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Associations of Fitness and Physical Activity with Orthostatic Responses of Heart Rate and Blood Pressure at Mid-Life

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Abstract

Cardiorespiratory fitness (CRF) and physical activity (PA) are associated with autonomic function but their associations to orthostatic autonomic responses are unclear in epidemiological setting. We hypothesized that higher CRF and PA would associate with higher immediate vagal responses and lower incidence of adverse findings during orthostatic test. At age of 46, 787 men and 938 women

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without cardiorespiratory diseases and diabetes underwent an orthostatic test (3-min sitting, 3-min standing) with recording of R-R intervals (RRi) and blood pressure (BP) by finger plethysmography. Acute responses of RRi (30:15 ratio) and BP were calculated. CRF was measured by a submaximal step test and daily amount of moderate-to-vigorous PA (MVPA) for two weeks by wrist-worn accelerometer. Lifelong PA was based on questionnaires at ages of 14, 31 and 46. High CRF was significantly associated with higher RRi 30:15 ratio (adjusted standardized β=0.17, p<0.001) and milder acute decrease of systolic BP while standing (β=0.10, p=0.001), while MVPA was not (β=0.04 for RRi 30:15 ratio and β=0.05 for systolic BP acute response). High lifelong PA was significantly associated with higher RRi 30:15 ratio (β=0.08, p=0.002) but not with acute systolic BP response. Those in the lowest tertile of CRF had 9.2-fold risk (p=0.002) of having postural orthostatic tachycardia syndrome compared to more fit. Cardiorespiratory fitness and lifelong physical activity, but not current physical activity, were independently associated with higher cardiac vagal response to orthostasis. The present results underscore the importance fitness and lifelong physical activity in prevention of abnormal autonomic function and related cardiovascular risk.

Key Words: Exercise; Autonomic nervous system; Heart rate; Blood pressure

Introduction

Impaired autonomic function is associated with cardiovascular mortality in patients with cardiometabolic disease and in general population.[1, 2] It is also associated with aging and several risk factors for cardiometabolic disease, such as obesity and physical inactivity.[3-5] Abnormal autonomic function manifests typically as increased sympathetic activity and decreased vagal activity which increases risk for fatal cardiac arrhythmias – excessive and long-lasting sympathetic activity gradually damaging end organs irreversibly.[6, 7]

Low cardiorespiratory fitness (CRF) is an important risk factor of cardiovascular mortality.[8] Physical activity (PA) and exercise are keys to improve CRF but PA also has been associated with longevity independently of CRF.[9] Both higher CRF and higher PA are associated with more favourable cardiovascular autonomic function, i.e. higher cardiac vagal and lower sympathetic activity.[3, 10] Therefore, improving CRF and PA are key factors to reduce cardiometabolic risk,[11] where their effects on autonomic function form substantial component.[3, 5]

An orthostatic test is feasible way to determine cardiovascular function in response to sympathetic stimulus.[12, 13] Abnormal autonomic and hemodynamic responses, such as orthostatic hypotension,[14] orthostatic hypertension,[15] and postural orthostatic tachycardia syndrome (POTS),[16] have clinical significance. As higher CRF and PA have been associated with better steady-state cardiac autonomic function,[3, 5] contrasting results have been reported regarding in responses to orthostasis.[16-19] Also, contribution of CRF and PA to orthostatic response in epidemiological setting in unclear. Therefore, the purpose of this study was to determine the relationship between CRF and objectively measured PA with autonomic and hemodynamic responses to orthostatic test in population-based sample of middle-aged men and women. Secondly, the associations of lifelong PA (PA_{LIFE}) with the orthostatic responses were assessed. We hypothesized that a low CRF and PA are associated with attenuated immediate vagal response to orthostasis and higher incidence of adverse findings during orthostatic test. Furthermore, we tested the hypothesis that gender would modify the association of autonomic function to CRF and PA.

Materials and methods

Subjects

All those individuals living in northern Finland whose expected date of birth fell between January 1st and December 31st 1966 in Northern Finland (96.3% of all 1966 births, n = 12,058 live births) were included in the prospective NFBC1966-study. Since their mother's recruitment during her first visit to the maternity health clinics, data have been collected on their health, lifestyle and socioeconomic status. The study was conducted according to the Declaration of Helsinki and approved by the Ethical Committee of the Northern Ostrobothnia Hospital District in Oulu, Finland. The study participants provided their written informed consent for the study.

Protocol

Postal surveys enquiring about the participant's health status and lifestyle, including an invitation to attend a clinical examination, were sent in 2012-2014 to subjects who were living at known addresses in Finland (n=10,321). The response rate to the postal surveys was 66% (n=6,825). A total of 5,861 (57%) subjects participated in the clinical examinations in one of the three laboratory units (Oulu, southern and northern Finland) between April 2012 and March 2014. The present study included those who were examined in the Oulu laboratory unit (n=2,740) (Figure 1). The subjects entered the laboratory between 7:00 and 11:00 a.m. after overnight fasting (12 hours) and abstained from smoking and drinking coffee during the examination day. Venous blood samples were drawn for the analysis of glycemic status and lipid profile. Serum glucose was analyzed using an enzymatic hexokinase/glucose-6-phosphate dehydrogenase method. Total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, and triglycerides were determined using an enzymatic assay method. The concentration of glycated and total hemoglobin were measured using immunochemical assay methods. The ratio is reported as relative hemoglobin A1c (NGSP, %; IFCC mmol/mol). The samples were analyzed in NordLab Oulu, a testing laboratory (T113) accredited by Finnish Accreditation Service (FINAS) (EN ISO 15189) (All methods: Advia 1800; Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). Seated systolic (SBP) and diastolic blood pressures (DBP) were measured three times (the two lowest values averaged, Omron M10, Omron Healthcare, Kyoto, Japan) after 15 minutes of rest. After the anthropometric measurements, including body composition by bioimpedance (InBody720, InBody, Seoul, Korea), and other examinations, the participants had a light meal 60-90 min before the orthostatic test and performance of the submaximal exercise test. Subsequently, the two-week monitoring of PA was initiated. On a separate day, an oral glucose tolerance test was conducted according to the recommendations of the World Health Organization in those participants without medication for diabetes.

Inclusions/Exclusions

Out of 2,740 subjects, who were examined in the Oulu laboratory unit, the main outcome variables were successfully analyzed in 2,337 subjects. Further exclusions are described in Figure 1. The final population included 1,731 subjects (787 men and 938 women) of whom CRF, objectively measured PA and PA_{LIFE} were determined for 1,626, 1,650 and 1,389 subjects, respectively (Table 1).

Lifestyle factors

PA was self-reported at 14, 31 and 46 years of age. At the age of 14, the subjects were asked how often they participated in sports after school hours with the following alternatives 1) daily, 2) every other day, 3) twice a week, 4) once a week, 5) every other week, 6) once a month and 7) generally not at all. The answer options 6 and 7 were combined. At the ages of 31 and 46, the subjects were asked how often they participated in brisk PA/exercise during their leisure-time. The term 'brisk' was defined as PA causing at least some sweating and getting out of breath, corresponding to moderate-to-vigorous intensity. The six response alternatives were 1) daily, 2) 4-6 times a week, 3) 2-3 times a week, 4) once a week, 5) 2-3 times a month, and 6) once a month or less often. History and frequency of smoking was enquired and the subjects were classified as non-, ex- and current smokers. The amount of alcohol consumed per day was estimated from the items enquiring the frequency and the usual amount of beverage consumed on one occasion. Total sitting time during waking hours was established by asking the subjects how many hours on average they sat on weekdays (at work, at home, in a vehicle and elsewhere) and the total sum of sitting hours was used. Finally, Athens Insomnia Score for nocturnal sleep was assessed.[20]

Physical activity monitoring

PA was objectively measured with a wrist-worn Polar Active device (Polar Electro Oy, Kempele Finland). Participants were asked to wear the Polar Active monitor for 24 hours every day for at least 14 days, also while sleeping, in the non-dominant hand's wrist. The first day when activity monitors were given was excluded from the analysis. An eligible day was considered as at least 600 min/day wearing time during waking hours. Participants with four or more eligible days were included in the analyses. In the whole dataset, mean (SD) for eligible days was 13.6 (1.2), ranging from 4 to 19 days and including weekends. Polar Active provides daily PA based on estimated metabolic equivalent (MET) values every half minute.[21] Daily averages of duration spent in different PA levels (min/day) were calculated in all participants using the cutoff values provided by the manufacturer (very light: 1–2 MET, light: 2–3.5 MET, moderate: 3.5–5 MET, vigorous: 5–8 MET and very vigorous >8 MET). The three highest activity levels were combined as moderate-to-vigorous physical activity (MVPA). Genderwise tertiles and percentiles of MVPA were formed. Although the amount of MVPA measured by the wrist-worn Polar Active was previously reported to be higher compared to hip worn accelerometers when using standard cutoffs of 3 MET and 6 MET for moderate and vigorous PA, the differences between Polar Active and hip-worn monitors were shown to decline when using the cutoffs values provided by the Polar Active manufacturer.[21]

Lifelong physical activity

Latent Class Analysis was used to obtain clusters in which the individuals had a similar profile of PA from adolescence to middle-age. The method has been described elsewhere in detail.[22] Briefly, three lifelong PA trajectory groups (active, semi-active and inactive) were formed according to the self-reported frequency of PA at 14, 31 and 46 years of age (PA_{LIFE}). The number of clusters (1-7) is increased until the most appropriate model is found using

Bayesian Information Criterion. The clustering was performed for all the applicable subjects and both genders together, not only for those subjects with measured orthostatic test.

Orthostatic test

Orthostatic test consisted of 3 min of seated rest followed by 3 min active standing. Each participant sat down on a chair to allow instrumentation and was provided with a review of the protocol. Standard lead-II ECG (Cardiolife, Nihon Kohden, Tokyo, Japan) and blood pressure (BP) by finger photoplethysmography accompanied with the measurement of cardiac output (Nexfin, BMEYE Medical Systems, Amsterdam, the Netherlands) were recorded with a sampling frequency of 1,000 Hz (PowerLab 8/35, ADInstruments, Bella Vista, New South Wales, Australia). The finger cuff was adjusted so that SBP and DBP assessed by finger photoplethysmography (left arm, supported by an arm sling) did not differ by more than 10 mmHg from the values measured by the automated sphygmomanometer (right arm, Omron M10). Physiological calibration of finger BP was then turned off. After these procedures (5-10 min), there was at least a 1-min period allowing stabilization of heart rate (HR) before the recording of 3 min in the seated position and following 3 min of active standing. The participants were allowed to breathe spontaneously.

Analysis of orthostatic responses

Analysis software (Labchart 7 Pro; ADInstruments) was used to extract beat-to-beat values of heart rate HR, SBP, DBP, mean blood pressure (MBP) and cardiac output (CO). Stroke volume (SV) and systemic vascular resistance (SVR) were derived from these data. Cardiac index (CI) and stroke volume index (SVI) were calculated by dividing CO and SV, respectively, by body surface area. SVR index (SVRI) was calculated by diving CI by MBP. For the acute responses, minimum and subsequent maximum values of R-R interval RRi 30:15 ratio), SBP and DBP were detected from the first 30 seconds after command to stand up (AcuteMin or AcuteMax). The minimum and maximum RRi were detected around 15th and 30th beat after standing up, respectively. Continuous decrease in RRi after the maximum RRi was confirmed. The RRi 30:15 ratio was computed by dividing the maximum RRi by minimum RRi.[12] The mean values of all hemodynamic variables were analyzed from 60-180 seconds while seated and from 120-180 seconds while standing (Standing 2-3'). Absolute and relative changes from seated position were calculated. The relative changes (Δ) were used in analysis when the acute and later responses were investigated as continuous variables.

The abnormal responses to the orthostatic test were defined according to the following limiting value. The RRi 30:15 ratio was defined to be abnormal when the value was < 1.00 and borderline case when the value was 1.00-1.03. POTS was defined as condition where the HR was in standing position ≥120 bpm or the HR increased ≥30 bpm.[23] Orthostatic hypertension was defined as condition where the SBP increased in standing position ≥20 mmHg. Orthostatic hypotension was defined as condition where the SBP decreased ≥20 mmHg or DBP decreased ≥10 mmHg in standing position.[12, 13, 24]

Cardiorespiratory fitness

CRF was measured by a submaximal 4-min single-step test with a stepping rate of 23 ascents per minute paced by metronome and expressed as peak HR during the step test (HR_{STEP}) (34). In a sub-sample (n=124) of NFBC1966 at the age of 31, the correlation between HR_{STEP} and directly measured maximal oxygen uptake during a maximal cycle ergometer test was shown to be -0.52.[25] Stepping was performed without shoes on a bench adjusted to a height of 33 cm for women and 40 cm for men. HR was measured during and 90 s after the stepping in a seated position (RS800CX). The population was divided into CRF gender-wise tertiles and percentiles according to HR_{STEP}. The participants who terminated the test due to exhaustion were placed in the lowest tertile or percentile. Out of 1,731 participants, 1,570 successfully performed the test, 56 terminated the test due to exhaustion (test duration > 60 s), 4 terminated the test due to some reason other than exhaustion, 98 did not perform the test due to impaired health status (e.g. musculoskeletal problems, elevated blood pressure or exercise-induced angina pectoris) or unwillingness, and in 3 there were technical problems with HR recording.

Statistical analysis

The distributions of the outcome variables (orthostatic test) were first assessed by analyzing the skewness of the data by visual inspection of histograms. In the case of skewed distributions (|skewness|>1; RRi 30:15 ratio), the variable was transformed into its natural logarithm (ln), which eliminated skewness in the dependent variable. Thereafter, this transformed variable was verified to be Gaussian. The t-test was used for continuous variables to analyze the statistical significance of the differences between the genders. Gender-differences in categorical variables were analyzed using Chi-square test. Interactions of CRF, MVPA and PA_{LIFE} (in tertiles) with gender were assessed by ANCOVA (continuous outcome variables) or logistic regression (categorical outcome variables). Associations of CRF, MVPA and PA_{LIFE} with the outcome variables were assessed by linear regression analysis and the models were further adjusted for the potential contributing factors (gender, percent body fat, smoking, alcohol consumption, sitting time, Athens Insomnia Score, glycated hemoglobin, serum total and high-density lipoprotein cholesterol and triglycerides). The relative changes, instead of absolute, in hemodynamic variables were used in linear regression to minimize the effect of baseline value. Low-density lipoprotein cholesterol was excluded from the covariates due to its significant collinearity with total cholesterol (variance inflation factor > 5). The data were analyzed using SPSS software (IBM SPSS Statistics 24, IBM Corp., New York). A p-value <0.05 was considered significant.

Results

Cardiorespiratory fitness and orthostatic responses

Hemodynamics at seated rest and in response to standing are presented for both genders in Table 1. In the univariate analysis, high CRF (low HR_{STEP}) was significantly associated with lower HR_{Seated} and $HR_{\Delta AcuteMin}$ and higher $HR_{\Delta Standing\ 2\text{-}3'}$, $HR_{\Delta AcuteMax}$ and RRi 30:15 ratio (Table 2, Figure 2). These associations remained significant in the multivariate analysis, except for $HR_{\Delta Standing\ 2\text{-}3'}$ (Table 3). In the univariate analysis high CRF was significantly associated with lower SBP_{Seated} and DBP_{Seated} and higher $SBP_{\Delta AcuteMin}$ (Table 2, Figure 2). The associations of CRF with DBP_{Seated} and $SBP_{\Delta AcuteMin}$ remained significant in the multivariate analysis (Table 3). In the univariate analysis high CRF was significantly associated with lower CI_{Seated} and $SVI_{\Delta Standing\ 2\text{-}3'}$, and higher SVI_{Seated} and $SVRI_{Seated}$ (Table 2). These results remained significant in the multivariate analysis, except for $SVI_{\Delta Standing\ 2\text{-}3'}$ (Table 3). CRF was significantly associated with PA_{Life} (crude standardized $\beta=0.25$, $p<0.001$) and the amount of MVPA ($\beta=0.311$, $p<0.001$).

In the multivariate analysis, the body fat percentage was observed as more significant determinant of some orthostatic responses than CRF. The body fat percentage was significantly associated with $HR_{\Delta Standing\ 2-3'}$ (adjusted standardized β=-0.10, p=0.012), $SBP_{\Delta Standing\ 2-3'}$ (β=0.09, p=0.016), $DBP_{\Delta Standing\ 2-3'}$ (β=0.08, p=0.037), and $SVRI_{\Delta Standing\ 2-3'}$ (β=0.11, p=0.003) whereas contribution of CRF was not significant. Also, the body fat percentage was significantly associated with $SBP_{\Delta AcuteMax}$ (β=0.17, p<0.001) and $DBP_{\Delta AcuteMax}$ (β=0.10, p<0.001) despite the significant relationship of these markers to CRF.

Moderate-to-vigorous physical activity and orthostatic responses

In the univariate analysis high MVPA was significantly associated with lower HR_{Seated}, and higher $HR_{\Delta Standing\ 2-3'}$, $HR_{\Delta AcuteMax}$ and RRi 30:15 ratio (Table 2, Figure 2). After adjustments for covariates, all association remained significant, except for RRi 30:15 ratio (Table 3). In the univariate analysis high MVPA was significantly associated with lower CI_{Seated} and $SVI_{\Delta Standing\ 2-3'}$, and higher $SVRI_{Seated}$ (Table 2). After adjustments for covariates, the associations for CI_{Seated} and $SVRI_{Seated}$ remained significant (Table 3).

Lifelong physical activity and orthostatic responses

In the univariate analysis high PA_{LIFE} was significantly associated with lower HR_{Seated}, and higher $HR_{\Delta AcuteMax}$ and RRi 30:15 ratio (Table 2, Figure 3). After adjustments for covariates, all association remained significant (Table 4). In the univariate analysis high PA_{LIFE} was significantly associated lower CI_{Seated} and $SVI_{\Delta Standing\ 2-3'}$, and higher $SVRI_{Seated}$ (Table 2). After adjustments for covariates, all associations remained significant (Table 3).

Abnormal responses to orthostatic test

Cardiovascular autonomic function according to gender-wise tertiles of CRF, MVPA and PA_{LIFE} are presented in Table 4. Lower CRF was significantly associated with higher prevalence of POTS. Those in the lowest tertile of CRF had 9.2-fold adjusted risk (p=0.002) of having postural orthostatic tachycardia syndrome compared to more fit participants.

Gender-interactions in orthostatic responses

There was a linear and positive relationship between CRF and $HR_{\Delta AcuteMax}$ in both genders, the relationship being stronger in men (p=0.014). A trend of similar interaction was observed with association of high CRF to higher RRi 30:15 ratio (p=0.053). Low CRF was linearly associated with higher SBP_{Seated} in both genders, and the association was stronger in women (p=0.053). MVPA-gender interaction (p=0.024) was observed with $DBP_{\Delta Standing\ 2-3'}$. In women, both low and high MVPA were associated with higher $DBP_{\Delta Standing\ 2-3'}$, whereas in men this relationship was linear (Figure 4). In women, both low and high MVPA were associated with greater $SVRI_{\Delta Standing\ 2-3'}$, whereas in men they correlated with lower $SVRI_{\Delta Standing\ 2\text{-}3'}$ (p=0.007) (Figure 4). No gender-interactions were observed in associations of CRF, MVPA and PA_{LIFE} with prevalence of abnormal orthostatic responses.

Discussion

The main finding of the present study was that both cardiorespiratory fitness and lifelong physical activity were positively associated with immediate vagal response to upright standing. High cardiorespiratory fitness was also associated with lower incidence of postural orthostatic tachycardia syndrome. The present results suggest that high cardiorespiratory fitness and lifelong physical activity may prevent development autonomic dysfunction related to orthostasis.

It has been well established that higher CRF is associated with lower resting HR driven by cardiac vagal activity and greater stroke volume.[26] The present results suggest that CRF is also positively related to immediate vagal responses to upright standing, i.e. greater or faster vagal withdrawal, which potentially diminished acute decrease in BP, followed by efficient vagal rebound. It is also reasonable to expect that those with higher CRF and baseline vagal activity have more capacity for immediate vagal withdrawal.[27] While orthostatic responses are mediated mainly via baroreflex[12, 24] and CRF is positively associated baroreflex sensitivity,[3] baroreflex serves a potential factor explaining the present findings. Complementary analysis with our present and previous data showed that baroreflex sensitivity correlated strongly with RRi 30:15 ratio (r=0.43 for seated and r=0.55 for standing position).[3, 22] Also, increased cardiovagal response to Valsalva maneuver after aerobic training in young men also supports the present finding.[28] However, lower cardiovagal response to Valsalva maneuver has been reported in female athletes compared to sedentary counterparts.[29] Also, in the present study, men tended to benefit more from higher CRF than women regarding RRi 30:15 ratio. In contrast, Gabbett et al. reported no significant changes in initial (30 s) responses to passive head-up tilt after aerobic training in elderly despite evident improvement in CRF.[17] Notably, they did not observe improved baroreflex sensitivity either, which may underscore the importance of baroreflex in the immediate responses to orthostasis. For the lesser immediate decrease in BP among those with higher CRF, higher plasma volume, which often accompanies higher CRF, may play a role in addition to effective baroreflex.[16] While the present findings on immediate hemodynamic responses to standing describe mainly cardiac responses, some peripheral vascular effects may also be involved in this cascade.[30]

The present results suggest that low CRF would associate with greater prevalence of POTS that supports the vast majority of previous studies.[16] However, the relative change in HR in response to sustained standing was not substantially associated with CRF. Therefore, greater incidence of POTS with lower CRF may largely be explained by higher basal (resting) HR due to lower cardiac vagal activity among those with lower CRF.[3] However, higher CRF was substantially associated with lower CI, DBP and higher SVRI at seated rest. This finding may be explained by improved oxygen extraction accompanying high CRF resulting in lesser need for perfusion.[31] In this study, CRF was positively associated with SVRI, which is in contrast with previous studies, where exercise training has been associated with lower total peripheral resistance and decrease of sympathetic activity at rest.[10, 32] Also, CRF seemed not to be associated with later orthostatic relative responses of central hemodynamics in multivariate analyses, suggesting that CRF may not be determinant of in later cardiac or even peripheral responses to upright position. Therefore, it seems that CRF is mainly associated with overall vagal activity, regardless of position, and with immediate but not later hemodynamic response to orthostasis.

Regular PA has been associated with cardiovascular health.[11] The relationship between CRF and cardiovascular health is even stronger, suggesting that improved cardiovascular health with PA, as well as autonomic function, may be largely related to response of CRF to PA with interactions with genetic factors.[3, 9, 33] The present study verified the importance of CRF over PA for autonomic function and central hemodynamics at rest and during immediate response to upright standing. The associations of PA to outcome variables were similar but evidently weaker than observed with CRF. PA was not associated with the incidence of POTS. Both objective and lifelong subjective measurement of PA were positively associated with HR response and decrease in SVI during sustained standing. Reduction in SVI from lying to standing position, accompanied with increased HR, has been observed indicating increased venous pooling,[34] which may also relate to acute exercise effects.[35] However, we cannot conclude to which extent acute effects of habitual exercise may play part in the objectively measured and lifelong PA.

While the associations between CRF and immediate autonomic responses followed similar pattern between men and women, the relationship between CRF and immediate HR responses to upright standing were stronger in men. In other words, men may benefit from higher CRF more than women in terms of vagal responses orthostasis. Women exhibit partly different mechanisms in blood pressure regulation to men, e.g. lesser sympathetic effects on peripheral vasculature.[36] Therefore, it could be hypothesized that factors mediating the association between CRF and vagal responses may differ between genders. Later orthostatic responses in DBP and SVRI suggested U-shaped association with daily amount of MVPA in women and inverse U-shaped association in men. This underscores the complexity of physiology underlying gender-interactions in associations between CRF, MVPA and hemodynamic responses to orthostasis, which we cannot establish with the present data. On average, men had greater $HR_{\Delta AcuteMax}$ and RRI 30:15 ratio and lower $HR_{\Delta AcuteMin}$ than women. Although POTS or other orthostatic abnormalities were not more common in women than men in the present study, women have been overrepresented in patient populations suffering from these syndromes.[37] Better immediate autonomic response in men than in women may support these previous observations.

In addition to the traditional cardiometabolic risk factors, higher PA and CRF seems to improve the overall prognosis.[9] Independent roles of PA and CRF were also present in the current study suggesting that high CRF and PA have significant contribution to rapid vagal responses to upright standing – probably reflecting proper baroreflex-mediated changes in autonomic outflow. This may underscore and verify the role of antiarrhytmic vagal activity of potent mechanistic link in the association of CRF to cardiovascular morbidities.[1, 2, 8, 38] Compared to PA, CRF was more strongly associated with immediate orthostatic responses. In regard to orthostatic function, the primary goal of PA and exercise should preferably be improved fitness, while PA may have some effects on autonomic function independently of CRF.[3] Previously, CRF was suggested to be more important contributor than adiposity to long-term health outcomes and CVD risk was reported to be higher with inactive obese compared to their active counterparts.[9] These findings are consistent with the present results, albeit the contribution of percent body fat and serum triglyceride concentration were remarkable with orthostatic responses (Supporting information). Interestingly, higher body fat percentage was related to higher BP and SVRI and lower HR response during later phase of orthostasis, whereas CRF was not. These findings suggest that CRF contribute mainly to acute cardiovagal responses to orthostasis, whereas the body fat percentage to later responses to orthostasis. Higher BP and SVRI response to orthostasis may be precursor of orthostatic hypertension, where peripheral adrenergic hypersensitivity has been observed.[39] However, Wu et al. reported that orthostatic hypertension is not related to obesity although its association to diabetes mellitus was evident.[19]

The present study is limited by the time elapsing since the preceding meal may have affected autonomic function, which was relatively short but controlled. Thus, its confounding effects are presumably small. Also, the objective PA measurements were based on wrist-worn accelerometry with known limitations regarding PA without arm movement and sensitivity.[21] Yet, the ability of the present PA method to identify the fulfilment of daily PA recommendation is comparable to hip-worn devices.[21] The CRF was estimated by achieved HR in the submaximal step test, which induces bias caused by individual differences in maximal HR[40] and does not fully concur with the direct measurement of maximal oxygen uptake.[25] Furthermore, we cannot establish the causality in the present observations due to the study's cross-sectional design. The study is limited by the small number of cases with clinically abnormal orthostatic responses. This was most probably due to short standing period and milder hemodynamic adjustments needed when changing position from seated to upright.

In conclusion, both cardiorespiratory fitness and lifelong physical activity were positively associated with immediate vagal response to upright standing. The present results suggest that high cardiorespiratory fitness and lifelong physical activity may prevent development autonomic dysfunction related to orthostasis, particularly postural tachycardia syndrome.

Perspectives

High cardiorespiratory fitness was independently associated with immediate vagal response to standing countering acute fall in blood pressure. Also, high cardiorespiratory fitness appeared to be associated with lower incidence of postural tachycardia syndrome. Whereas the role of habitual physical activity seems to be lesser, physical activity should targeted to improve cardiorespiratory fitness to prevent development of abnormal autonomic function.

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References

1. Tsuji H, Larson MG, Venditti FJ, Jr., Manders ES, Evans JC, Feldman CL, Levy D. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation 1996;94:2850-2855.

2. Kiviniemi AM, Tulppo MP, Hautala AJ, Perkiomaki JS, Ylitalo A, Kesaniemi YA, Ukkola O, Huikuri HV. Prognostic significance of impaired baroreflex sensitivity assessed from Phase IV of the Valsalva maneuver in a population-based sample of middle-aged subjects. Am J Cardiol 2014;114:571-576.

3. Kiviniemi AM, Perkiomaki N, Auvinen J, Niemela M, Tammelin T, Puukka K, Ruokonen A, Keinanen-Kiukaanniemi S, Tulppo MP, Jarvelin MR, Jamsa T, Huikuri HV, Korpelainen R. Fitness, Fatness, Physical Activity, and Autonomic Function in Midlife. Med Sci Sports Exerc 2017;49:2459-2468.

4. Pikkujamsa SM, Makikallio TH, Sourander LB, Raiha IJ, Puukka P, Skytta J, Peng CK, Goldberger AL, Huikuri HV. Cardiac interbeat interval dynamics from childhood to senescence : comparison of conventional and new measures based on fractals and chaos theory. Circulation 1999;100:393-399.

5. Rennie KL, Hemingway H, Kumari M, Brunner E, Malik M, Marmot M. Effects of moderate and vigorous physical activity on heart rate variability in a British study of civil servants. Am J Epidemiol 2003;158:135-143.

6. Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. J Am Coll Cardiol 2008;51:1725-1733.

7. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care 2003;26:1553-1579.

8. Laukkanen JA, Makikallio TH, Rauramaa R, Kiviniemi V, Ronkainen K, Kurl S. Cardiorespiratory fitness is related to the risk of sudden cardiac death: a population-based follow-up study. J Am Coll Cardiol 2010;56:1476-1483.

9. Myers J, McAuley P, Lavie CJ, Despres JP, Arena R, Kokkinos P. Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: their independent and interwoven importance to health status. Progress in cardiovascular diseases 2015;57:306-314.

10. Joyner MJ, Green DJ. Exercise protects the cardiovascular system: effects beyond traditional risk factors. J Physiol 2009;587:5551-5558.

11. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE, Nonas CA, Sacks FM, Smith SC, Jr., Svetkey LP, Wadden TA, Yanovski SZ. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:S76-99.

12. Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. British medical journal 1982;285:916-918.

13. Freeman R. Assessment of cardiovascular autonomic function. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2006;117:716-730.

14. Angelousi A, Girerd N, Benetos A, Frimat L, Gautier S, Weryha G, Boivin JM. Association between orthostatic hypotension and cardiovascular risk, cerebrovascular risk, cognitive decline and falls as well as overall mortality: a systematic review and meta-analysis. J Hypertens 2014;32:1562-1571; discussion 1571.

15. Kario K. Orthostatic hypertension: a measure of blood pressure variation for predicting cardiovascular risk. Circ J 2009;73:1002-1007.

16. Fu Q, Levine BD. Exercise and non-pharmacological treatment of POTS. Auton Neurosci 2018;215:20-27.

17. Gabbett TJ, Gass GC, Thalib L, Morris N, Gass EM. Does endurance training affect orthostatic responses in healthy elderly men? Med Sci Sports Exerc 2001;33:1279-1286.

18. Lansimies EA, Rauhala E. Orthostatic tolerance and aerobic capacity. Aviat Space Environ Med 1986;57:1158-1164.

19. Wu JS, Yang YC, Lu FH, Wu CH, Chang CJ. Population-based study on the prevalence and correlates of orthostatic hypotension/hypertension and orthostatic dizziness. Hypertens Res 2008;31:897-904.

20. Soldatos CR, Dikeos DG, Paparrigopoulos TJ. Athens Insomnia Scale: validation of an instrument based on ICD-10 criteria. J Psychosom Res 2000;48:555-560.

21. Leinonen A-M, Ahola R, Kulmala J, Hakonen H, Vähä-Ypyä H, Herzig K-H, Auvinen J, Keinänen-Kiukaanniemi S, Sievänen H, Tammelin TH, Korpelainen R, Jämsä T. Measuring physical activity in free-living conditions—Comparison of three accelerometry-based methods. Front Physiol 2017;7:681.

22. Kiviniemi AM, Perkiomaki N, Auvinen J, Herrala S, Hautala AJ, Ahola R, Tammelin T, Tulppo MP, Jarvelin MR, Korpelainen R, Huikuri HV. Lifelong Physical Activity and Cardiovascular Autonomic Function in Midlife. Med Sci Sports Exerc 2016;48:1506-1513.

23. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, Cheshire WP, Chelimsky T, Cortelli P, Gibbons CH, Goldstein DS, Hainsworth R, Hilz MJ, Jacob G, Kaufmann H, Jordan J, Lipsitz LA, Levine BD, Low PA, Mathias C, Raj SR, Robertson D, Sandroni P, Schatz IJ, Schondorf R, Stewart JM, van Dijk JG. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Auton Neurosci 2011;161:46-48.

24. Piha SJ. Cardiovascular autonomic reflex tests: normal responses and age-related reference values. Clin Physiol 1991;11:277-290.

25. Tammelin T, Nayha S, Rintamaki H. Cardiorespiratory fitness of males and females of northern Finland birth cohort of 1966 at age 31. Int J Sports Med 2004;25:547-552.

26. Lavie CJ, Arena R, Swift DL, Johannsen NM, Sui X, Lee DC, Earnest CP, Church TS, O'Keefe JH, Milani RV, Blair SN. Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. Circ Res 2015;117:207-219.

27. Stratton JR, Levy WC, Caldwell JH, Jacobson A, May J, Matsuoka D, Madden K. Effects of aging on cardiovascular responses to parasympathetic withdrawal. J Am Coll Cardiol 2003;41:2077-2083.

28. Cooke WH, Reynolds BV, Yandl MG, Carter JR, Tahvanainen KU, Kuusela TA. Effects of exercise training on cardiovagal and sympathetic responses to Valsalva's maneuver. Med Sci Sports Exerc 2002;34:928-935.

29. Middleton N, De Vito G. Cardiovascular autonomic control in endurance-trained and sedentary young women. Clin Physiol Funct Imaging 2005;25:83-89.

30. Olufsen MS, Ottesen JT, Tran HT, Ellwein LM, Lipsitz LA, Novak V. Blood pressure and blood flow variation during postural change from sitting to standing: model development and validation. Journal of applied physiology 2005;99:1523-1537.

31. Heinonen I, Kudomi N, Kemppainen J, Kiviniemi A, Noponen T, Luotolahti M, Luoto P, Oikonen V, Sipila HT, Kopra J, Mononen I, Duncker DJ, Knuuti J, Kalliokoski KK. Myocardial blood flow and its transit time, oxygen utilization, and efficiency of highly endurance-trained human heart. Basic research in cardiology 2014;109:413.

32. Winker R, Barth A, Bidmon D, Ponocny I, Weber M, Mayr O, Robertson D, Diedrich A, Maier R, Pilger A, Haber P, Rudiger HW. Endurance exercise training in orthostatic intolerance: a randomized, controlled trial. Hypertension 2005;45:391-398.

33. Bouchard C, An P, Rice T, Skinner JS, Wilmore JH, Gagnon J, Perusse L, Leon AS, Rao DC. Familial aggregation of VO(2max) response to exercise training: results from the HERITAGE Family Study. J Appl Physiol 1999;87:1003-1008.

34. Low PA, Opfer-Gehrking TL, Textor SC, Schondorf R, Suarez GA, Fealey RD, Camilleri M. Comparison of the postural tachycardia syndrome (POTS) with orthostatic hypotension due to autonomic failure. J Auton Nerv Syst 1994;50:181-188.

35. Kiviniemi AM, Hautala AJ, Kinnunen H, Nissila J, Virtanen P, Karjalainen J, Tulppo MP. Daily exercise prescription on the basis of HR variability among men and women. Med Sci Sports Exerc 2010;42:1355-1363.

36. Hart EC, Joyner MJ, Wallin BG, Charkoudian N. Sex, ageing and resting blood pressure: gaining insights from the integrated balance of neural and haemodynamic factors. J Physiol 2012;590:2069-2079.

37. Cheng YC, Vyas A, Hymen E, Perlmuter LC. Gender differences in orthostatic hypotension. Am J Med Sci 2011;342:221-225.

38. La Rovere MT, Bersano C, Gnemmi M, Specchia G, Schwartz PJ. Exercise-induced increase in baroreflex sensitivity predicts improved prognosis after myocardial infarction. Circulation 2002;106:945-949.

39. Benowitz NL, Zevin S, Carlsen S, Wright J, Schambelan M, Cheitlin M. Orthostatic hypertension due to vascular adrenergic hypersensitivity. Hypertension 1996;28:42-46.

40. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. J Am Coll Cardiol 2001;37:153-156.

Table 1. Characteristics of the study population.

		Men n=787	Women n=938
Lifestyle			
Smoking status, n§	Non-smoker	315 (42 %)	465 (52 %)
	Ex-smoker	223 (30 %)	207 (23 %)
	Current smoker	209 (28 %)	230 (26 %)
Alcohol consumption, $g{\cdot}d^{-1}$		15 (21)	6 (9)‡
Athens Insomnia Score for Nocturnal Sleep		3 (3)	3 (3)
Sitting time on weekdays, self-report, h/day		8 (3)	7 (3)‡
MVPA, mean min/day		82 (40)	62 (30)‡
Lifelong PA§	Active	170 (28 %)	181 (23 %)
	Semi-Active	267 (44 %)	400 (51 %)
	Inactive	172 (28 %)	199 (26 %)
Cardiorespiratory fitness by step test			
HR_{STEP}, bpm		147 (15)	150 (15)
Clinical and laboratory measurements			
Body mass index, $kg{\cdot}m^{-2}$		26.5 (3.5)	25.8 (4.6)‡
Waist-hip-ratio		0.96 (0.06)	0.85 (0.05)‡
Body fat, %		22.3 (6.3)	31.9 (8.0)‡
HbA1c, %		5.5 (0.3)	5.4 (0.3)‡
mmol/mol		37 (4)	36 (4)
Plasma glucose, $mmol{\cdot}L^{-1}$		5.6 (0.5)	5.2 (0.4)‡
Total cholesterol, $mmol{\cdot}L^{-1}$		5.6 (1.0)	5.2 (0.9)‡
LDL cholesterol, $mmol{\cdot}L^{-1}$		3.8 (0.9)	3.2 (0.9)‡
HDL cholesterol, $mmol{\cdot}L^{-1}$		1.4 (0.3)	1.7 (0.4)‡

Triglycerides, mmol·L^{-1}	1.4 (1.0)	1.0 (0.5) ‡
Orthostatic test		
Heart rate		
Seated, bpm	74 (12)	75 (11)*
ΔStanding 2-3’, %	16.6 (8.0)	16.2 (7.4)
ΔAcuteMax, %	32.4 (12.0)	27.9 (10.0)‡
ΔAcuteMin, %	3.3 (9.1)	4.6 (7.3)†
RRi 30:15 ratio	1.29 (0.16)	1.23 (0.11)‡
Systolic blood pressure		
Seated, mmHg	125 (14)	118 (16)‡
ΔStanding 2-3’, %	-1.0 (5.1)	-0.8 (5.6)
ΔAcuteMin, %	-21.7 (9.7)	-20.4 (8.5)†
ΔAcuteMax, %	8.6 (7.8)	5.1 (7.9)‡
Diastolic blood pressure		
Seated, mmHg	74 (8)	70 (9)‡
ΔStanding 2-3’, %	2.8 (4.1)	4.2 4.7)‡
ΔAcuteMin, %	-26.7 (9.8)	-21.9 (8.8)‡
ΔAcuteMax, %	9.9 (7.3)	9.8 (7.9)
Cardiac Index		
Seated, L/min/m^2	3.15 (0.51)	3.25 (0.57)‡
ΔStanding 2-3’, %	2.29 (5.85)	0.37 (6.54)‡
Stroke Volume Index		
Seated, mL/m^2	43.2 (5.8)	43.7 (6.3)
ΔStanding 2-3’, %	-11.9 (6.7)	-13.4 (7.1)‡
Systemic Vascular Resistance Index,		
Seated, mmHg·m^2/L/min	30.0 (5.6)	28.0 (6.1)‡
ΔStanding 2-3’, %	-1.6 (6.0)	1.3 (7.1)‡

Abnormal responses to orthostatic test		
POTS (HR_{stand} ≥ 120 bpm or ΔHR_{stand} ≥ 30 bpm)	13 (1.7 %)	10 (1.1 %)
Ortostatic hypertension (ΔSBP ≥ 20 mmHg)	1 (0.1 %)	5 (0.5 %)
Ortostatic hypotension (ΔSBP ≤ -20 or ΔDBP ≤ -10 mmHg)	2 (0.3 %)	5 (0.5 %)
Any abnormal	15 (1.9 %)	20 (2.1 %)

The values are absolute or relative (%) number of cases, means (SD) and p value for sex-difference. *MVPA* moderate-to-vigorous physical activity, *HbA1c* glycated hemoglobin, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *HR* heart rate, *RRi* average of difference of successive heart rate intervals, *RRi 30:15 ratio* immediate heart rate maximum/minimum (30:15) ratio*, POTS* postural orthostatic tachycardia syndrome, HR_{stand} heart rate in standing position * p<0.05, † p<0.01 and ‡ p<0.001 compared to men.

Table 2. Associations between cardiovascular autonomic function, cardiorespiratory fitness (CRF) by peak heart rate during submaximal stepping-test (HR_{STEP}), daily amount of moderate-to-vigorous physical activity (MVPA) and lifelong physical activity (PA_{LIFE}).

	n=1626	n=1650	n=1389
Orthostatic test	CRF (HR_{STEP})	MVPA	PA_{LIFE}
Heart rate			
Seated	-0.56‡	-0.17‡	-0.16‡
ΔStanding 2-3’	0.05*	0.10‡	0.05*
ΔAcuteMax	0.19‡	0.15‡	0.13‡
ΔAcuteMin	-0.05*	0.04	-0.01
RRi 30:15 ratio (ln)	0.18‡	0.10‡	0.11‡
Systolic blood pressure			
Seated	-0.12‡	0.01	-0.01
ΔStanding 2-3’	-0.01	-0.01	-0.06*
ΔAcuteMin	0.09‡	0.05	0.02
ΔAcuteMax	-0.03	0.02	0.02
Diastolic blood pressure			
Seated	-0.18‡	0.01	-0.01
ΔStanding 2-3’	0.03	0.01	-0.02
ΔAcuteMin	0.01	-0.02	-0.02
ΔAcuteMax	0.01	0.02	-0.02
Cardiac Index			
Seated	-0.36‡	-0.17‡	-0.15‡
ΔStanding 2-3’	-0.02	0.03	-0.06*
Stroke Volume Index			
Seated	0.16‡	-0.03	0.00
ΔStanding 2-3’	-0.05*	-0.06*	-0.09†
Systemic Vascular Resistance Index			

Seated	0.22‡	0.14‡	0.11†
ΔStanding 2-3’	0.01	-0.03	0.02

Values are standardized betas by linear regression. *RRi* average of difference of successive heart rate intervals, *RRi 30:15 ratio* immediate heart rate maximum/minimum (30:15) ratio, * p<0.05, † p<0.01, ‡p<0.001.

Table 3. Multivariate analysis of associations between cardiovascular autonomic function, cardiorespiratory fitness (CRF) by peak heart rate during submaximal stepping-test (HR_{STEP}), daily amount of moderate-to-vigorous physical activity (MVPA) and lifelong physical activity (PA_{LIFE}) in men and women.

	n=1611 CRF (HR_{STEP})	n=1611 MVPA	n=1389 PA_{LIFE}
Orthostatic test			
Heart rate			
Seated	-0.60‡	-0.10‡	-0.11‡
ΔStanding 2-3'	-0.01	0.06*	0.03
ΔAcuteMax	0.14‡	0.08†	0.08†
ΔAcuteMin	-0.08†	-	-
RRi 30:15 ratio (ln)	0.17‡	0.04	0.08†
Systolic blood pressure			
Seated	-0.04	-	-
ΔStanding 2-3'	-	-	-0.05
ΔAcuteMin	0.10†	-	-
Diastolic blood pressure			
Seated	-0.13‡	-	-
Cardiac Index			
Seated	-0.40‡	-0.12‡	-0.12‡
ΔStanding 2-3'	-	-	-0.07*
Stroke Volume Index			
Seated	0.16‡	-	-
ΔStanding 2-3'	0.00	-0.04	-0.07†
Systemic Vascular Resistance Index			
Seated	0.27‡	0.11‡	0.10‡

Values are standardized betas by linear regression that are presented only in case of significant univariate associations. *RRi* average of difference of successive heart rate intervals, *RRi 30:15 ratio* immediate heart rate maximum/minimum (30:15) ratio, * $p<0.05$, † $p<0.01$, ‡$p<0.001$. Values are adjusted for gender, percent body fat, smoking, alcohol consumption, sitting time, Athens Insomnia Score, glycated hemoglobin, serum total and high-density lipoprotein cholesterol and triglycerides.

Table 4. Cardiovascular autonomic function according to tertiles of cardiorespiratory fitness (CRF) by peak heart rate during submaximal stepping-test (HR_{STEP}), daily amount of moderate-to-vigorous physical activity (MVPA) and lifelong physical activity (PA_{LIFE}) in men and women.

	CRF (HR_{STEP})			MVPA			PA_{LIFE}		
	High	Middle	Low	High	Middle	Low	High	Middle	Low
	n=440	n=598	n=555	n=512	n=543	n=556	n=345	n=654	n=362
POTS	0 (0.0)	3 (0.5)	16 (2.8)*†	5 (0.9)	1.6 %	8 (1.5)	3 (0.9)	9 (1.3)	7 (1.9)
Orthostatic hypertension	1 (0.2)	0 (0.0)	3 (0.5)	2 (0.4)	0.0 %	3 (0.6)	1 (0.3)	2 (0.3)	1 (0.3)
Orthostatic hypotension	2 (0.5)	1 (0.2)	3 (0.5)	2 (0.4)	1 (0.2)	4 (0.8)	2 (0.6)	3 (0.4)	1 (0.3)
Any abnormal	3 (0.7)	4 (0.7)	21 (3.6)*†	9 (1.6)	10 (1.8)	14 (2.7)	6 (1.7)	13 (1.9)	9 (2.4)

The values are absolute or relative (%) number of cases, *HR* heart rate, *POTS* postural orthostatic tachycardia syndrome. * $p<0.05$ compared to High, † $p<0.05$ compared to Middle.

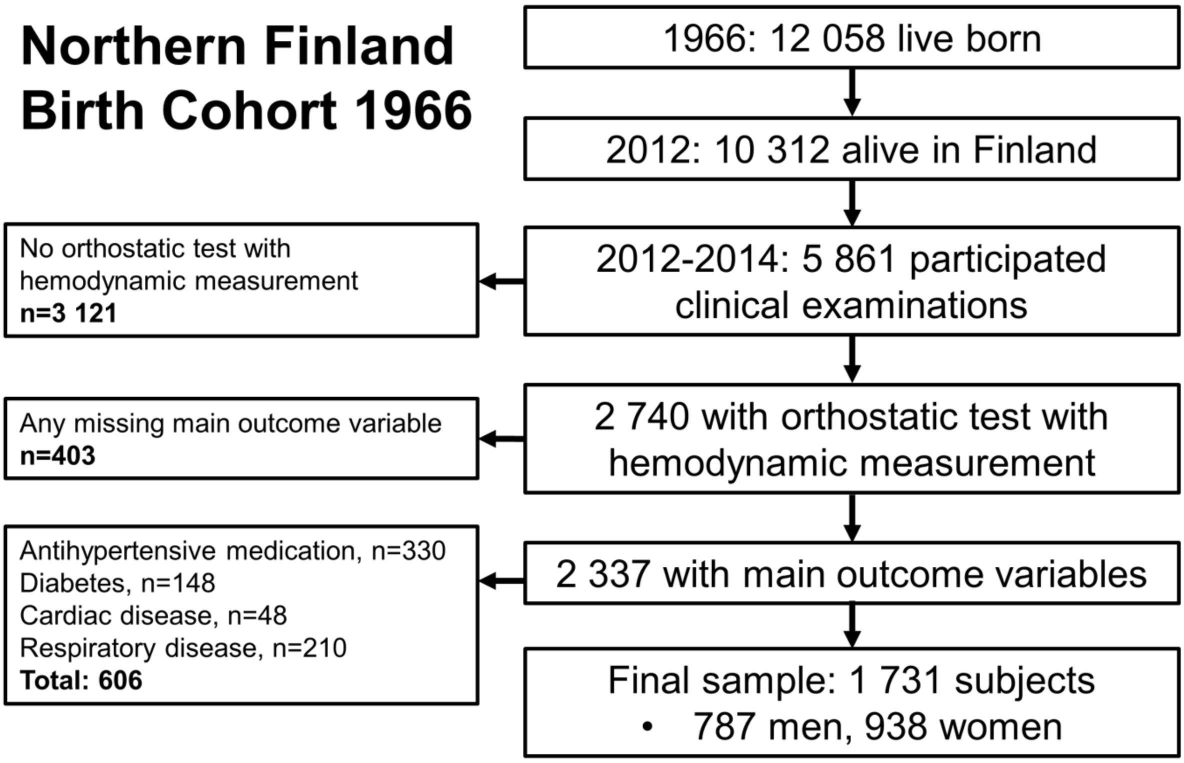
Figure legends

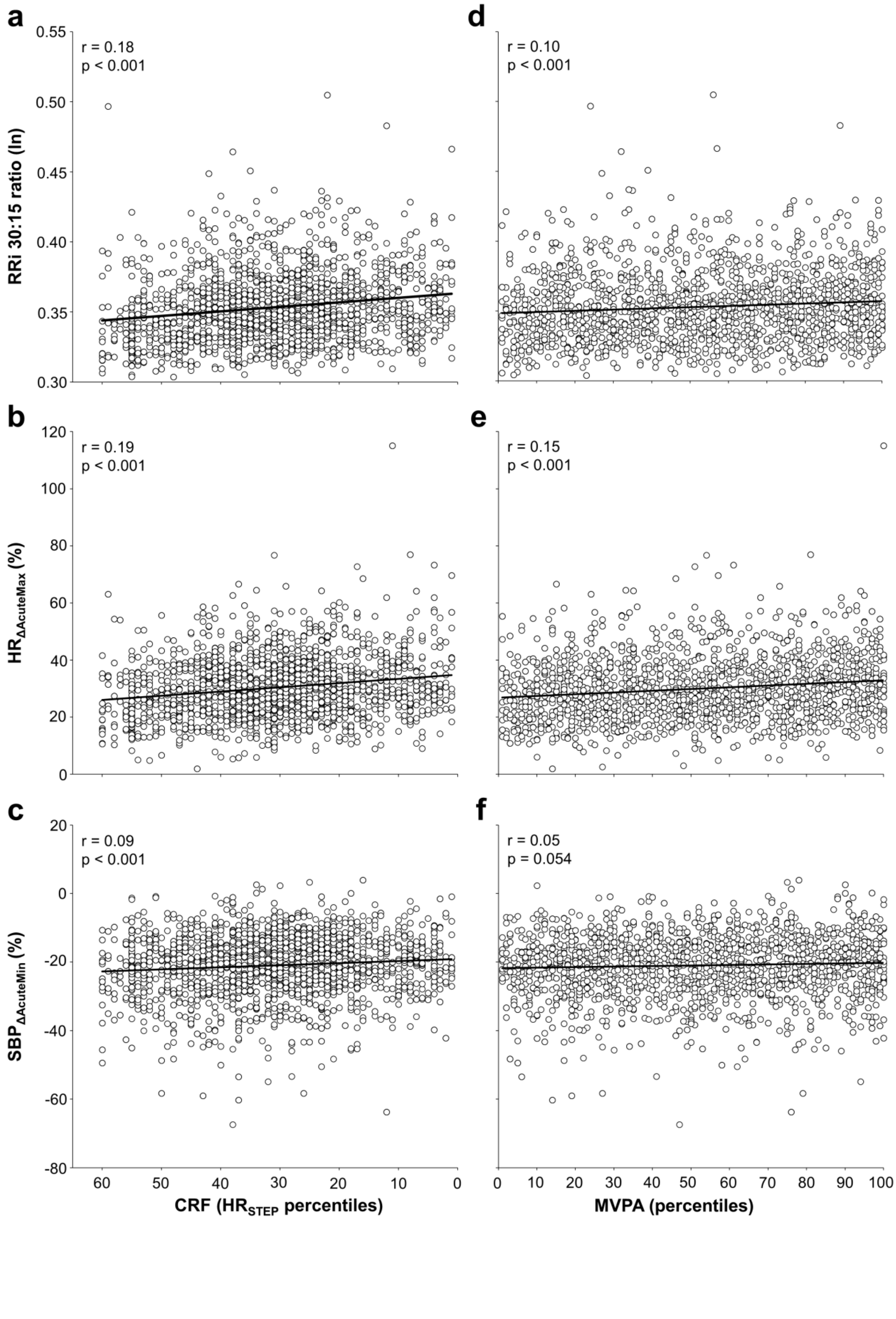
Figure 1. The selection of the study population from the Northern Finland Birth Cohort 1966. Antihypertensive medication included β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics and calcium channel blockers. *HR* heart rate, *BP* blood pressure, *CO* cardiac output, *CRF* cardiorespiratory fitness, *MVPA* moderate-to-vigorous physical activity and PA_{LIFE} lifelong physical activity measurement successfully performed.

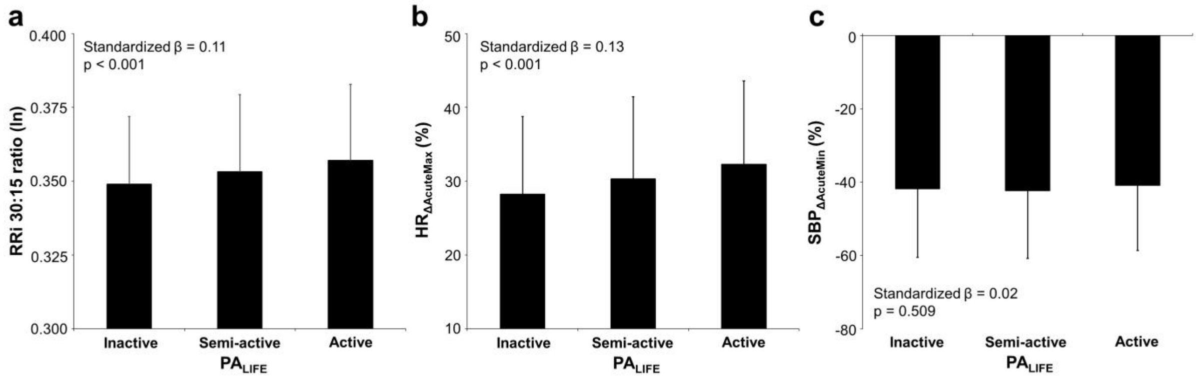
Figure 2. Correlations of cardiorespiratory fitness (CRF) as evaluated by peak heart rate during the step test (HR_{STEP}) and daily amount of moderate-to-vigorous physical activity (MVPA) to immediate heart rate and blood pressure responses to upright standing. *RRi 30:15 ratio (ln)* immediate heart rate maximum/minimum (30:15) ratio (a, d), $HR_{\Delta AcuteMax}$ relative change of HR within first 30 seconds while standing (b, e), $SBP_{\Delta AcuteMin}$ relative change of systolic blood pressure within first 30 seconds while standing (c, f).

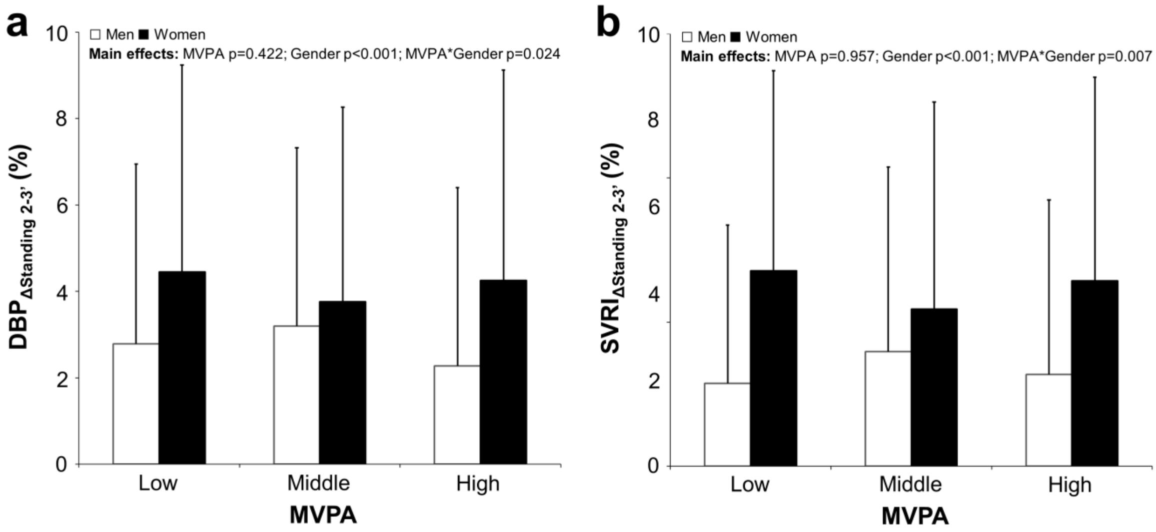
Figure 3. The immediate responses of heart rate and blood pressure to upright standing across the groups based on lifelong physical activity (PA_{LIFE}). *RRi 30:15 ratio (ln)* immediate heart rate maximum/minimum (30:15) ratio (a), $HR_{\Delta AcuteMax}$ relative change of HR within first 30 seconds while standing (b), $SBP_{\Delta AcuteMin}$ relative change of systolic blood pressure within first 30 seconds while standing (c).

Figure 4. The responses of diastolic blood pressure and systemic vascular resistance to upright standing across the tertiles of daily amount of moderate-to-vigorous physical activity (MVPA). $DBP_{\Delta Standing\ 2\text{-}3'}$ relative change of diastolic blood pressure within third minute while standing (a), $SVRI_{\Delta Standing\ 2\text{-}3'}$ relative change of systemic vascular resistance index within third minute while standing (b).


Northern Finland Birth Cohort 1966
1966: 12 058 live born
2012: 10 312 alive in Finland
No orthostatic test with hemodynamic measurement n=3 121
2012-2014: 5 861 participated clinical examinations
Any missing main outcome variable n=403
2 740 with orthostatic test with hemodynamic measurement
Antihypertensive medication, n=330
Diabetes, n=148
Cardiac disease, n=48
Respiratory disease, n=210
Total: 606
2 337 with main outcome variables
Final sample: 1 731 subjects
• 787 men, 938 women


a
0.55
0.50
0.45
0.40
0.35
0.30
r = 0.18
p < 0.001
RRi 30:15 ratio (ln)
d
r = 0.10
p < 0.001
b
120
100
80
60
40
20
0
r = 0.19
p < 0.001
HRΔAcuteMax (%)
e
r = 0.15
p < 0.001
c
20
0
-20
-40
-60
-80
r = 0.09
p < 0.001
SBPΔAcuteMin (%)
f
r = 0.05
p = 0.054
60 50 40 30 20 10 0
CRF (HRSTEP percentiles)
0 10 20 30 40 50 60 70 80 90 100
MVPA (percentiles)


a
Standardized β = 0.11
p < 0.001
RRi 30:15 ratio (ln)
0.400
0.375
0.350
0.325
0.300
Inactive
Semi-active
Active
PALIFE
b
Standardized β = 0.13
p < 0.001
HRΔAcuteMax (%)
50
40
30
20
10
Inactive
Semi-active
Active
PALIFE
c
0
-20
-40
-60
-80
SBPΔAcuteMin (%)
Standardized β = 0.02
p = 0.509
Inactive
Semi-active
Active
PALIFE


a
□ Men ■ Women
Main effects: MVPA p=0.422; Gender p<0.001; MVPA*Gender p=0.024
DBP ΔStanding 2-3' (%)
10
8
6
4
2
0
Low
Middle
High
MVPA
b
□ Men ■ Women
Main effects: MVPA p=0.957; Gender p<0.001; MVPA*Gender p=0.007
SVRI ΔStanding 2-3' (%)
10
8
6
4
2
0
Low
Middle
High
MVPA