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Physical activity and impaired left ventricular relaxation in middle aged adults

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The aim of this study was to examine the relationship between physical activity level and impaired left ventricular (LV) relaxation in a large sample of apparently healthy men and women. We conducted a cross-sectional study in 57,449 adults who underwent echocardiography as part of a comprehensive health examination between March 2011 and December 2014. Physical activity level was assessed using the Korean version of the International Physical Activity Questionnaire Short Form. The presence of impaired LV relaxation was determined based on echocardiographic findings. Physical activity levels were inversely associated with the prevalence of impaired LV relaxation. The multivariable-adjusted odds ratios (95% confidence interval) for impaired LV relaxation comparing minimally active and health-enhancing physically active groups to the inactive group were 0.84 (0.77–0.91) and 0.64 (0.58–0.72), respectively (P for trend < 0.001). These associations were modified by sex (p for interaction < 0.001), with the inverse association observed in men, but not in women. This study demonstrated an inverse linear association between physical activity level and impaired LV relaxation in a large sample of middle-aged Koreans independent of potential confounders. Our findings suggest that increasing physical activity may be independently important in reducing the risk of impaired LV relaxation.

Heart failure is a major public health problem that affects more than 5.8 million people in the United States and more than 23 million people worldwide and it results in significant morbidity, mortality and healthcare expenditures^{1–4}. Several epidemiological studies have reported that nearly half of subjects with heart failure have left ventricular (LV) diastolic dysfunction^{5–7}. Recent studies have described a rise in the proportion of heart failure with preserved LV ejection fraction relative to heart failure with reduced LV ejection fraction in recent decades^{8,9}. Because of the serious consequences of overt heart failure, there is substantial interest in identifying potentially modifiable risk factors that may prevent or reduce the progression of LV diastolic dysfunction. Aging, diabetes, hypertension, obesity, connective tissue disease, exercise training are risk factors known to affect LV diastolic function^{10–12}.

Especially, physical activity has multiple beneficial cardiovascular effects^{13,14} and is associated with reduced incidence of and lower mortality from cardiovascular disease^{15,16}. Recent epidemiological studies have reported a close link between LV diastolic dysfunction and metabolic disorders including obesity, metabolic syndrome and insulin resistance^{11,17}, all of which are also related to reduced physical activity. Most studies of physical activity and LV dysfunction, however, have focused on small cohorts of young male endurance athletes^{14,18,19} or of patients with overt heart disease^{20–23}.

Impaired LV relaxation is likely to go ahead of LV chamber stiffness or systolic dysfunction during the development of heart failure and has been assigned as a sensitive sign of LV diastolic dysfunction²⁴. Despite the fact

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that exercise is associated with better LV diastolic dysfunction, the relationship between physical activity and impaired LV relaxation remains largely unexplored in general population cohorts. Therefore, the aim of this study was to examine the association between physical activity and impaired LV relaxation in a large sample of Korean men and women free of clinical cardiovascular disease.

Methods

Study population. The Kangbuk Samsung Health Study was a cohort study of Korean men and women who attended a comprehensive annual or biennial health exam at the Kangbuk Samsung Hospital Total Healthcare Centers in Seoul and Suwon, South Korea²⁵. The study population was composed of 61,775 participants who completed a physical activity questionnaire and underwent echocardiography as part of a comprehensive screening examination from March, 2011 to December, 2014.

We excluded 4,326 participants with one or more of the following exclusion criteria: self-reported history of malignancy ($N = 1,495$); self-reported history of cardiovascular disease ($N = 537$); presence of echocardiographic abnormalities, including ejection fraction $< 50\%$, hypertrophic or dilated cardiomyopathy, ischemic cardiomyopathy, valvular replacement or valvular surgery, mitral stenosis or regurgitation, atrial fibrillation and congenital disease ($N = 2,218$). Because some exclusion criteria overlapped, the total number of patients eligible for the present study was 57,449.

The Institutional Review Board of the Kangbuk Samsung Hospital approved this study. The requirement for informed consent was waived as we used only anonymized retrospective data routinely collected during the health screening process.

Measurements. All examinations were conducted at the Kangbuk Samsung Hospital Total Healthcare Centers clinics in Seoul and Suwon. Data on demographic characteristics, medication use, medical history, smoking, alcohol consumption and education level were collected by self-administered, standardized questionnaires as previously described²⁵.

We measured physical activity levels using the validated Korean version of the International Physical Activity Questionnaire (IPAQ) Short Form^{26,27}, as previously described²⁵. IPAQ Short Form measures the frequency and duration of walking or any other moderate to vigorous physical activity undertaken for more than 10 continuous minutes across all contexts (i.e., work, home and leisure) during a seven-day period. Physical activity levels were classified into three categories: inactive, minimally active (600 MET-minutes per week), and health-enhancing physically active (HEPA; 3000 MET-minutes per week)²⁵. The total amount of weekday sitting time was assessed using the following single question: "During the last seven days, how much time did you usually spend sitting on a weekday?"²⁶. The sitting time was divided into the following categories commonly found in previous studies: < 5 , 5–9, and ≥ 10 hours/day²⁸.

The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality²⁹. We used component 3 of the PSQI, which is concerned with the number of hours of actual nighttime sleep obtained during the past month, to assess sleep duration. We measured usual dietary intake using a 103-item, self-administered food frequency questionnaire designed and validated for use in Korea³⁰. We calculated total energy and nutrient intake with a food composition tables developed by the Korean Nutrition Society³⁰.

Trained nurses measured height and weight while the participants wore a lightweight hospital gown and no shoes. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Obesity was defined as $\text{BMI} > 25.0 \text{ kg}/\text{m}^2$ according to the criteria proposed for Asian populations³¹. Blood pressure was measured using an automated oscillometric device (53000, Welch Allyn, New York, USA) with the participants in a sitting position with the arm supported at heart level. Hypertension was defined as a systolic blood pressure $\geq 140 \text{ mmHg}$, a diastolic blood pressure $\geq 90 \text{ mmHg}$, or current use of antihypertensive medication.

Measurements for serum biochemical parameters, including total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), insulin, glucose, hemoglobin A1c, and high-sensitivity C reactive protein (hsCRP) are described in detail elsewhere²⁵.

Echocardiography. Conventional echocardiography was performed with ultrasound scanners (Vivid 7 and E9, General Electric, Milwaukee, WI, USA) by trained sonographers following a standardized protocol³². Linear measurements of intraventricular septum thickness (IVST), left posterior wall thickness (PWT) and diameter of the left ventricular cavity at the end of diastole and systole were obtained in M-mode in the parasternal long axis view. LV mass in grams was calculated using the following equation: $\text{LV mass} = 0.8 \times [1.04 \times (\text{LVEDD} + \text{IVST} + \text{PWT})^3 - \text{LVEDD}^3] + 0.6$ ^{33,34}. Left ventricular mass index (LVMI) was determined as LV mass/body surface area (g/m^2). The anteroposterior diameter of the left atrium (LA) was measured in all participants.

Diastolic function was evaluated using pulse-wave Doppler transmittal LV inflow in an apical four-chamber view. Early diastolic mitral inflow peak velocity (E), late diastolic peak velocity (A) during atrial contraction, and deceleration time of the E velocity were also measured. The early (E') and late (A') tissue velocities were obtained from Tissue Doppler imaging of the septal mitral annuli. Since E' is primarily determined by myocardial relaxation and to a lesser extent by restoring forces and filling pressures, impaired LV relaxation was defined based on decreased E' ($< 7 \text{ cm}/\text{s}$) in this study³⁵. In this study, only 102 participants (0.18%) had increased E/E' (> 15).

Statistical analyses. The characteristics of the study participants were explored using physical activity categories. Mean values (95% confidence intervals [CIs]) of echocardiographic parameters were also estimated using physical activity categories. We conducted a logistic regression to estimate the odds ratios (with 95% CIs) for impaired LV relaxation by comparing the categories of physical activity with the reference category. We used three models with progressive adjustments. Model 1 was adjusted for age, sex, study center (Seoul, Suwon), and year of screening exam (one-year categories). Model 2 further included alcohol intake (0, < 20 , $\geq 20 \text{ g}/\text{d}$, or unknown),

Characteristics	Overall	Physical activity			P for trend
		Inactive	Minimally active	HEPA	
Number	57,449	25,865	22,261	9,323	
Men (%)	75.8	72.2	80.4	74.6	<0.001
Age (years) ^a	40.4 (7.6)	40.0 (7.1)	40.4 (7.6)	41.6 (8.7)	<0.001
BMI (kg/m ²) ^a	24.0 (3.2)	23.8 (3.3)	24.0 (3.1)	24.2 (3.1)	<0.001
Seoul center (%)	56.3	55.0	57.3	57.4	0.001
Obesity (%)	34.5	33.5	35.0	36.1	<0.001
Current smoker (%)	24.9	25.3	25.2	23.1	<0.001
Alcohol intake (%) ^b	25.7	24.7	25.4	29.4	<0.001
High education level (%) ^c	86.3	86.1	89.2	80.0	<0.001
Family history of CVD (%)	6.4	6.4	6.2	6.8	0.441
History of diabetes (%)	10.9	2.8	3.0	4.0	<0.001
History of hypertension (%)	3.1	9.8	11.0	13.3	<0.001
Systolic BP (mmHg) ^a	111.0 (12.8)	110.1 (12.9)	111.5 (12.6)	112.2 (12.7)	<0.001
Diastolic BP (mmHg) ^a	72.3 (10.2)	72.0 (10.4)	72.6 (10.1)	72.2 (10.1)	0.002
Glucose (mg/dL) ^a	96.5 (15.3)	96.2 (15.7)	96.8 (15.1)	96.9 (14.7)	<0.001
Total cholesterol (mg/dL) ^a	198.0 (34.5)	198.1 (34.8)	198.5 (34.3)	196.7 (33.8)	0.015
LDL-C (mg/dL) ^a	124.3 (31.6)	124.2 (32.0)	125.0 (31.3)	122.5 (31.3)	0.006
HDL-C (mg/dL) ^a	55.6 (14.3)	55.1 (14.3)	55.1 (13.9)	57.8 (14.9)	<0.001
Triglycerides (mg/dL) ^d	105 (73–156)	109 (75–160)	106 (75–157)	95 (67–138)	<0.001
HOMA-IR ^d	1.32 (0.87–1.96)	1.36 (0.90–2.03)	1.32 (0.87–1.94)	1.17 (0.77–1.78)	<0.001
hsCRP (mg/L) ^d	0.5 (0.3–1.0)	0.5 (0.3–1.0)	0.5 (0.3–0.9)	0.4 (0.3–0.9)	<0.001
Sleep duration (h/day) ^a	6.38 (1.02)	6.40 (1.05)	6.38 (0.99)	6.36 (1.02)	0.001
Total energy intake (kcal/d) ^{d,e}	1554.8 (1218.4–1933.0)	1509.9 (1174.9–1876.9)	1591.7 (1264.9–1972.4)	1597.0 (1241.3–1989.4)	<0.001

Table 1. Baseline characteristics of the study participants according to physical activity level. Data are ^amean (standard deviation), ^dmedian (interquartile range), or percentage. Abbreviations: BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance. ^b ≥ 20 g/day; ^c ≥ College graduate; ^e among 40,298 participants with plausible estimated energy intake levels (within three standard deviations from the log-transformed mean energy intake).

smoking (never, past, current, or unknown), educational level (high school graduate or less, community college or university graduate, graduate school or higher, and unknown), total calorie intake (quintile of total calorie intake or missing), sleep duration, family history of heart disease, history of hypertension and history of diabetes. Model 3 further adjusted for BMI, HOMA-IR, hsCRP, blood pressure and LVMI. To test for linear trends, we use the category rank as a continuous variable in the regression models. In addition, we examined the relationship between sitting time and impaired LV relaxation.

We performed stratified analyses in clinically relevant subgroups defined by sex (female vs male), age (<50 vs ≥50 years), smoking (never or ex-smoker vs current smoker), alcohol intake (<20 vs ≥20 g of alcohol per day), BMI (<25 vs ≥25 kg/m²), diabetes (no vs yes) and hypertension (no vs yes). Interactions between subgroups were tested using likelihood ratio tests to compare models with and without product terms.

All P-values were two-tailed, and P values < 0.05 were considered statistically significant. We used STATA version 14.0 (Stata Corp., College Station, TX, USA) for data analysis.

Results

The mean (SD) age, BMI, physical activity, and sitting time of study participants were 40.4 (7.6) years, 24.0 (3.2) kg/m², 1,549.5 (3,257.9) METs, and 8.0 (3.7) hours, respectively. The correlation between physical activity level (MET) and sitting time was −0.14 (P < 0.001). The proportions of inactive, minimally active and HEPA participants were 45.0, 38.8, and 16.2%, respectively. Compared to inactive participants, those with HEPA were more likely to be older, and obese, more likely to have a history of diabetes and hypertension, more likely to have higher total calorie intake, alcohol intake, systolic and diastolic blood pressure, glucose and HDL-C levels, less likely to be smokers, and more likely to have lower levels of education total cholesterol, LDL-C, triglycerides, HOMA-IR and sleep duration (Table 1).

In models adjusted for age, sex, center and year of screening exam, E, A, E/E', E/A ratio, LVEDD, LV mass, LVMI and LA size were positively related to physical activity level whereas heart rate and septal E' were inversely related to physical activity level (Table 2).

The overall prevalence of impaired LV relaxation was 6.7%. After adjusting for age, sex, center and year of screening exam, the odds ratios (95% CIs) for impaired LV relaxation comparing minimally active and HEPA groups to the inactive group were 0.84 (0.78–0.91) and 0.68 (0.62–0.76), respectively (Table 3). Further adjustment for potential confounding variables did not materially alter the findings. When adjusted for potential intermediate variables, the association was still statistically significant. The respective odds ratios (95% CIs) for

Characteristics	Physical activity			P for trend
	Inactive	Minimally active	HEPA	
Number of participants	25,865	22,261	9,323	
Heart rate	65.5 (65.3–65.6)	64.5 (64.4–64.6)	62.3 (62.1–62.5)	<0.001
Ejection fraction	66.7 (66.6–66.8)	66.7 (66.6–66.7)	66.6 (66.5–66.8)	0.31
E (cm/s)	69.7 (69.2–70.1)	71.0 (70.5–71.5)	72.1 (71.3–72.8)	<0.001
A (cm/s)	52.5 (51.0–54.0)	54.0 (52.4–55.6)	52.6 (50.2–55.1)	<0.001
E/E'	7.42 (7.37–7.47)	7.49 (7.44–7.54)	7.53 (7.45–7.61)	<0.001
E/A ratio	1.41 (1.39–1.42)	1.42 (1.41–1.44)	1.44 (1.42–1.46)	<0.001
Septal E' (cm/s)	10.7 (10.3–11.1)	10.7 (10.2–11.1)	10.6 (9.8–11.3)	<0.001
Septal A' (cm/s)	8.9 (8.5–9.2)	8.9 (8.5–9.2)	8.6 (8.0–9.2)	0.26
LVEDD (mm)	48.7 (48.6–48.7)	49.0 (48.9–49.0)	49.8 (49.7–49.8)	<0.001
LV mass (g)	133.3 (133.0–133.7)	135.3 (134.9–135.6)	142.0 (141.5–142.6)	<0.001
LVMI (g/BSA, g/m ²)	73.3 (73.2–73.5)	74.4 (74.2–74.5)	77.8 (77.5–78.0)	<0.001
LA size (mm)	34.0 (33.7–34.2)	34.1 (33.8–34.4)	35.3 (34.9–35.7)	<0.001

Table 2. Estimated^a mean values (95% CIs) of echocardiographic characteristics of the study participants by physical activity level. ^aAdjusted for age, sex, center, and year of screening exam. Early diastolic mitral inflow peak velocity (E), late diastolic peak velocity (A) during atrial contraction, and deceleration time of the E velocity were measured. The early (E') and late (A') tissue velocities were obtained from tissue Doppler imaging of the septal mitral annulus. Abbreviations: BSA, body surface area; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVMI, left ventricular mass index.

Physical activity level	Number	Cases	Multivariate-adjusted OR ^a		
			Model 1	Model 2	Model 3
Inactive	25,865	1,742	1.00 (reference)	1.00 (reference)	1.00 (reference)
Minimally active	22,261	1,460	0.84 (0.78–0.91)	0.84 (0.77–0.91)	0.84 (0.78–0.92)
HEPA	9,323	644	0.68 (0.62–0.76)	0.64 (0.58–0.72)	0.65 (0.58–0.73)
<i>P for trend</i>			<0.001	<0.001	<0.001

Table 3. Odds ratios^a (95% CIs) of impaired left ventricular relaxation by physical activity level. ^aEstimated from logistic regression models. Multivariable Model 1 was adjusted for age, sex, center, and year of screening exam; Model 2: Model 1 plus adjustments for smoking status, alcohol intake, educational level, total calorie intake, sleep duration, family history of heart disease, history of diabetes, and history of hypertension; Model 3: Model 2 plus adjustments for BMI, HOMA-IR, systolic blood pressure, hsCRP, heart rate and LVMI (g/BSA, g/m²).

impaired LV relaxation comparing minimally active and HEPA groups to the inactive group were 0.84 (0.78–0.92) and 0.65 (0.58–0.73), respectively (*P* for trend < 0.001) (Table 3). On the other hand, sitting time was not significantly associated with impaired LV relaxation (Appendix Table 1). The interaction of physical activity and sitting time for impaired LV relaxation was not statistically significant (*p* for interaction = 0.36). The multivariable adjusted odds ratios (95% CIs) for impaired LV relaxation comparing HEPA groups to the minimally active group were 0.77 (0.69–0.86) (Appendix Table 2).

The association between physical activity and impaired LV relaxation was similar in pre-specified subgroups of study participants except those divided based on sex (Table 4 and Fig. 1). The association between physical activity and impaired LV relaxation was observed in men, but not in women (Fig. 1, *P* interaction < 0.001). The association between physical activity levels and impaired LV relaxation was still present in non-obese participants (BMI < 25 kg/m²).

Discussion

There were several novel findings in this large sample of Korean men and women. First, we observed an inverse linear association between physical activity level and impaired LV relaxation independent of potential confounders. Both minimally active levels and HEPA were inversely associated with impaired LV relaxation. Second, these associations were modified by sex. The inverse association between physical activity and impaired LV relaxation was observed only for men. Lastly, the association between physical activity level and impaired LV relaxation was still observed in non-obese participants.

Many epidemiologic studies have reported an association of inadequate physical activity with diabetes, coronary heart disease, stroke and increased cardiovascular mortality^{15,16,36}. However, the relationship between physical activity and impaired LV relaxation in general a population sample remains largely unexplored. Most studies of the cardiac effects of physical activity have focused on LV function among elderly patients with heart problems or in small cohorts of young male endurance athletes^{14,18–23}. A small investigation of 36 healthy participants reported that a sedentary lifestyle was related to decreased LV compliance, leading to diminished diastolic performance³⁷. To our knowledge, this is the first study to show an inverse linear association between physical activity

Subgroup	Physical activity levels			P for trend	P for interaction
	Inactive	Minimally active	HEPA		
Sex					<0.001
Female (N = 13,912)	1.00 (reference)	0.88 (0.70–1.11)	0.85 (0.66–1.10)	0.196	
Male (N = 43,537)	1.00 (reference)	0.82 (0.76–0.89)	0.61 (0.55–0.69)	<0.001	
Age					0.073
<50 years (N = 51,642)	1.00 (reference)	0.83 (0.75–0.91)	0.62 (0.54–0.71)	<0.001	
≥50 years (N = 5,807)	1.00 (reference)	0.91 (0.79–1.04)	0.83 (0.71–0.97)	0.019	
Current smoker					0.695
No (N = 40,135)	1.00 (reference)	0.86 (0.78–0.95)	0.61 (0.54–0.70)	<0.001	
Yes (N = 13,310)	1.00 (reference)	0.81 (0.70–0.94)	0.62 (0.49–0.77)	<0.001	
Alcohol intake					0.081
<20 g/day (N = 41,254)	1.00 (reference)	0.85 (0.77–0.95)	0.69 (0.60–0.79)	<0.001	
≥20 g/day (N = 14,293)	1.00 (reference)	0.92 (0.72–0.94)	0.57 (0.48–0.68)	<0.001	
BMI					0.071
<25 kg/m ² (N = 37,538)	1.00 (reference)	0.85 (0.76–0.96)	0.70 (0.59–0.81)	<0.001	
≥25 kg/m ² (N = 19,769)	1.00 (reference)	0.83 (0.75–0.92)	0.60 (0.52–0.70)	<0.001	
Diabetes					0.601
No (N = 54,654)	1.00 (reference)	0.83 (0.77–0.91)	0.64 (0.57–0.72)	<0.001	
Yes (N = 2,794)	1.00 (reference)	0.82 (0.66–1.02)	0.66 (0.50–0.87)	0.002	
Hypertension					0.038
No (N = 49,123)	1.00 (reference)	0.85 (0.77–0.94)	0.67 (0.58–0.76)	<0.001	
Yes (N = 8,252)	1.00 (reference)	0.81 (0.71–0.92)	0.61 (0.52–0.72)	<0.001	

Table 4. Odds ratios^a (95% CIs) of impaired left ventricular relaxation according to physical activity level in clinically relevant subgroups. ^aEstimated from logistic regression. The multivariable model was adjusted for age, sex, center, year of screening exam, smoking status, alcohol intake, educational level, total calorie intake, sleep duration, family history of heart disease, history of diabetes, and history of hypertension.

and the prevalence of impaired LV relaxation in a large sample of adults who were not elite athletes or patients with heart failure.

The mechanism by which physical activity was inversely related to the prevalence of impaired LV relaxation has yet to be identified. Because obesity is associated with changes in cardiac structure and function, including LV diastolic dysfunction, adiposity might represent a possible mechanism linking physical activity with impaired LV relaxation^{11,38,39}. In this study, adjusting for BMI did not change the inverse association between physical activity levels and impaired LV relaxation. In addition, an inverse relationship between physical activity and impaired LV relaxation was still observed even in participants with a BMI <23 kg/m², the group in which confounding from BMI should be the smallest.

Insulin resistance might also be another possible mechanism to explain the association of physical activity with impaired LV relaxation. Physical activity leads to greater insulin sensitivity due to increases in the glucose transport protein-4 levels and muscle glycogen synthase activity, decreases in serum triglyceride concentrations and increases in the muscle capillary network⁴⁰. Indeed, recent epidemiological studies have described a close link between LV diastolic dysfunction and insulin resistance or metabolic syndrome^{17,41}. In our study, however, the relationship between physical activity and impaired LV relaxation remained statistically significant after further adjusting for HOMA-IR suggesting that physical activity may directly affect LV diastolic function through biological pathways independent of obesity or insulin resistance. The positive association between physical activity and impaired LV relaxation might be explained by high blood pressure. The relationship of hypertension with LV diastolic dysfunction has been established^{42,43}. These results did not change after adjustment for history of hypertension and systolic blood pressures.

Prolonged endurance exercise leads to a balanced enlargement of ventricular mass and dimensions¹⁴, resulting in enhanced cardiac performance without an obvious change in contractility, which thus might explain the low prevalence of impaired LV relaxation among participants with minimally active levels or HEPA levels^{37,44}. Furthermore, prolonged exercise could have beneficial effects due to the maintenance of vascular elasticity and thus smaller arterial load³⁷. Endurance training preserves vascular elasticity with aging and therefore might prevent changes in cardiac adaptation, such as focal proliferation of matrix or alteration of myocyte morphology^{45,46}.

In the current analyses, the association between physical activity levels and impaired LV relaxation was statistically significant in men, but not in women. Despite conflicting results on possible sex differences in the protective effects of physical activity, several investigations have shown that there is differential remodeling in responses to aerobic exercise by sex. Although the reasons for sex-dependent effects of physical activity on impaired LV relaxation are not fully understood, there could be strong genetic modifiers of cardiac adaptation and exercise capacity^{47,48}. A recent experimental study showed that the α 1-adrenergic system is very important in determining heart size and the ability of the heart to respond to pathological and physiologic stimuli only in male mice, and this sex difference remained following ovariectomy in females⁴⁹. Sex-related difference could also be related to

Figure 1. Multivariate-adjusted odds ratios^a (95% CIs) of impaired LV relaxation according to physical activity level in women and men. ^aEstimated from a logistic regression model. The multivariable model was adjusted for age, sex, year of screening exam, center, educational level, alcohol intake, smoking status, total calorie intake, sleep duration, family history of heart disease, history of hypertension, and history of diabetes. The P-value for the interaction of sex and physical activity levels for impaired LV relaxation was < 0.001.

shorter stature, hence earlier wave reflection and diastolic dysfunction⁵⁰. Further research is needed to understand this sex-related difference.

Our study had some limitations that should be considered in the interpretation of our findings. First, we don't have any information related to cardiorespiratory fitness, and because physical activity was self-reported, measurement error was inevitable. Specifically, people often have trouble recalling light-intensity exercise and tend to misreport the amount of time spent doing in such activities⁵¹. Misclassification is likely but might be non-differential. As a consequence, the true association of physical activity with LV diastolic function could be much stronger than shown here. Second, the cross-sectional design in this study limited our ability to determine temporality and prove causal relationships. Third, we have no information about LA volume or peak tricuspid velocity among the measurements recommended by the American Society of Echocardiography to assess LV diastolic function³⁵. Future prospective studies that assess all four variables: annular E' velocity, E/E' ratio, LA volume, and peak tricuspid velocity are needed to examine potential causal associations of physical activity with the development of LV diastolic dysfunction. Finally, participants in our study were highly educated, young and middle-aged Koreans who regularly underwent health check-up exams, most often as a part of work-related health screening programs; thus, the results from our study may not be generalizable to other populations with different demographic composition. Despite these potential limitations, major strengths of our study were its large sample size, a comprehensive inclusion of potential confounding variables, and the availability of high-quality imaging and laboratory procedures with extensive quality control measures.

Conclusion

This study demonstrated an inverse linear association between physical activity level and impaired LV relaxation independently of potential confounders in a large sample of young and middle-aged Koreans. This association was shown primarily in men, but not in women. Our findings suggest that increasing physical activity may be independently associated with reduced risk of impaired LV relaxation.

References

- Hunt, S. A. American College of, C. & American Heart Association Task Force on Practice, G. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *Journal of the American College of Cardiology* **46**, e1–82, <https://doi.org/10.1016/j.jacc.2005.08.022> (2005).
- Mosterd, A. *et al.* The prognosis of heart failure in the general population: The Rotterdam Study. *European heart journal* **22**, 1318–1327, <https://doi.org/10.1053/euhj.2000.2533> (2001).
- Cowie, M. R. *et al.* Survival of patients with a new diagnosis of heart failure: a population based study. *Heart* **83**, 505–510 (2000).
- Dunlay, S. M. *et al.* Hospitalizations after heart failure diagnosis a community perspective. *Journal of the American College of Cardiology* **54**, 1695–1702, <https://doi.org/10.1016/j.jacc.2009.08.019> (2009).
- Vasan, R. S. *et al.* Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *Journal of the American College of Cardiology* **33**, 1948–1955 (1999).
- Mosterd, A. *et al.* Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. *European heart journal* **20**, 447–455 (1999).
- Senni, M. *et al.* Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation* **98**, 2282–2289 (1998).
- Roger, V. L. Epidemiology of heart failure. *Circulation research* **113**, 646–659, <https://doi.org/10.1161/CIRCRESAHA.113.300268> (2013).
- Gerber, Y. *et al.* A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med* **175**, 996–1004, <https://doi.org/10.1001/jamainternmed.2015.0924> (2015).

10. Abhayaratna, W. P., Marwick, T. H., Smith, W. T. & Becker, N. G. Characteristics of left ventricular diastolic dysfunction in the community: an echocardiographic survey. *Heart* **92**, 1259–1264, <https://doi.org/10.1136/hrt.2005.080150> (2006).
11. Russo, C. *et al.* Effect of obesity and overweight on left ventricular diastolic function: a community-based study in an elderly cohort. *Journal of the American College of Cardiology* **57**, 1368–1374, <https://doi.org/10.1016/j.jacc.2010.10.042> (2011).
12. Vegh, J., Hegedus, I., Szegei, G., Zeher, M. & Bodolay, E. Diastolic function of the heart in mixed connective tissue disease. *Clin Rheumatol* **26**, 176–181, <https://doi.org/10.1007/s10067-006-0257-7> (2007).
13. Rerych, S. K., Scholz, P. M., Sabiston, D. C. Jr. & Jones, R. H. Effects of exercise training on left ventricular function in normal subjects: a longitudinal study by radionuclide angiography. *The American journal of cardiology* **45**, 244–252 (1980).
14. Pluim, B. M., Zwinderman, A. H., van der Laarse, A. & van der Wall, E. E. The athlete's heart. A meta-analysis of cardiac structure and function. *Circulation* **101**, 336–344 (2000).
15. Sattelmair, J. *et al.* Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation* **124**, 789–795, <https://doi.org/10.1161/CIRCULATIONAHA.110.010710> (2011).
16. Manson, J. E. *et al.* Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *The New England journal of medicine* **347**, 716–725, <https://doi.org/10.1056/NEJMoa021067> (2002).
17. Hwang, Y. C. *et al.* Metabolic syndrome and insulin resistance are associated with abnormal left ventricular diastolic function and structure independent of blood pressure and fasting plasma glucose level. *International journal of cardiology* **159**, 107–111, <https://doi.org/10.1016/j.ijcard.2011.02.039> (2012).
18. Scharhag, J. *et al.* Athlete's heart: right and left ventricular mass and function in male endurance athletes and untrained individuals determined by magnetic resonance imaging. *Journal of the American College of Cardiology* **40**, 1856–1863 (2002).
19. Perseghin, G. *et al.* Effect of the sporting discipline on the right and left ventricular morphology and function of elite male track runners: a magnetic resonance imaging and phosphorus 31 spectroscopy study. *American heart journal* **154**, 937–942, <https://doi.org/10.1016/j.ahj.2007.06.039> (2007).
20. Alves, A. J. *et al.* Exercise training improves diastolic function in heart failure patients. *Medicine and science in sports and exercise* **44**, 776–785, <https://doi.org/10.1249/MSS.0b013e31823cd16a> (2012).
21. Panovsky, R. *et al.* The effect of regular physical activity on the left ventricle systolic function in patients with chronic coronary artery disease. *Physiological research/Academia Scientiarum Bohemoslovaca* **60**, 869–875 (2011).
22. Nishi, I. *et al.* Effects of exercise training in patients with chronic heart failure and advanced left ventricular systolic dysfunction receiving beta-blockers. *Circulation journal: official journal of the Japanese Circulation Society* **75**, 1649–1655 (2011).
23. Aggelopoulos, P. *et al.* Sex differences regarding the impact of physical activity on left ventricular systolic function in elderly patients with an acute coronary event. *Hellenic journal of cardiology: HJC = Hellenike kardiologike epitheorese* **55**, 448–456 (2014).
24. Yamamoto, K. The time constant of left ventricular relaxation: extrication from load dependence and overestimation of functional abnormality. *Circ Heart Fail* **3**, 178–180, <https://doi.org/10.1161/CIRCHEARTFAILURE.110.941773> (2010).
25. Ryu, S. *et al.* Relationship of sitting time and physical activity with non-alcoholic fatty liver disease. *Journal of hepatology* **63**, 1229–1237, <https://doi.org/10.1016/j.jhep.2015.07.010> (2015).
26. Craig, C. L. *et al.* International physical activity questionnaire: 12-country reliability and validity. *Medicine and science in sports and exercise* **35**, 1381–1395, <https://doi.org/10.1249/01.MSS.0000078924.61453.FB> (2003).
27. Oh, J. Y., Yang, Y. J., Kim, B. S. & Kang, J. H. Validity and reliability of Korean version of International Physical Activity Questionnaire (IPAQ) short form. *Korean J Fam Med* **28**, 532–541 (2007).
28. Aadahl, M. *et al.* Recent temporal trends in sleep duration, domain-specific sedentary behaviour and physical activity. A survey among 25–79-year-old Danish adults. *Scandinavian journal of public health* **41**, 706–711, <https://doi.org/10.1177/1403494813493151> (2013).
29. Buysse, D. J., Reynolds, C. F. 3rd, Monk, T. H., Berman, S. R. & Kupfer, D. J. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* **28**, 193–213, 0165-1781(89)90047-4 [pii] (1989).
30. Ahn, Y. *et al.* Validation and reproducibility of food frequency questionnaire for Korean genome epidemiologic study. *European journal of clinical nutrition* **61**, 1435–1441, <https://doi.org/10.1038/sj.ejcn.1602657> (2007).
31. Wen, C. P. *et al.* Are Asians at greater mortality risks for being overweight than Caucasians? Redefining obesity for Asians. *Public Health Nutr* **12**, 497–506, <https://doi.org/10.1017/s1368980008002802> (2009).
32. Lang, R. M. *et al.* Recommendations for chamber quantification. *European Heart Journal-Cardiovascular Imaging* **7**, 79–108 (2006).
33. Devereux, R. B. *et al.* Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *The American journal of cardiology* **57**, 450–458 (1986).
34. de Simone, G. *et al.* Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. *Journal of the American College of Cardiology* **20**, 1251–1260 (1992).
35. Nagueh, S. F. *et al.* Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography* **29**, 277–314, <https://doi.org/10.1016/j.echo.2016.01.011> (2016).
36. Krishnan, S., Rosenberg, L. & Palmer, J. R. Physical activity and television watching in relation to risk of type 2 diabetes: the Black Women's Health Study. *American journal of epidemiology* **169**, 428–434, <https://doi.org/10.1093/aje/kwn344> (2009).
37. Arbab-Zadeh, A. *et al.* Effect of aging and physical activity on left ventricular compliance. *Circulation* **110**, 1799–1805, <https://doi.org/10.1161/01.CIR.0000142863.71285.74> (2004).
38. Cil, H. *et al.* Impact of body mass index on left ventricular diastolic dysfunction. *Echocardiography* **29**, 647–651, <https://doi.org/10.1111/j.1540-8175.2012.01688.x> (2012).
39. DeVallance, E. *et al.* Is obesity predictive of cardiovascular dysfunction independent of cardiovascular risk factors? *International journal of obesity* **39**, 244–253, <https://doi.org/10.1038/ijo.2014.111> (2015).
40. Henriksson, J. Influence of exercise on insulin sensitivity. *Journal of cardiovascular risk* **2**, 303–309 (1995).
41. Ayalon, N. *et al.* Preclinical left ventricular diastolic dysfunction in metabolic syndrome. *The American journal of cardiology* **114**, 838–842, <https://doi.org/10.1016/j.amjcard.2014.06.013> (2014).
42. Erdogan, D. *et al.* Aortic elastic properties and left ventricular diastolic function in white-coat hypertensive individuals. *Blood Press Monit* **11**, 191–198, <https://doi.org/10.1097/01.mbp.0000209079.17246.7d> (2006).
43. Clement, D. L., De Buyzere, M. & Duprez, D. Left ventricular function and regression of left ventricular hypertrophy in essential hypertension. *Am J Hypertens* **6**, 14S–19S (1993).
44. Levine, B. D., Lane, L. D., Buckey, J. C., Friedman, D. B. & Blomqvist, C. G. Left ventricular pressure-volume and Frank-Starling relations in endurance athletes. Implications for orthostatic tolerance and exercise performance. *Circulation* **84**, 1016–1023 (1991).
45. Lakatta, E. G. Cardiovascular aging research: the next horizons. *Journal of the American Geriatrics Society* **47**, 613–625 (1999).
46. Harris, T. S. *et al.* Constitutive properties of hypertrophied myocardium: cellular contribution to changes in myocardial stiffness. *American journal of physiology. Heart and circulatory physiology* **282**, H2173–2182, <https://doi.org/10.1152/ajpheart.00480.2001> (2002).
47. Hoit, B. D. *et al.* Naturally occurring variation in cardiovascular traits among inbred mouse strains. *Genomics* **79**, 679–685, <https://doi.org/10.1006/geno.2002.6754> (2002).
48. Lerman, I. *et al.* Genetic variability in forced and voluntary endurance exercise performance in seven inbred mouse strains. *Journal of applied physiology* **92**, 2245–2255, <https://doi.org/10.1152/japplphysiol.01045.2001> (2002).

49. O'Connell, T. D. *et al.* The alpha(1A/C)- and alpha(1B)-adrenergic receptors are required for physiological cardiac hypertrophy in the double-knockout mouse. *The Journal of clinical investigation* **111**, 1783–1791, <https://doi.org/10.1172/JCI16100> (2003).
50. Chirinos, J. A. *et al.* Early and late systolic wall stress differentially relate to myocardial contraction and relaxation in middle-aged adults: the Asklepios study. *Hypertension* **61**, 296–303, <https://doi.org/10.1161/HYPERTENSIONAHA.111.00530> (2013).
51. Washburn, R. A. Assessment of physical activity in older adults. *Research quarterly for exercise and sport* **71**, S79–88 (2000).

Author Contributions

Seungho Ryu designed the research; Hocheol Shin, Eliseo Guallar and Yoosoo Chang supervised the research; Seungho Ryu conducted the data analyses; Seungho Ryu wrote the draft of initial manuscript; Jeonggyu Kang, Kyung Eun Yun, Hyun-Suk Jung, Chan-Won Kim, Juhee Cho, Joao A Lima and Ki-Chul Sung critically contributed to data reanalysis and draft revision; Seungho Ryu, Yoosoo Chang, Jeonggyu Kang, Kyung Eun Yun, Hyun-Suk Jung, Chan-Won Kim, Juhee Cho, Joao A Lima, Ki-Chul Sung, Hocheol Shin and Eliseo Guallar contributed to the interpretation of the data and preparation of the manuscript. All authors were involved in the preparation of the manuscript, have read the manuscript, agree with the analyses of the data and the conclusions reached in the manuscript and are accountable for all aspects of the work.

Additional Information

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