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

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23   **Abstract**

25   **Background:** Several obesity related factors are reported to exacerbate premature

26   arterial stiffening, including inactivity and metabolic disarray. The aim of the present

27   study was to investigate the relationship between physical activity, arterial stiffness

28   and adiposity using objective methods. To further explore the role of adiposity in this

29   complex process, obesity associated anthropometric and humoral biomarkers were

30   measured.

31   **Methods:** Seventy-nine healthy, lifelong non-smoking, subjects were recruited.

32   Habitual physical activity was measured using accelerometry. Arterial stiffness

33   (augmentation index; AIx & pulse wave velocity; PWV), was measured using

34   tonometry. Body composition was estimated using bioimpedence. Adipose associated

35   biomarkers, leptin and adiponectin, were also measured.

36   **Results:** Sedentary time was significantly associated with AIx (r=0.38, $P<0.001$),

37   PWV (r=0.33, $P<0.01$), body fat composition (r=0.40, $P<0.001$) and age (r=0.30,

38    $P<0.01$). Moderate + vigorous activity was inversely correlated with AIx (r= -0.28,

39    $P<0.05$) body fat composition (r=-0.30, $P<0.01$), postprandial insulin (r=-0.35,

40    $P<0.01$) and leptin/adiponectin ratio (r=-0.28, $P<0.05$). Moderate + Vigorous activity,

41   body fat composition and post prandial insulin remained independent predictors of

42   AIx but not PWV.

43   **Conclusion:** The more time healthy individuals spend being sedentary, the greater

44   their body fat and arterial stiffness. Conversely higher activity levels are associated

45   with reduced body fat and less arterial stiffness.

48

49 Arterial stiffening is an independent predictor of cardiovascular risk and target organ

50 damage such as left ventricular hypertrophy, myocardial infarction, renal failure,

51 retinopathy and vascular dementia.[1] Several factors, such as smoking, metabolic

52 disease, adiposity and physical inactivity, are reported to accelerate vascular

53 stiffening.[2,3,4,5,6,7] Many of these factors are inter-related with inactivity predisposing

54 to adiposity, low-grade inflammation, metabolic disarray and arterial damage.[3,7,8,9,10]

55 In contrast, when subjects spend more time being vigorously active during

56 adolescence they have less arterial stiffness in adulthood and the observed benefits are

57 related to changes in blood pressure, body composition, cardiorespiratory fitness and

58 their metabolic profile.[6] Consequently activity levels are considered of key

59 importance in maintaining metabolic and arterial health.

60 However, many studies examining the impact of physical activity on arterial stiffness

61 have used subjective questionnaires to quantify activity patterns with few studies

62 adopting more objective methods such as accelerometry.[2,3,5,6,10,11,12] In addition many

63 of these studies have focused on subjects in different age/gender groups and in

64 patients with established metabolic risk factors.[10,11,13]

65 Therefore, the aim of the present experiment was to simultaneously evaluate the

66 association between activity levels and arterial wall changes in clinically healthy,

67 middle-aged subjects, using objective methods. In order to further explore the

68 complex relationship between physical activity, arterial wall properties and obesity,

69 we investigated if the interrelationship of activity levels and arterial changes were

70 correlated with adiposity associated anthropometric, metabolic, hormonal and

71 inflammatory markers.

72

73 **Methods**

74 Seventy-nine (51 male & 28 female) subjects were recruited from the general

75 population via poster advertisements in the local community within a 5 km radius of

76 the hospital where all the study protocols were performed. The study was approved by

77 Trinity College Dublin Ethics Committee. Written informed consent was obtained

78 from all subjects prior to testing protocols. Subjects were included if they were

79 lifelong never-smokers, free from cardiovascular disease, normotensive (<140/90

80 mmHg), had normal lipid profile (LDLc <4.0 mmol.L^{-1}), normal oral glucose

81 tolerance test responses (fasting & post prandial glucose <7 & <11 mmol.L^{-1}) and

82 moderate alcohol intake (male <21 units per week; female <14 units per week).

83 Subjects were excluded if they were receiving treatment for or had a history of

84 hypertension, hyperlipidaemia, diabetes or were taking any medications that affected

85 haemodynamic and/or metabolic responses.

86 Following a 12-hour overnight fast, enrolled subjects attended the Cardiovascular

87 Research Unit at Tallaght hospital. Various anthropometrical measurements were

88 recorded, including height (Seca 202, SECA, UK), weight (Avery E101, Avery, UK)

89 and waist circumference (Creative Health Products, USA). Body fat composition was

90 estimated using whole-body bioimpedance (TBF 410 GS, Tanita, UK).

91

92 Subjects completed a 2-hour oral glucose tolerance test (OGTT). Blood glucose and

93 insulin values were measured from venous blood samples before and after a 75g oral

94 glucose challenge. Homeostasis model assessment (HOMA), a measure of glycaemic

95 homeostasis, was calculated from fasting glucose and fasting insulin values (fasting

96 glucose $\times$ fasting insulin / 22.1). In addition, for each subject, glycosylated

97 haemoglobin (HbA_{1c}), full fasting lipid profile and the adipose associated blood

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98   markers, adiponectin and leptin were measured. Nonspecific markers of systemic

99   inflammation such as white cell count (WCC) and high sensitivity c-reactive protein

100   (hsCRP) were also measured to determine the potential impact of adipose associated

101   inflammation.

102

103   *Pulse wave analysis*

104   The aortic augmentation index (AIx), a measure of wave reflection and surrogate

105   marker of arterial stiffness, was calculated from pressure waveform measurements

106   recorded from the radial artery using a previously validated method (Sphygmacor,

107   AtCor Medical, Australia).[4,14] Central aortic systolic and diastolic blood pressure was

108   calculated from the radial artery waveform using a previously validated transfer

109   function (Sphygmacor, AtCor Medical, Australia).[14] The sphygmacor software

110   automatically generates an "operator index" as an indication of quality control. The

111   operator index is based on the pulse wave height/shape variation over ten successive

112   cardiac cycles. In the present experiment, the mean of three values with an operator

113   index ≥90% were used.

114

115   *Pulse wave velocity*

116   Pulse wave velocity, a direct measure of carotid-femoral arterial stiffness, was

117   calculated from simultaneous recordings of the carotid and femoral pressure

118   waveform using a previously validated semi-automated method (Vicorder, Skidmore

119   Medical, U.K.).[15] Briefly, two pressure sensitive transducer cuffs were fixed to the

120   subject's neck and leg, recording the time delay (Td; ms^{-1}) between the carotid and

121   femoral pulse waveforms using the foot-to-foot method.[15] The distance between the

122 two sites was measured using a tape-measure (Dist; m). PWV was calculated by the

123 "in-built" software (Td/Dist; m.s^{-1}).[14]

124

125 *Physical activity*

126 A triaxial accelerometer (RT3, Stayhealthy, USA) was used to record routine daily

127 physical patterns. The accelerometer records activity counts as mean acceleration

128 (m.s^{-2}) in the vertical (x), anteroposterior (y) and mediolateral (z) planes. The activity

129 counts are then summarized as vector magnitude ($VM=[x^2 + y^2 + z^2]^{0.5}$).[16] Physical

130 activity data was recorded at 1 min intervals over seven consecutive days. A day was

131 defined as the period where 70% of the subjects had recorded accelerometer data and

132 80% of that period constituted a minimal day for inclusion in the data analysis.[17] Data

133 from five consecutive days, including one weekend day (Tuesday-Saturday or

134 Sunday-Thursday), were used to calculate the absolute and relative time spent being

135 sedentary and participating in light, moderate and vigorous activity.[18,19]

136

137 *Statistics*

138 Pearson's Univariate correlation and Spearman's Univariate correlation was used to

139 examine the relationship between parametric and non-parametric data. Stepwise

140 multiple regression was used to assess the relative contribution of chosen variables

141 and arterial stiffness. An unpaired student's t-test was used to detect differences

142 between groups for normally distributed data and Wilcoxan's test for non-normally

143 distributed data. Data are presented as mean±SD unless otherwise stated. (JMP

144 Version 4.0, SAS Institute Inc, NC, USA).

145

146 **Results**

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147   The physical, metabolic, haemodynamic characteristics and gender comparisons are

148   outlined in Table 1. Similar to Irish general population averages, 53% of the group

149   had normal BMI, 38% were overweight and the remaining 9% were obese.[20] In

150   addition, 48% of the group had a waist/height ratio >0.5 and had high body fat

151   composition with respect to their age and gender. Gender comparisons revealed that

152   Augmentation index was markedly higher in females compared to males, yet no

153   differences in PWV, central BP or brachial BP were observed.

154

155   All subjects had normal lipid profile, normal glycaemic profile and normal OGTT

156   responses. All subjects had normal 24-hour ambulatory blood pressure responses (Sys

157   <135/Dia <85 mmHg) and normal arterial stiffness with respect to age and gender.[21,22]

158   The non-specific markers of systemic inflammation, hsCRP and WCC, were also

159   within normal ranges.

160

161   Age was strongly correlated with both AIx (r=0.52; P<0.0001) and PWV (r=0.49;

162   P<0.0001). In addition, body fat composition was strongly correlated with AIx

163   (r=0.55; P<0.0001) and 24-hour ambulatory diastolic blood pressure was associated

164   with PWV (r=0.25; P<0.05).

165

166   Mean daily wearing (on) duration of the accelerometer was 701±91 min and mean

167   daily "non-wearing" (off) duration was 728±90 min (Figure 1a). Absolute and relative

168   time spent within activity thresholds can be seen in Figure 1b. Subjects spent 240±63

169   min (16.71±4.44%) being sedentary and 448±90 min (31.06±6.21%), 13±14 min

170   (1.45±2.23%) & 4±8 min (0.19±0.35%) participating in Light, Moderate & Vigorous

171   activities.

172

173   The results of the univariate correlation between the relative time spent in the four

174   activity zones (Sed, Light, Mod & Vig) and physical measures of obesity, arterial

175   stiffness, blood pressure, metabolic and adipose related humoral markers can be seen

176   in Table 2. Time spent being sedentary was significantly associated with age, body fat

177   composition, AIx and PWV. There was a significant inverse correlation between time-

178   spent being moderately active and body fat composition and fasting insulin.

179   Subjects spent little time participating in moderate activity and 28 subjects did not

180   spend any time participating in vigorous activity. In an attempt to overcome this

181   limitation, moderate and vigorous activity time was amalgamated (Mod+Vig) in a

182   univariate analysis. Mod+Vig activity was inversely correlated with body fat

183   composition   (r=-0.30, $P<0.01$),   postprandial   insulin   (r=-0.35, $P<0.01$),

184   leptin/adiponectin ratio (r=-0.28, $P<0.05$) and AIx (r=-0.28, $P<0.05$).

185   In order to identify the relative contribution of associated variables on arterial

186   stiffness, age, gender, body fat composition, heart rate, mean arterial pressure and

187   physical activity were included in two separate stepwise regression models to predict

188   AIx and PWV. Age, gender, body fat composition and heart rate remained significant

189   ($P<0.05$) correlates of AIx for all activity zones. The combined Mod+Vig activity, but

190   not individual Sed, Light, Mod and Vig activity zones, also remained as an

191   independent predictor of AIx ($P<0.05$). However, age remained the only significant

192   ($P<0.0001$) predictor of PWV.

193   To further identify the metabolic/hormonal consequences of physical inactivity and

194   premature arterial stiffening, age, body fat composition, leptin/adiponectin ratio,

195   postprandial insulin and arterial stiffness indices were included in separate regression

196   models. Body fat composition and postprandial insulin remained independent

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197   predictors of AIx. Again, age remained the only significant ($P<0.0001$) predictor of

198   PWV.

199

Discussion

201   The main findings of the study were that subjects who spend more time being

202   sedentary have stiffer arteries and more body fat. Conversely, subjects that spend

203   more time being active have less arterial stiffness and lower body fat. Unsurprisingly,

204   in this healthy population, age remained the strongest predictor of arterial stiffness.

205   However, body fat composition and postprandial insulin remained independent

206   predictors of AIx indicating the presence of a disease continuum whereby physical

207   inactivity and adiposity augment early vascular changes.

208

209   Our findings are similar with previous studies using objective methods to quantify

210   daily physical activity.[3,10,11] Previous studies report that carotid β-stiffness in

211   postmenopausal women is inversely correlated with time spent participating in low

212   intensity (<4 MET) physical activity.[23] In addition, further studies report that older

213   subjects, especially those with low cardiorespiratory fitness, that spend more time

214   being lightly active (<3 METs) have less arterial stiffness, lower body fat, lower

215   blood pressure and lower fasting glucose.[24] More recent research reports that physical

216   activity is an independent predictor of arterial stiffness in hypertensive adults with

217   varying degrees of metabolic disarray.[10]

218

219   In the present study, females had significantly higher AIx compared to males despite

220   no differences in age, heart rate and PWV were observed. Gender differences in AIx

221   are mainly attributable to differences in height. In shorter individuals, the pulse wave

222   path length is smaller, and so, reflected waves coalesce with incident waves at an

223   earlier time point during systole resulting in greater AIx.[25] These gender differences

224   are not observed for PWV because it is calculated relative to distance $(m.s^{-1})$.

225

226   The link between physical activity and arterial stiffness is complex. Physical activity

227   can benefit arterial stiffness via its direct effects on the vasculature or indirectly via

228   exercise induced changes in body composition and associated changes in metabolic

229   and cardiovascular risk factors.

230

231   Physical activity and exercise can directly benefit arterial stiffness and prevent

232   premature arterial ageing via its effect on blood pressure and heart rate.[26,27] Blood

233   pressure is one of the major determinants of arterial stiffness. Exercise induced

234   changes in microvascular structure and function can directly affect systolic and

235   diastolic blood pressure, thereby improving arterial stiffness.[28,29] Increased heart rate

236   negatively affects arterial stiffness via the viscoelastic effects of heart rate on the

237   arterial wall.[30] Increased heart rate is also associated with increased sympathetic

238   outflow, which is known to stiffen large and medium sized vessels.[31] In the present

239   study, no significant association was observed between 24-hour ambulatory or central

240   aortic blood pressure and physical activity and no association was observed between

241   physical activity and heart rate. These data suggest that the relationship between

242   physical activity, or lack thereof, and arterial stiffness was not mediated by the direct

243   effect of activity on the vasculature.

244

245 Physical activity can also indirectly impact arterial stiffness via its affect on body

246 composition and subsequent alteration in adipose related inflammatory, metabolic and

247 hormonal factors.[6]

248

249 Obesity and adipose tissue distribution, specifically increased central/abdominal

250 visceral adipose tissue, is strongly correlated with increased arterial stiffness.[8,4,32]

251 Activity induced changes in body fat composition can benefit arterial stiffness via

252 modification of inflammatory, metabolic and adipose related humoral factors.[6,13,33]

253

254 Non-specific systemic inflammatory markers, such as hsCRP and WCC, and adipose

255 associated inflammatory markers, such as interleukin-6 (IL6), tumour necrosis factor

256 alpha (TNFα) and monocyte chemoattractant protein 1 (MCP-1), are associated with

257 increased adiposity, premature vascular ageing and arterial stiffness.[5,9,34] In the

258 present study, although the adipocytokines were not measured, hsCRP and WCC were

259 clinically normal and not associated with any of the activity parameters or indices of

260 arterial stiffness. These results suggest that abnormal immune responses were

261 probably not related to the activity related changes in arterial stiffness.

262

263 In the present study, all subjects had normal OGTT responses yet postprandial insulin

264 was inversely associated with time spent being moderately & vigorously active and

265 independently associated with arterial stiffness. These results suggest that the

266 relationship between physical activity, arterial stiffness and adiposity may be

267 mediated via the deleterious affects of adiposity on endocrine function and glycaemic

268 homeostasis. In support of this, previous studies have consistently reported the

269   relationship between abdominal/visceral adiposity, metabolic disorder and arterial

270   stiffness in both healthy and diseased populations.[35,36]

271

272   Leptin/adiponectin ratio was associated with time spent being sedentary and moderate

273   & vigorous activity. The link between adiposity, leptin, adiponectin, metabolic

274   disarray and cardiovascular disease has been consistently reported.[37,38] Furthermore, it

275   is suggested that hypertrophy of adipocytes, especially those at key anatomic

276   locations, results in abnormal paracrine function, disrupting vascular and metabolic

277   homeostasis.[39,40,41]

278

279   In summary, the major findings of the present study were that time spent being

280   sedentary and time spent participating in moderate and vigorous activity was

281   associated with increased and decreased arterial stiffness and body fat. This is the first

282   study demonstrate the relationship between habitual physical activity and arterial wall

283   changes in healthy, middle-aged, life-long non-smoking subjects. Furthermore, the

284   results also indicate that adiposity and hyperinsulinaemia may be responsible for the

285   increased arterial stiffness in less active subjects. Future studies are needed to explore

286   the protective effect of physical activity and premature arterial stiffening or whether

287   weight loss alone is sufficient to actuate beneficial changes.

288

289   A major strength of the present study was that objective methods were used to

290   quantify daily habitual physical activity patterns. However, arbitrary activity

291   thresholds were used to determine time spent being sedentary, lightly active,

292   moderately active and vigorously active. Therefore, the relative intensity of the

293   activity categories may have differed for the wide age range of subjects (range: 21-59

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294   years) that participated in the study. Further studies adopting accelerometry as a

295   means to examine routine physical activity patterns should consider these factors.

296

299

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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

466 Table 1. Physical characteristics and risk factors. Body mass index (BMI), waist
467 height ratio (waist/height) high density lipoprotein cholesterol (HDLc), low density
468 lipoprotein cholesterol (LDLc), postprandial glucose (Glucose PP), postprandial
469 insulin (Insulin PP), glycosylated haemoglobin (HbA$_{1c}$), homeostasis model
470 assessment of insulin resistance (HOMA$_{IR}$), high sensitivity c-reactive protein
471 (hsCRP), white cell count (WCC), 24-hour ambulatory brachial systolic blood
472 pressure (24h Brachial Sys BP), 24-hour ambulatory brachial diastolic blood pressure
473 (24h Brachial Dia BP), aortic systolic blood pressure (Aortic Sys BP), aortic diastolic
474 blood pressure (Aortic Dia BP), augmentation index (AIx), pulse wave velocity

Physical activity and arterial stiffness

475   (PWV). ** P<0.01, *** P<0.001, **** P<0.0001 significantly different compared to
476   males.
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Physical activity and arterial stiffness

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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

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

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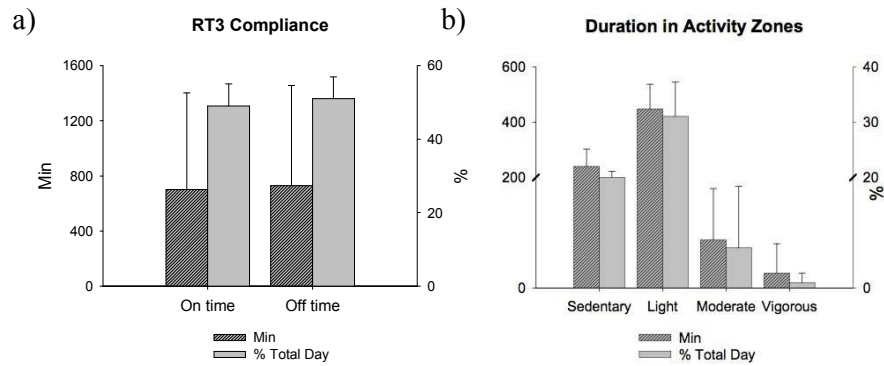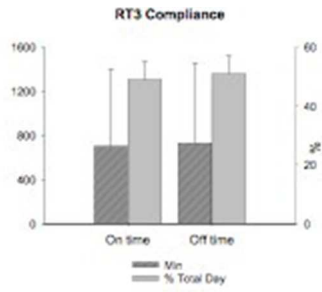Physical activity and arterial stiffness

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489 Figure 1. a) RT3 compliance. Absolute (min) and relative (%) time spent wearing (On
490 time) and not wearing (Off time) the RT3. b) Absolute (Min) and relative (%) time
491 spent within activity thresholds. Relative time is expressed as a percentage of an
492 entire day (1440 min). Results are mean±SD.
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62x50mm (72 x 72 DPI)

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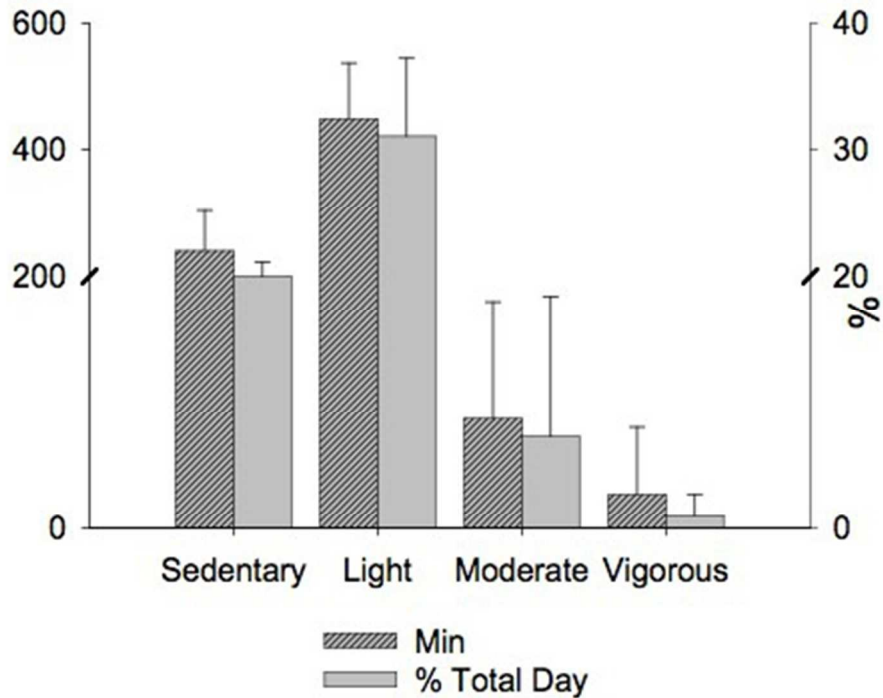48
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