxial accelerometer (RT3, Stayhealthy, USA) was used to record routine daily physical patterns. The accelerometer records activity counts as mean acceleration ($m.s^{-2}$) in the vertical (x), anteroposterior (y) and mediolateral (z) planes. The activity counts are then summarized as vector magnitude ($VM=[x^2 + y^2 + z^2]^{0.5}$).[16] Physical activity data was recorded at 1 min intervals over seven consecutive days. A day was defined as the period where 70% of the subjects had recorded accelerometer data and 80% of that period constituted a minimal day for inclusion in the data analysis.[17] Data from five consecutive days, including one weekend day (Tuesday-Saturday or Sunday-Thursday), were used to calculate the absolute and relative time spent being sedentary and participating in light, moderate and vigorous activity.[18,19]

Statistics

Pearson's Univariate correlation and Spearman's Univariate correlation was used to examine the relationship between parametric and non-parametric data. Stepwise multiple regression was used to assess the relative contribution of chosen variables and arterial stiffness. An unpaired student's t-test was used to detect differences between groups for normally distributed data and Wilcoxan's test for non-normally distributed data. Data are presented as mean±SD unless otherwise stated. (JMP Version 4.0, SAS Institute Inc, NC, USA).

Results

The physical, metabolic, haemodynamic characteristics and gender comparisons are outlined in Table 1. Similar to Irish general population averages, 53% of the group had normal BMI, 38% were overweight and the remaining 9% were obese.[20] In addition, 48% of the group had a waist/height ratio >0.5 and had high body fat composition with respect to their age and gender. Gender comparisons revealed that Augmentation index was markedly higher in females compared to males, yet no differences in PWV, central BP or brachial BP were observed.

All subjects had normal lipid profile, normal glycaemic profile and normal OGTT responses. All subjects had normal 24-hour ambulatory blood pressure responses (Sys <135/Dia <85 mmHg) and normal arterial stiffness with respect to age and gender.[21,22] The non-specific markers of systemic inflammation, hsCRP and WCC, were also within normal ranges.

Age was strongly correlated with both AIx (r=0.52; $P<0.0001$) and PWV (r=0.49; $P<0.0001$). In addition, body fat composition was strongly correlated with AIx (r=0.55; $P<0.0001$) and 24-hour ambulatory diastolic blood pressure was associated with PWV (r=0.25; $P<0.05$).

Mean daily wearing (on) duration of the accelerometer was 701±91 min and mean daily “non-wearing” (off) duration was 728±90 min (Figure 1a). Absolute and relative time spent within activity thresholds can be seen in Figure 1b. Subjects spent 240±63 min (16.71±4.44%) being sedentary and 448±90 min (31.06±6.21%), 13±14 min (1.45±2.23%) & 4±8 min (0.19±0.35%) participating in Light, Moderate & Vigorous activities.

The results of the univariate correlation between the relative time spent in the four activity zones (Sed, Light, Mod & Vig) and physical measures of obesity, arterial stiffness, blood pressure, metabolic and adipose related humoral markers can be seen in Table 2. Time spent being sedentary was significantly associated with age, body fat composition, AIx and PWV. There was a significant inverse correlation between time-spent being moderately active and body fat composition and fasting insulin.

Subjects spent little time participating in moderate activity and 28 subjects did not spend any time participating in vigorous activity. In an attempt to overcome this limitation, moderate and vigorous activity time was amalgamated (Mod+Vig) in a univariate analysis. Mod+Vig activity was inversely correlated with body fat composition ($r=-0.30$, $P<0.01$), postprandial insulin ($r=-0.35$, $P<0.01$), leptin/adiponectin ratio ($r=-0.28$, $P<0.05$) and AIx ($r=-0.28$, $P<0.05$).

In order to identify the relative contribution of associated variables on arterial stiffness, age, gender, body fat composition, heart rate, mean arterial pressure and physical activity were included in two separate stepwise regression models to predict AIx and PWV. Age, gender, body fat composition and heart rate remained significant ($P<0.05$) correlates of AIx for all activity zones. The combined Mod+Vig activity, but not individual Sed, Light, Mod and Vig activity zones, also remained as an independent predictor of AIx ($P<0.05$). However, age remained the only significant ($P<0.0001$) predictor of PWV.

To further identify the metabolic/hormonal consequences of physical inactivity and premature arterial stiffening, age, body fat composition, leptin/adiponectin ratio, postprandial insulin and arterial stiffness indices were included in separate regression models. Body fat composition and postprandial insulin remained independent predictors of AIx. Again, age remained the only significant ($P<0.0001$) predictor of PWV.

Discussion

The main findings of the study were that subjects who spend more time being sedentary have stiffer arteries and more body fat. Conversely, subjects that spend more time being active have less arterial stiffness and lower body fat. Unsurprisingly, in this healthy population, age remained the strongest predictor of arterial stiffness. However, body fat composition and postprandial insulin remained independent predictors of AIx indicating the presence of a disease continuum whereby physical inactivity and adiposity augment early vascular changes.

Our findings are similar with previous studies using objective methods to quantify daily physical activity.[3,10,11] Previous studies report that carotid β-stiffness in postmenopausal women is inversely correlated with time spent participating in low intensity (<4 MET) physical activity.[23] In addition, further studies report that older subjects, especially those with low cardiorespiratory fitness, that spend more time being lightly active (<3 METs) have less arterial stiffness, lower body fat, lower blood pressure and lower fasting glucose.[24] More recent research reports that physical activity is an independent predictor of arterial stiffness in hypertensive adults with varying degrees of metabolic disarray.[10]

In the present study, females had significantly higher AIx compared to males despite no differences in age, heart rate and PWV were observed. Gender differences in AIx are mainly attributable to differences in height. In shorter individuals, the pulse wave path length is smaller, and so, reflected waves coalesce with incident waves at an earlier time point during systole resulting in greater AIx.[25] These gender differences are not observed for PWV because it is calculated relative to distance ($m.s^{-1}$).

The link between physical activity and arterial stiffness is complex. Physical activity can benefit arterial stiffness via its direct effects on the vasculature or indirectly via exercise induced changes in body composition and associated changes in metabolic and cardiovascular risk factors.

Physical activity and exercise can directly benefit arterial stiffness and prevent premature arterial ageing via its effect on blood pressure and heart rate.[26,27] Blood pressure is one of the major determinants of arterial stiffness. Exercise induced changes in microvascular structure and function can directly affect systolic and diastolic blood pressure, thereby improving arterial stiffness.[28,29] Increased heart rate negatively affects arterial stiffness via the viscoelastic effects of heart rate on the arterial wall.[30] Increased heart rate is also associated with increased sympathetic outflow, which is known to stiffen large and medium sized vessels.[31] In the present study, no significant association was observed between 24-hour ambulatory or central aortic blood pressure and physical activity and no association was observed between physical activity and heart rate. These data suggest that the relationship between physical activity, or lack thereof, and arterial stiffness was not mediated by the direct effect of activity on the vasculature.

Physical activity can also indirectly impact arterial stiffness via its affect on body composition and subsequent alteration in adipose related inflammatory, metabolic and hormonal factors.[6]

Obesity and adipose tissue distribution, specifically increased central/abdominal visceral adipose tissue, is strongly correlated with increased arterial stiffness.[8,4,32] Activity induced changes in body fat composition can benefit arterial stiffness via modification of inflammatory, metabolic and adipose related humoral factors.[6,13,33]

Non-specific systemic inflammatory markers, such as hsCRP and WCC, and adipose associated inflammatory markers, such as interleukin-6 (IL6), tumour necrosis factor alpha (TNFα) and monocyte chemoattractant protein 1 (MCP-1), are associated with increased adiposity, premature vascular ageing and arterial stiffness.[5,9,34] In the present study, although the adipocytokines were not measured, hsCRP and WCC were clinically normal and not associated with any of the activity parameters or indices of arterial stiffness. These results suggest that abnormal immune responses were probably not related to the activity related changes in arterial stiffness.

In the present study, all subjects had normal OGTT responses yet postprandial insulin was inversely associated with time spent being moderately & vigorously active and independently associated with arterial stiffness. These results suggest that the relationship between physical activity, arterial stiffness and adiposity may be mediated via the deleterious affects of adiposity on endocrine function and glycaemic homeostasis. In support of this, previous studies have consistently reported the relationship between abdominal/visceral adiposity, metabolic disorder and arterial stiffness in both healthy and diseased populations.[35,36]

Leptin/adiponectin ratio was associated with time spent being sedentary and moderate & vigorous activity. The link between adiposity, leptin, adiponectin, metabolic disarray and cardiovascular disease has been consistently reported.[37,38] Furthermore, it is suggested that hypertrophy of adipocytes, especially those at key anatomic locations, results in abnormal paracrine function, disrupting vascular and metabolic homeostasis.[39,40,41]

In summary, the major findings of the present study were that time spent being sedentary and time spent participating in moderate and vigorous activity was associated with increased and decreased arterial stiffness and body fat. This is the first study demonstrate the relationship between habitual physical activity and arterial wall changes in healthy, middle-aged, life-long non-smoking subjects. Furthermore, the results also indicate that adiposity and hyperinsulinaemia may be responsible for the increased arterial stiffness in less active subjects. Future studies are needed to explore the protective effect of physical activity and premature arterial stiffening or whether weight loss alone is sufficient to actuate beneficial changes.

A major strength of the present study was that objective methods were used to quantify daily habitual physical activity patterns. However, arbitrary activity thresholds were used to determine time spent being sedentary, lightly active, moderately active and vigorously active. Therefore, the relative intensity of the activity categories may have differed for the wide age range of subjects (range: 21-59 years) that participated in the study. Further studies adopting accelerometry as a means to examine routine physical activity patterns should consider these factors.

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Physical, metabolic, endocrine, inflammatory and haemodynamic characteristics		
	Male	Female
n	n=51	n=28
Age (years)	38±9	40±9
Height (cm)	177.9±6.7	164.4±5.2
Body mass (kg)	83.1±13.9	64.5±6.8
BMI (kg.m^2)	26.2±3.7	23.9±2.9
Waist (cm)	91.9±11.8	78.3±6.6
Waist/Height	0.52±0.06	0.47±0.05
Body fat (%)	22.3±6.7	30.1±5.3
Total Cholesterol (mmol.L^{-1})	3.20±0.75	3.07±0.71
Triglyceride (mmol.L^{-1})	1.04±0.43	0.87±0.29
HDLc (mmol.L^{-1})	1.33±0.36	1.66±0.41***
LDLc (mmol.L^{-1})	2.72±0.68	2.67±0.67
Glucose fast (mmol.L^{-1})	5.17±0.39	4.91±0.45
Glucose PP (mmol.L^{-1})	4.77±1.01	4.92±1.20
Insulin Fast (mU.L^{-1})	7.56±2.82	7.37±3.55
Insulin PP (mU.L^{-1})	23.85±28.03	27.52±23.94
HbA$_{1c}$ (%)	5.30±0.30	5.21±0.31
HOMA$_{IR}$	1.78±0.70	1.65±0.77
Leptin (pg.mL^{-1}.10^{-2})	118.61±113.40	137.88±78.03
Adiponectin (pg.mL-1.10^{-2})	59.10±27.42	60.68±32.19
Lept/Adipo	2.99±4.97	2.77±1.88
hsCRP (mg.L^{-1})	2.5±2.89	1.30±1.62
WCC (10^9.L^{-1})	5.90±1.75	5.87±1.71
24h Brachial Sys BP (mmHg)	119±7	111±9
24h Brachial Dia BP (mmHg)	69±6	66±7
Aortic Sys BP (mmHg)	109±8	105±10
Aortic Dia BP (mmHg)	75±7	71±7
Heart rate (beats.min^{-1})	60±8	63±9
AIx (%)	9.90±11.90	21.75±10.67****
PWV (m.s^{-1})	6.88±0.91	6.89±0.98

Table 1. Physical characteristics and risk factors. Body mass index (BMI), waist height ratio (waist/height) high density lipoprotein cholesterol (HDLc), low density lipoprotein cholesterol (LDLc), postprandial glucose (Glucose PP), postprandial insulin (Insulin PP), glycosylated haemoglobin (HbA$_{1c}$), homeostasis model assessment of insulin resistance (HOMA$_{IR}$), high sensitivity c-reactive protein (hsCRP), white cell count (WCC), 24-hour ambulatory brachial systolic blood pressure (24h Brachial Sys BP), 24-hour ambulatory brachial diastolic blood pressure (24h Brachial Dia BP), aortic systolic blood pressure (Aortic Sys BP), aortic diastolic blood pressure (Aortic Dia BP), augmentation index (AIx), pulse wave velocity

(PWV). ** $P<0.01$, *** $P<0.001$, **** $P<0.0001$ significantly different compared to males.

Univariate analysis of activity and physical, metabolic, endocrine, inflammatory and haemodynamic characteristics

	Sed r	Light r	Mod r	Vig r	Mod+Vig r
Age	0.30**	-0.11	-0.03	-0.20	-0.13
Body mass	0.06	-0.06	0.06	-0.06	0.10
BMI	0.20	-0.07	-0.04	-0.18	-0.07
Waist	0.18	0.01	-0.08	-0.16	-0.06
W/Height	0.23	-0.01	-0.18	-0.20	-0.16
Body fat	0.40***	0.04	-0.25*	-0.21	-0.30*
Total Cholesterol	0.07	-0.05	0.08	-0.08	-0.14
Triglyceride	0.10	-0.01	-0.20	-0.10	-0.16
HDLc	-0.06	-0.10	0.10	0.02	0.03
LDLc	0.16	-0.03	0.04	-0.11	-0.14
Glucose Fast	0.18	0.01	0.00	0.08	0.01
Glucose Post	0.09	0.01	-0.13	0.06	-0.05
Insulin Fast	0.14	-0.13	-0.14	-0.13	-0.20
Insulin Post	0.19	0.02	-0.25*	-0.21	-0.35**
HbA1c	-0.06	0.18	0.11	-0.03	0.03
HOMA	0.18	-0.14	-0.15	-0.12	-0.20
Leptin	0.27	0.04	-0.17	-0.17	-0.25
Adiponectin	0.05	-0.23	0.16	0.10	0.07
Lept/Adipo	0.23	0.10	-0.26	-0.22	-0.28*
hsCRP	0.04	0.16	-0.10	0.06	-0.05
WCC	-0.05	-0.18	-0.09	0.03	-0.05
24 h Sys	-0.07	0.07	0.12	0.02	0.17
24 h Dia	0.14	-0.01	0.07	-0.14	0.01
Aortic Sys	0.18	0.01	0.01	0.02	0.07
Aortic Dia	0.10	0.00	0.07	0.12	0.13
Heart rate	0.02	0.02	-0.04	-0.13	-0.09
AIx	0.38***	-0.04	-0.17	-0.10	-0.28*
PWV	0.33**	-0.23	0.00	-0.18	-0.12

Table 2. Spearman’s Univariate analysis of relative time spent being sedentary (Sed), lightly active (Light), moderately active (Mod), vigorously active (Vig), combined moderate & vigorous activity (Mod+Vig) and indices of obesity, humoral factors and arterial stiffness. * P<0.05, ** P<0.01, *** P<0.001.

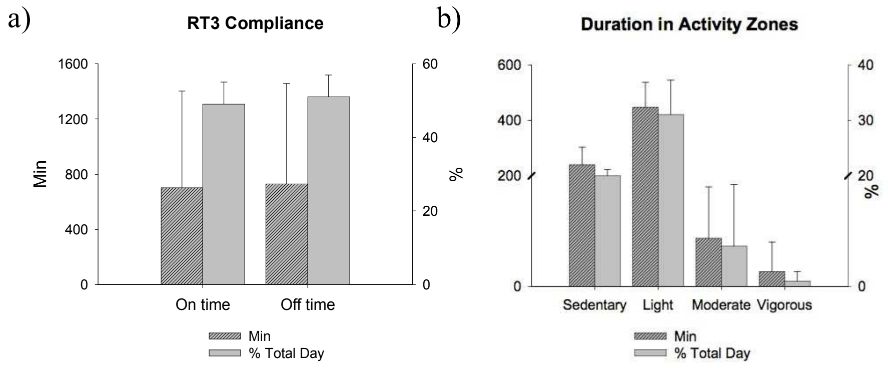
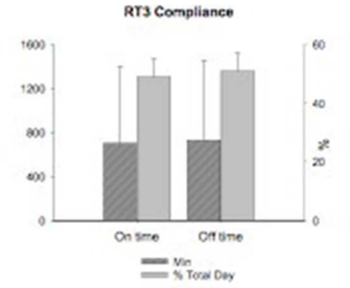
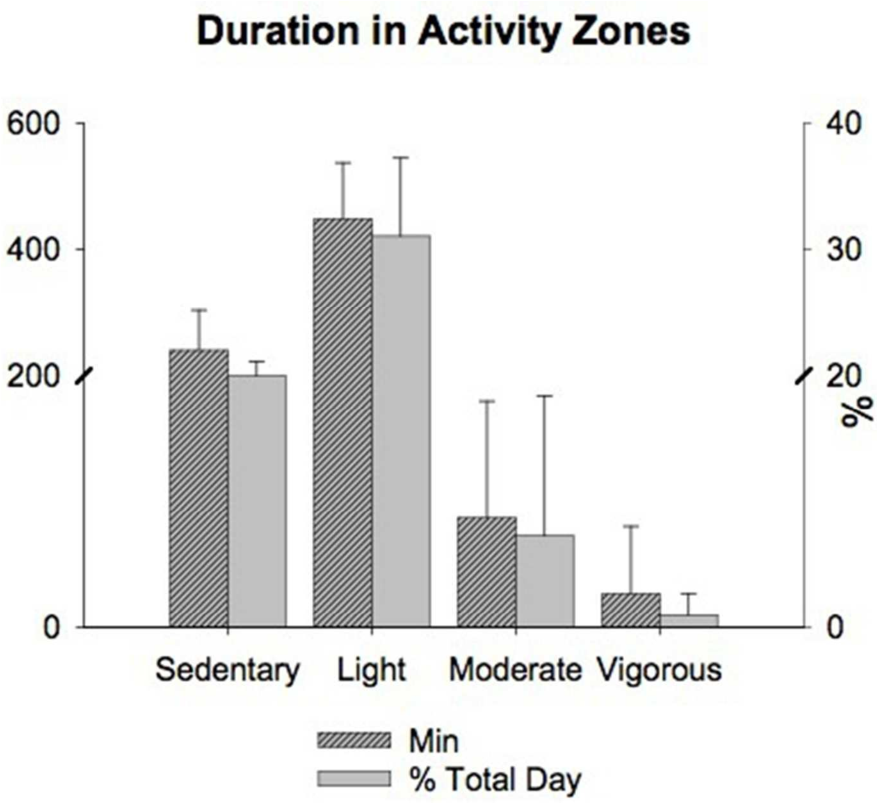


Figure 1. a) RT3 compliance. Absolute (min) and relative (%) time spent wearing (On time) and not wearing (Off time) the RT3. b) Absolute (Min) and relative (%) time spent within activity thresholds. Relative time is expressed as a percentage of an entire day (1440 min). Results are mean±SD.



62x50mm (72 x 72 DPI)



174x143mm (72 x 72 DPI)