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Objectively measured physical activity and cardiac biomarkers: A cross sectional population based study in older men

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ABSTRACT

Background: N-terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitivity Troponin T (hsTnT) are markers of cardiac injury used in diagnosis of heart failure and myocardial infarction respectively, and associated with increased risk of cardiovascular disease. Since physical activity is protective against cardiovascular disease and heart failure, we investigated whether higher levels of physical activity, and less sedentary behaviour were associated with lower NT-proBNP and hsTnT.

Methods and results: Cross sectional study of 1130 men, age 70–91 years, from the British Regional Heart Study, measured in 2010–2012. Fasting blood samples were analysed for NT-proBNP and hsTnT. Physical activity and sedentary behaviour were measured using ActiGraph GT3X accelerometers. Relationships between activity and NT-proBNP or hsTnT were non-linear; biomarker levels were lower with higher total activity, steps, moderate/vigorous activity and light activity only at low to moderate levels of activity. For example, for each additional 10 min of moderate/vigorous activity, NT-proBNP was lower by 35.7% (95% CI −47.9, −23.6) and hsTnT by 8.4% (95% CI -11.1, −5.6), in men who undertook <25 or 50 min of moderate/vigorous activity per day respectively. Biomarker levels increased linearly with increasing sedentary behaviour, but not independently of moderate/vigorous activity.

Conclusion: Associations between biomarkers and moderate/vigorous activity (and between hsTnT and light activity) were independent of sedentary behaviour, suggesting activity is driving the relationships. In these older men with concomitantly low levels of physical activity, activity may be more important in protecting against cardiac health deterioration in less active individuals, although reverse causality might be operating.

1. Introduction

N-terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitivity Troponin T (hsTnT) are routinely measured clinical biomarkers. Although the biologically active natriuretic peptides have protective diuretic, natriuretic, and metabolic effects, elevated NT-proBNP is used in the diagnosis and monitoring of heart failure [1], and is a strong marker of ventricular stretch and cardiac overload. In contrast hsTnT is a marker of myocardial ischaemia used in the diagnosis of myocardial infarction [2]. In observational studies both are associated with increased risk of cardiovascular disease and all-cause mortality, over and above other routine risk factors, even in apparently healthy people [3–6]. Importantly, both biomarkers have been shown to predict cardiovascular events [6], and it has been recently suggested that NTproBNP assessment could integrate heart failure into CVD primary prevention [7].

Two recent systematic reviews have reported that physical activity is protective against incident heart failure [8,9], and a number of studies suggest that the benefits are greater at or confined to higher levels of physical activity [9]. Physical activity improves many of the established heart failure risk factors such as hypertension, obesity, diabetes, smoking and coronary artery disease [10], and may also reduce the age-related decline in cardiac structure and function [11]. Sedentary behaviour, defined as sitting or reclining as distinct from a low level of physical activity has been little investigated in relation to heart failure but there is some evidence that sedentary behaviour may increase heart failure risk independently of physical activity [12].

Few studies have investigated relationships between physical activity and NT-proBNP or hsTnT, and findings are inconsistent. A study of

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older adults (≥65 years) found that more time spent in accelerometer measured walking was associated with lower levels of NT-proBNP and hsTnT [13], whilst of two studies using self-reported measures of physical activity, one found that participants doing more activity were less likely to experience an increase in NT-proBNP or hsTnT level during follow up [14], and the other found no associations between physical activity and biomarkers [15]. Self-report data for physical activity has limitations, particularly for light activity and sedentary behaviour and in older adults who have lower levels of physical activity and are more sedentary [16]. We investigated associations between both objectively measured physical activity and sedentary behaviour and biomarkers NT-proBNP and hsTnT, in a sample of community dwelling older men.

2. Methods

2.1. Sample

The British Regional Heart Study is a population-based cohort study following 7735 men recruited from primary care practices in 24 British towns in 1978–80. In 2010–2012, 3137 survivors were invited to (i) a physical examination, which included providing a fasting blood sample and (ii) wear a physical activity monitor. 1722 men (55%) attended, 1603 of whom provided a blood sample with NT-proBNP and hsTnT levels analysed. We excluded 272 men with a reported diagnosis of heart attack, heart failure, or stroke, leaving 1331 men with biomarker data. The National Research Ethics Service (NRES) Committee London provided ethical approval. Participants provided informed written consent to the investigation in accordance with the Declaration of Helsinki.

2.2. Objective physical activity assessment

Men wore the GT3X accelerometer (Actigraph, Pensacola, Florida) over the right hip for 7 days, during waking hours, removing it for swimming or bathing. Counts per minute (CPM) were calculated from movements registering on the vertical axis. Data were processed using standard methods [17]. Non-wear time was excluded using the R package "Physical Activity" [18]. Valid wear days were defined by convention as ≥600 min wear time, and participants with ≥3 valid days were included in analyses. Each minute of activity was categorised using widely used intensity threshold values of counts per minute developed for older adults: <100 for sedentary behaviour (<1.5 MET), 100–1040 for light activity (1.5–3 MET) and >1040 for moderate/vigorous activity,(≥3 MET) [19].

2.3. Cardiac injury biomarkers

Men were requested to fast for at least 6 h and instructed to drink only water during this time and take medications as usual. Blood samples were collected between 08:00 h and 19:00 h, centrifuged and separated the same day and stored on site at −20 °C until they were transferred (within 2 weeks) to a central freezer storage location at −70 °C. Samples were subsequently transferred to a central laboratory on dry ice and thawed immediately prior to analysis. NT-proBNP and hsTnT were measured using electrochemiluminescence immunoassays, performed on a Roche Elecsys 2010 automated platform (Roche Diagnostics, Burgess Hill, UK). The NT-proBNP and hsTnT assays have lower detection limits of 5 pg/mL and 3 ng/L, respectively [20,21]. For both assays, results below the limit of detection were assigned a value of 50% of the functional limit of detection (2.5 pg/mL for NT-proBNP and 1.5 ng/L for hsTnT). Assays were performed using the manufacturer's calibrators and quality controls. NT-proBNP and hsTnT had assay coefficients of variation of 6.5% and 4.5% for the low control and 3.8% and 9.1% for the high control, respectively.

2.4. Covariates

Men completed a questionnaire including information about: current cigarette smoking, alcohol consumption, living alone, current use of antihypertensives, statins and anticoagulants, ever receiving a doctor diagnosis of heart attack, heart failure, and stroke (with symptoms lasting >24 h). Social class was based on longest held occupation at study entry (1978–80) and categorised as manual and non-manual. Region of residence (1978–80) was grouped into Scotland, North, Midlands and South of England. Body mass index (BMI, kg/m^2) was calculated from height (Harpenden stadiometer) and weight in light indoor clothing (Tanita body composition analyser (BC-418) or Tanita scales if the participant had a pacemaker or defibrillator).

2.5. Statistical methods

We excluded men reporting a diagnosis of heart attack, heart failure, or stroke (with symptoms lasting >24 h) from analyses. Descriptive statistics for social and demographic characteristics, physical activity and sedentary behaviour, were calculated by quartile of NT-proBNP and hsTnT levels. The distributions of NT-proBNP and hsTnT were skewed and therefore transformed using natural logarithm.

We investigated associations between a number of physical activity measures and NT-proBNP or hsTnT. Physical activity measures included total activity counts per day, steps per day, minutes per day of moderate and vigorous activity, light activity and sedentary behaviour. We first used generalised additive models (GAMs) to investigate whether the relationships between each physical activity measure and NT-proBNP or hsTnT were nonlinear, using the "mgcv" package in R (version 3.0.3). GAM is a non-parametric model that does not specify the shape of any nonlinearity. To quantify associations between physical activity and NT-proBNP/hsTnT we used linear regression models (Stata version 13), and where associations were nonlinear we used the Stata function "mkspline". Mkspline allows the relationship to be estimated as a piecewise linear function (a function composed of linear segments), joining at knots. The position of the knot(s) (turning point of the function) was estimated from the GAM plots. All models were adjusted for average accelerometer wear time (minutes/day), season of accelerometer wear (warm, May–September or cold, October–April), hour of blood sampling, age, region of residence, social class, living alone, smoking status and alcohol. For ease of interpretation we present percentage differences in biomarker levels for each additional 10,000 counts of total activity, 1000 steps, 30 min of sedentary behaviour or light activity and 10 min of moderate/vigorous activity per day. To evaluate the independence of associations of activity intensities, models were mutually adjusted; (i) moderate/vigorous activity and sedentary behaviour and (ii) moderate/vigorous activity and light activity in the same model. Sedentary behaviour and light activity were not included in the same model due to collinearity ($r = -0.62$). We further adjusted all models for BMI to investigate whether BMI modified relationships between physical activity/sedentary behaviour and the biomarkers. To explore the potential of undiagnosed heart failure influencing findings we repeated regression models after excluding men with NTproBNP >400 pg/L. We conducted a post hoc analysis to investigate whether baseline levels of biomarkers and their association with physical activity differed by hypertensive status.

3. Results

Of 1331 men with biomarker levels available, 45 had an undetectable level of NT-proBNP (allocated value 2.5 pg/L) and 38 men had undetectable hsTnT (allocated value 1.5 ng/L). 1130 men had data for biomarkers, physical activity and all covariates. Men spent on average 614, 200 and 41 min per day in sedentary behaviour, light activity and moderate/vigorous activity respectively, had a mean of 5004 steps and 167,397 accelerometer counts per day (Table 1). Eighty percent of men had 7 days of accelerometer data and 96% had ≥5 days of data. Men with higher levels of NT-proBNP or hsTnT were older, more likely to live alone, take statins or anti-hypertensive medication, consume less alcohol, have lower levels of physical activity and higher levels of sedentary behaviour (Tables 1 & 2). Men with higher levels of hsTnT were also more likely to have diabetes (Table 2).

Generalised additive models showed that men who spent more time in physical activity had lower levels of NTproBNP and hsTnT, but relationships were non-linear and significant only at lower levels of physical activity, as illustrated by daily steps in Fig. 1, panels A and C. Total counts, moderate/vigorous activity and light activity each showed a similar pattern (not presented). In contrast, men who spent more time in sedentary behaviour had higher levels of NTproBNP and hsTnT and these associations were linear, as illustrated by daily steps in Fig. 1, panels B and D.

Results from regression models including a spline, are given in Table 3. Higher levels of physical activity were associated with lower levels of NT-proBNP, but significantly only below 150,000 counts per day, 4000 steps per day, 25 min of moderate/vigorous activity per day and 3 h of light activity per day, whereas associations above these knots were not significant (Table 3). For example, in men who undertook <25 min of moderate/vigorous activity per day, NT-proBNP was 35.7% lower (95% CI −47.9, −23.6) for each additional 10 min of moderate/vigorous activity (Table 3, Model 3). For each of the physical activity measures, coefficients above and below the knots were significantly different from each other, $p < 0.05$.

Similarly, higher levels of physical activity were associated with lower levels of hsTnT, but associations were significant only below the daily levels of counts, steps, moderate/vigorous activity and light activity indicated in Table 3. For example, in men who undertook <6000 steps per day, hsTnT was 10.0% lower (95% CI −12.9, −7.2) for each additional 1000 steps, but there was no significant association above 6000 steps per day (Table 3, Model 2).

Associations between sedentary behaviour and cardiac injury markers were linear and in the opposite direction. For each additional 30 min of sedentary behaviour, NT-proBNP levels were 6.3% higher