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Association of Cardiorespiratory Fitness and Hemodynamic Responses to Submaximal Exercise Testing With the Incidence of Chronic Kidney Disease: The Framingham Heart Study

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Abstract

Objective: To relate cardiorespiratory fitness (CRF) and hemodynamic responses to exercise to the incidence of chronic kidney disease (CKD).

Methods: We evaluated 2715 Framingham Offspring Study participants followed up (mean, 24.8 years) after their second examination (1979–1983) until the end of their ninth examination (2011–2014). Participants (mean age, 43 years; 1397 women [51.5%]) without prevalent CKD or cardiovascular disease at baseline were included. We examined the associations of CRF and hemodynamic response to exercise with incident CKD using multivariable Cox proportional hazards regression with discrete intervals.

Results: Compared with low CRF (first tertile), participants with moderate (second tertile) or high (third tertile) CRF had a lower risk of CKD (hazard ratios [95% CIs]: 0.74 [0.61–0.91] and 0.73 [0.59–0.91], respectively). Participants with chronotropic incompetence (hazard ratio, 1.38 [95% CI, 1.06 to 1.79]), higher exercise systolic blood pressure (hazard ratio per SD, 1.20 [95% CI, 1.07 to 1.34]), and impaired heart rate recovery (hazard ratio, 1.51 [95% CI, 1.08 to 2.10]) had a higher risk of CKD compared with those with chronotropic competence, lower exercise systolic blood pressure, and normal heart rate recovery, respectively. These associations remained robust when the exercise variables were mutually adjusted for. The third tertile of a standardized exercise test score comprising the statistically significant variables was associated with a higher risk of CKD compared with the first tertile (hazard ratio, 1.85; 95% CI, 1.45 to 2.36).

Conclusion: Higher CRF and favorable hemodynamic responses to submaximal exercise in young adulthood may be markers of lower risk of CKD in later life.

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SUPPLEMENTAL ONLINE MATERIAL

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Chronic kidney disease (CKD) is characterized by a sustained reduction in kidney function and structural damage over time.[1] The presence of CKD has been associated with an increased risk of cardiovascular disease (CVD), including myocardial infarction, ischemic stroke, heart failure, and CVD death.[2] Furthermore, most patients with CKD, especially those with end-stage renal disease (ESRD), have a diminished quality of life.[3] In addition, the incidence and prevalence of ESRD are both projected to increase by 18% to 30% between 2015 and 2030 in the United States.[4] Therefore, prevention and early detection of CKD is a public health priority.

Exercise tests provide information about endurance capacity, heart rate (HR), and blood pressure (BP) responses during exercise, as well as regarding postexercise HR and BP recovery, all of which may be important in understanding disease risk.[5] Greater cardiorespiratory fitness (CRF) and favorable hemodynamic responses to exercise testing have been consistently and inversely associated with incident CVD,[6–9] CVD death,[10,11] and all-cause mortality.[12–15] However, little is known about the association of CRF and hemodynamic responses to a submaximal exercise test with the incidence of CKD.

Accordingly, we related CRF and hemodynamic responses to submaximal exercise to the incidence of CKD in a community-based sample. We hypothesized that higher CRF and favorable hemodynamic responses to submaximal exercise are associated with a lower risk of CKD.

METHODS

Study Design and Sample

The Framingham Offspring Study (FOS) is a longitudinal, community-based study established in 1971 that enrolled 5124 men and women who were the children and the spouses of the children of the Original Framingham Cohort.[16] The FOS participants who attended their second examination (1978–1982) were eligible for the present investigation. Of the 3863 eligible participants, 1148 were excluded for the following reasons: age younger than 20 years (n=10), prevalent CKD (estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m^2; n=119), prevalent CVD (fatal or nonfatal myocardial infarction, unstable angina [prolonged ischemic episode with documented reversible ST-segment changes], peripheral vascular disease [intermittent claudication], cerebrovascular disease [ischemic or hemorrhagic stroke or transient ischemic attack], or heart failure; n=151), unavailable data on exercise test variables (n=341), missing data on covariates at baseline (n=118), and unavailable data on serum creatinine level during follow-up (n=409), resulting in a final sample size of 2715 participants. The study was approved by the Boston University Medical Center institutional review board, and all participants provided written informed consent.

Submaximal Exercise Test

At their second examination, all participants underwent a submaximal exercise treadmill test using the Bruce protocol. Exercise was terminated when participants achieved 85% of their age-predicted maximal target HR.[17] The BP and HR responses were recorded

at the midpoint of each exercise stage. Immediately after the exercise test, participants were assisted off the treadmill and placed in a supine position. Both BP and HR recovery were measured at the end of each minute for 4 minutes of the recovery phase on the supine participant. For this investigation, we used the following exercise variables: CRF, chronotropic incompetence (CI), systolic BP (SBP) during the second stage of the exercise test (Exercise SBP), and HR recovery index 1 minute after the exercise test (ΔHR_1).

The CRF was estimated based on the participant's exercise duration on the treadmill and was classified based on age group (20–29, 30–39, 40–49, 50–59, ≥60 years) and using sex-specific tertiles (low [first tertile], moderate [second tertile], and high [third tertile]). The CI was defined as $HR_{peak} < [(220 - age) \times 0.85]$. Exercise SBP was measured during the second stage of the exercise test (2.5 miles/h at 12% of grade). Also, the ΔHR_1 was defined as the change in HR from peak exercise to recovery after 1 minute of exercise. A ΔHR_1 <12 beats/min was classified as impaired HR recovery.[6]

Chronic Kidney Disease

Serum creatinine level was measured using the modified Jaffé method between examination cycles 2 and 9. Serum creatinine measures can vary widely across different laboratories. Therefore, we used a 2-step serum creatinine calibration process: (1) calibration of Third National Health and Nutrition Examination Survey creatinine values to the Cleveland Clinic Laboratory, resulting in an average difference in serum creatinine calibration of 0.23 mg/dL (to convert to μmol/L, multiply by 88.4) (correction factor) and (2) alignment of mean serum creatinine values from the FOS by sex-specific age groups (20–39, 40–59, 60–69, and ≥70 years) with the corresponding corrected Third National Health and Nutrition Examination Survey age- and sex-specific mean values.[18] Kidney function was estimated using the CKD-Epidemiology Collaboration equation.[19] We defined CKD based on the National Kidney Foundation Kidney Disease Outcome Quality Initiative Working Group definition of kidney disease, which is an eGFR less than 60 mL/min per 1.73 m^2.[20] A participant who had an eGFR less than 60 mL/min per 1.73 m^2 at any of follow-up examination cycles 5 through 9 was considered to have incident CKD.

Statistical Methods

Cardiorespiratory fitness was categorized into tertiles of age- and sex-specific duration of the submaximal treadmill exercise test. The CI was dichotomized (presence vs absence). Exercise SBP was included in the analysis as a continuous variable. The HR recovery was modeled as a binary variable (ΔHR_1 ≥12 beats/min vs <12 beats/min).[6] In addition to modeling the individual exercise test variables, we also created a composite exercise test score, as follows: first, we dichotomized each primary exercise test variable (ie, tertiles of CRF, CI, Exercise SBP, and ΔHR_1) into normal (0) or abnormal (1) as follows: CRF=0 if CRF is in the third or second tertile, CRF=1 if CRF is in the first tertile; CI=0 if HR_{peak} is at least $(220 - age) \times 0.85$, CI=1 if HR_{peak} is less than $(220 - age) \times 0.85$; Exercise SBP=0 if SBP at stage 2 is less than 160 mm Hg (median), Exercise SBP=1 if SBP at stage 2 is 160 mm Hg or greater (median); and ΔHR_1=0 if ΔHR_1 is 12 beats/min or greater, ΔHR_1=1 if ΔHR_1 is less than 12 beat/min.

Then, we summed all exercise test scores to create an exercise test score ranging from 0 to 4, with a lower score indicating a favorable exercise test result. We categorized exercise test scores as excellent (score of 0), moderate (score of 1–2), and poor (score of 3–4) (Supplemental Figure 1, available online at http://www.mayoclinicproceedings.org).

Pairwise age- and sex-adjusted Spearman rank-order correlations were estimated for the exercise test variables evaluated. We used Cox proportional hazards regression models with discrete time intervals[21] to relate each exercise test variable at baseline (examination 2) to incident CKD at follow-up. We confirmed that the proportional hazards assumption was met using visual inspection of Schoenfeld residuals and also including an interaction term between log time and each exercise variable in the regression models. All models were adjusted for age, sex, baseline eGFR, resting HR, current smoking status, body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared), total cholesterol to high-density lipoprotein cholesterol (TC:HDL-C) ratio, resting SBP, resting diastolic BP, use of antihypertensive medication, blood glucose level, diabetes (fasting glucose level ≥126 mg/dL [to convert to mmol/L, multiply by 0.0555] or use of antidiabetic medications), and use of lipid-lowering medications at baseline. All covariates were selected based on their previously published association with CKD or CVD outcomes.[6,10,22–24] The HR_{peak} was additionally included in the model evaluating the association between impaired HR recovery and CKD incidence. We conducted sensitivity analyses after excluding participants receiving (1) β-blocker therapy or (2) any type of antihypertensive therapy to mitigate the impact of antihypertensive therapy on the associations between hemodynamic responses to submaximal exercise and incident CKD.

We also performed a stepwise Cox proportional hazards regression model with discrete time intervals using P=.1 as a cutoff value for entry and removal to identify the exercise test variables that were more strongly related to the incidence of CKD, adjusting for age, sex, eGFR, resting HR, current smoking status, BMI, TC:HDL-C ratio, SBP, diastolic BP, blood glucose level, use of antihypertensive medications, diabetes, use of lipid-lowering medications, and HR_{peak}. Using the stepwise Cox proportional hazards regression model, we also created a standardized exercise test score (Supplemental Figure 2, available online at http://www.mayoclinicproceedings.org). Primary exercise test variables retained in the stepwise Cox proportional hazards regression model were weighted by their regression coefficients to calculate a standardized exercise test score as follows: $\beta_1 \times \text{CRF} + \beta_2 \times \text{CI} + \beta_3 \times \text{Exercise SBP} + \beta_4 \times \text{HR recovery}$.

We then categorized the standardized exercise test score into tertiles and related it to the incidence of CKD. As a sensitivity analysis, we performed a least absolute shrinkage and selection operator (LASSO) regression using cross-validation for variable selection and ran a multivariable-adjusted model using the variables selected by LASSO.[25]

A 2-sided value of P<.05 was considered statistically significant for all models. All analyses were performed using a statistical software program (SAS Version 9.4; SAS Institute, Inc).

RESULTS

Participant Characteristics

The baseline characteristics of the study participants are presented in Table 1. At examination cycle 2, 32.2% of the participants were categorized as high CRF, 9.4% had CI, and 4.6% had impaired HR recovery. Participants who were excluded from the analysis were older and had a higher BMI, higher BP, and an unfavorable lipid profile compared with those included in the analysis (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). We did not observe strong correlations among the primary exercise test variables (tertiles of CRF, CI, Exercise SBP, and HR recovery defined as ΔHR_1 <12 beats/min after exercise) (Table 2).

Association of Exercise Test Variables With CKD Incidence

During a mean follow-up of 24.8 years, 688 CKD events occurred in 2715 patients (25.3%; 366 women). The association of individual exercise test variables with the incidence of CKD is shown in Table 3. Participants in the highest CRF tertile had a lower risk of CKD compared with those in the first tertile. In addition, the presence of CI, higher Exercise SBP, and impaired HR recovery were also associated with a higher risk of CKD compared with those with chronotropic competence, lower Exercise SBP, and normal HR recovery after exercise, respectively. In multivariable stepwise analyses, adjusting for all exercise test variables and covariates in the same Cox model, the associations noted previously herein remained statistically significant. In these analyses, HR recovery was more strongly associated with CKD compared with the other primary exercise test variables (Table 4). In the sensitivity analysis using LASSO regression, all the exercise test variables were selected, along with age, sex, eGFR, smoking, BMI, TC:HDL-C ratio, blood glucose level, use of antihypertensive medication, diabetes, and HR_{peak}. The results from the multivariable-adjusted model using variables selected by LASSO were similar compared with the original model, although the association between CI and incident CKD was no longer statistically significant (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org). In another sensitivity analysis after excluding participants taking β-blockers, the results were similar in models adjusting for individual exercise variables and in those adjusting for the variables conjointly. However, the association between CI and incident CKD was no longer statistically significant in models adjusting for exercise variables conjointly. The associations between exercise test variables and incident CKD were similar in models adjusting for individual exercise variables and in those adjusting for the variables conjointly after excluding participants taking any type of antihypertensive medication. However, the association between CI and incident CKD was no longer statistically significant in models adjusting for individual exercise variables and in those adjusting for the variables conjointly (Tables 3 and 4).

Relations of Composite Exercise Test Scores and CKD Incidence

The association between the composite exercise test scores and the incidence of CKD is shown in Table 5. Participants with a poor exercise test score had a higher risk of CKD in later life compared with those with an optimal exercise test score. In addition, participants in the top tertile of the standardized exercise test score (a higher score indicating a worse

test result) had 1.85 times higher risk of CKD in later life compared with those in the first tertile of the exercise test score. The associations of the composite exercise test score and the standardized exercise test score with incident CKD were not changed even after excluding participants receiving β-blocker therapy or any type of antihypertensive therapy at baseline.

DISCUSSION

Principal Findings

We evaluated the association of CRF and hemodynamic responses to a submaximal exercise test in young adulthood with the incidence of CKD in later life in a large community-based sample. We observed several important findings. First, participants with low CRF in young adulthood had a higher risk of CKD in later life. Second, CI, higher Exercise SBP, and impaired HR recovery after exercise were also associated with a higher incidence of CKD in later life. In addition, participants with a poor exercise score and top tertile of standardized exercise score had an approximately 2-fold risk of developing CKD compared with those with an excellent exercise score and the first tertile of standardized exercise score, respectively. Last, among the various exercise response variables, HR recovery was more strongly associated with risk of developing CKD in later life. The associations were not changed substantially even after excluding those who were taking β-blockers or any type of antihypertensive medication at baseline.

Association Between CRF and CKD Incidence in Later Life

To date, few studies have investigated the relations of CRF with CKD risk in the community. Consistent with the current investigation, Kokkinos et al[24] reported an inverse association between CRF and risk of CKD in 5812 middle-aged male veterans (mean ± SD age, 58±12 years) after median follow-up of 7.9 years. In addition, DeFina et al[22] also identified that higher CRF measured in middle-aged individuals (mean ± SD age, 50±9 years) was associated with a lower risk of CKD in later life compared with those with low CRF among 17,979 participants (22% women, mean follow-up of 7.2 years) in the Cooper Center Longitudinal Study. The findings from the present investigation extend previous evidence by demonstrating the inverse association of CRF in young adulthood and the risk of developing CKD in later life over a much longer period and by assessing a more comprehensive panel of exercise and postexercise response variables.

Although the underlying mechanisms linking higher CRF to a lower risk of CKD are not fully understood, cardiometabolic profiles and endothelial function may be the potential biological factors that contribute to the inverse association between CRF and incidence of CKD.[26–28] It has been reported that atherogenic dyslipidemia and systemic inflammation are symptoms commonly seen in patients with CKD due to metabolic disturbances and the accumulation of vasotoxic substances.[29–31] In addition, ongoing endothelial damage in the capillary system of the renal medulla with vascular rarefaction is unfavorably associated with developing CKD.[32] On the other hand, evidence suggests that regular exercise confers cardiometabolic benefits and structural and functional adaptations of the endothelial response to vasoconstrictors.[33–35] Thus, fit individuals may have favorable cardiometabolic profiles, which in turn lowers vascular resistance during physical stress (eg, exercise), and

this response may be associated with a lower risk of CKD.[24] In a current American Heart Association scientific statement focused on CVD prevention, the importance of CRF has been elevated as a vital sign that needs to be considered in clinical practice.[36] Given that CKD is a strong risk factor for CVD and both diseases share common risk factors,[37,38] our investigation is consistent with the recent American Heart Association's emphasis on maintaining CRF over the life course. In addition, CRF has been directly associated with the intensity, frequency, and duration of physical activity in young adulthood or middle age.[38] Thus, the results from the present investigation should encourage young adults to initiate or maintain a regular physical activity schedule to prevent CKD in later life.

Hemodynamic Responses to the Exercise Test and CKD Incidence

Only a few cross-sectional studies have explored the association between hemodynamic responses to exercise and kidney function. These previous studies included patients with heart failure with preserved ejection fraction[39] and prevalent CKD.[40] Both studies reported that CI[39] and delayed HR recovery after 1 minute of exercise[40] were associated with lower eGFR, indicating worse kidney function. Moreover, no previous study has investigated the association between SBP response to exercise and the incidence of CKD, although numerous studies have reported an inverse association between exaggerated SBP response to exercise and the incidence of outcomes such as hypertension,[9] microalbuminuria,[41] increased arterial stiffness,[41] carotid atherosclerosis,[42] coronary artery disease,[43] and stroke.[8]

Accumulating evidence has proposed impaired cardiac autonomic responses and endothelial dysfunction as potential mechanisms underlying the relations between unfavorable hemodynamic responses to exercise and kidney disorders.[9,22,23,44–46] Several studies have reported that a functional imbalance of the autonomic nervous system (ANS) is unfavorably associated with the risk of CKD.[47,48] In addition, endothelial dysfunction is a commonly observed symptom in the development of CKD, and this is often accompanied by imbalance of the ANS, suggesting interrelations between these 2 systems.[49] It is widely accepted that habitual physical activity or exercise alleviates sympathetic overactivity and improves endothelial dysfunction.[35,50–56] Thus, the inverse association of chronotropic competence, lower Exercise SBP, and rapid HR recovery, which are the consequences of the habitual physical activity or exercise, with the incidence of CKD may be driven by improvements in ANS balance and endothelial function. Indeed, previous studies noted the association of the blunted ANS response with impaired postexercise HR recovery in patients with chronic heart failure (highly prevalent in patients with CKD and risk of ESRD) and CKD-related hospitalizations.[53] Also, other studies reported the inverse relations of CI and exaggerated BP response to exercise and the presence of endothelial dysfunction.[54–56]

In the present investigation, we observed strong and independent associations of each primary exercise test variable with the incidence of CKD in later life among healthy young adults in the community. Moreover, the associations remained statistically significant even after adjusting for the exercise test variables concomitantly in multivariable analyses. Thus, the present findings may provide valuable insights into the prevention of CKD in healthy young adults. In addition, exercise test scores composed of CRF, CI, Exercise SBP, and HR

recovery after exercise in young adulthood were also strongly associated with the incidence of CKD in later life after adjustment for established CVD risk factors. Therefore, these findings may suggest that hemodynamic responses to submaximal exercise testing could provide incremental prognostic information over CRF regarding CKD risk in young people.

Strengths and Limitations

The strengths of this investigation include the use of a well-characterized sample with a long follow-up (yielding a large number of new-onset CKD events), thereby facilitating a more precise estimation of CKD risk. However, several limitations of this approach must be acknowledged. Participants excluded from the analysis were older and had a higher BMI, higher BP, and an unfavorable lipid profile compared with those included in the analysis. Thus, we cannot rule out the possibility that selection bias may influence the findings. In addition, there were no available data on albuminuria or proteinuria at baseline and at each examination during follow-up. Thus, incident CKD was defined using single-occasion measurement of serum creatinine at serial quadrennial FOS examinations. Also, the reliability of hemodynamic responses to exercise testing may be questioned, although previous studies have reported good reproducibility of HR[57,58] and SBP responses[59,60] during exercise tests. We estimated CRF based on the duration of exercise on a submaximal treadmill exercise test. Previous studies have noted that the time on the treadmill using the Bruce protocol was highly correlated with maximum oxygen consumption, which is considered the most valid and accurate gold standard measure of CRF.[36] In addition, using 85% of age-predicted maximal HR as a submaximal exercise threshold may introduce some variance in the level of effort exerted by the participant. Last, the FOS participants are white individuals of European ancestry, so we were unable to assess effect modification by race/ethnicity, potentially limiting the generalizability of these findings.

CONCLUSION

Higher CRF and favorable hemodynamic responses to submaximal exercise testing in young adulthood may be key prognostic markers of a lower risk of CKD in later life. These findings support the importance of maintaining CRF in young adulthood to prevent CKD in later life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ANS	autonomic nervous system
BMI	body mass index
BP	blood pressure
CI	chronotropic incompetence
CKD	chronic kidney disease
CRF	cardiorespiratory fitness
CVD	cardiovascular disease
DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FOS	Framingham Offspring Study
HR	heart rate
ΔHR_1	heart rate recovery index 1 minute after the exercise test
LASSO	least absolute shrinkage and selection operator
SBP	systolic blood pressure
TC:HDL-C	total cholesterol to high-density lipoprotein cholesterol

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TABLE 1.

Baseline Characteristics of the Study Participants[a,b,c]

Variable	Men (n=1318)	Women (n=1397)
Clinical characteristics		
Age (y)	43±10	43±9
Body mass index	26.5±3.5	24.3±4.4
Total cholesterol (mg/dL)	208±37	202±40
HDL-C (mg/dL)	44±12	56±15
LDL-C (mg/dL)	139±34	129±37
Triglycerides (mg/dL)	125±86	88±75
Current smoking (No. [%])	444 (33.7)	494 (35.4)
SBP (mm Hg)	124±14	117±16
DBP (mm Hg)	80±9	75±9
Use of antihypertensive drugs (No. [%])	110 (8.4)	97 (6.9)
Hypertension (No. [%])[d]	313 (23.8)	198 (14.2)
Diabetes (No. [%])	33 (2.5)	16 (1.2)
Resting HR (beats/min)	71±11	77±11
eGFR (mL/min per 1.73 m^2)	99.1±19.7	101.4±21.4
Hemodynamic response to ET		
Reaching target HR (No. [%])	1058 (80.3)	1081 (77.4)
Duration of exercise (min)	10.6±2.8	8.3±2.4
Estimated VO_{2peak} (mL/kg/min)	37.0±10.8	32.6±10.5
HR_{peak} (beat/min)	165.7±12.4	165.1±12.5
High CRF (No. [%])[e]	418 (31.7)	455 (32.6)
Chronotropic incompetence (No. [%])[f]	119 (9.0)	135 (9.7)
Exercise SBP (mm Hg)	170.3±24.4	153.5±23.3
ΔHR_1 (beats/min)	29.2±12.1	30.0±12.0
ΔHR_1 <12 beats/min (No. [%])	62 (4.7)	62 (4.4)

[a] CRF = cardiorespiratory fitness; DBP= diastolic blood pressure; eGFR = estimated glomerular filtration rate; ET = exercise test; Exercise SBP = systolic blood pressure measured during the second stage of exercise (2.5 miles/h at a 12% grade); HDL-C = high-density lipoprotein cholesterol; HR = heart rate; $\Delta HR_1 = HR_{peak} - HR$ after 1 minute of exercise testing; LDL-C = low-density lipoprotein cholesterol; VO_{2peak} = highest value of oxygen uptake during exercise testing.

[b] SI conversion factors: To convert total, HDL, and LDL cholesterol values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113.

[c] Values are given as mean ± SD unless otherwise indicated.

[d] Hypertension is defined as having an SBP/DBP of at least 140/90 mm Hg or using antihypertensive medications.

[e] CRF is categorized into 3 mutually exclusive fitness groups: low (first tertile of exercise time), moderate (second tertile of exercise time), and high (third tertile of exercise time).

[f] Chronotropic incompetence is defined as $HR_{peak} < [(220 - age) \times 0.85]$ and dichotomized into presence or absence.

TABLE 2.

Age- and Sex-Specific Spearman Correlations Among Primary Exercise Test Variables[a]

Variable	CRF tertile	CI	Exercise SBP	ΔHR_1 <12 beats/min
CRF tertile	1	−0.11[b]	−0.26[b]	−0.03
CI		1	−0.006	0.08[b]
Exercise SBP			1	0.01
ΔHR_1 <12 beat/min				1

[a] CI = chronotropic incompetence (HR_{peak} < [(220 − age) × 0.85] and dichotomized into presence or absence); CRF = cardiorespiratory fitness (categorized into tertiles of age- and sex-specific duration of submaximal treadmill test); Exercise SBP = systolic blood pressure measured during the second stage of exercise; HR = heart rate; $\Delta HR_1 = HR_{peak} - HR$ after 1 minute of exercise testing.

[b] P<.001.

TABLE 3.

Associations Between Individual Exercise Test Variables and CKD Incidence[a,b]

Exercise variable	All participants			Participants not on β-blocker therapy			Participants not on antihypertensive treatment		
	Events/at risk (No.)	Hazard ratio (95% CI)	*P* value	Events/at risk (No.)	Hazard ratio (95% CI)	*P* value	Events/at risk (No.)	Hazard ratio (95% CI)	*P* value
CRF tertile 1	224/820	Referent		212/795	Referent		190/747	Referent	
CRF tertile 2	254/1022	0.74 (0.61–0.91)	.004	245/992	0.78 (0.63–0.96)	.02	223/935	0.79 (0.63–0.98)	.03
CRF tertile 3	210/873	0.73 (0.59–0.91)	.005	201/851	0.75 (0.60–0.94)	.01	191/826	0.76 (0.60–0.96)	.02
Chronotropic competence	598/2461	Referent		588/2424	Referent		541/2307	Referent	
Chronotropic incompetence[c]	90/254	1.38 (1.06–1.79)	.02	70/214	1.34 (1.00–1.78)	.05	63/201	1.27 (0.94–1.72)	.12
Exercise SBP[d]	688/2715	1.20 (1.07–1.34)	.002	658/2638	1.17 (1.04–1.32)	.007	604/2508	1.21 (1.07–1.37)	.002
ΔHR_1 ≥12 beats/min	636/2591	Referent		607/2516	Referent		556/2398	Referent	
ΔHR_1 <12 beats/min	52/124	1.51 (1.08–2.10)	.02	51/122	1.51 (1.07–2.11)	.02	48/110	1.60 (1.13–2.28)	.009

[a] CI, confidence interval; CKD = chronic kidney disease (defined as estimated glomerular filtration rate <60 mL/min per 1.73 m^2); CRF = cardiorespiratory fitness (categorized into tertiles of age- and sex-specific duration of submaximal treadmill testing); Exercise SBP = systolic blood pressure measured during the second stage of exercise (2.5 miles/h at a 12% grade); HR, heart rate; ΔHR_1 = HR_{peak} − HR after 1 minute of exercise testing.

[b] Models are adjusted for age, sex, estimated glomerular filtration rate, resting HR, current smoking status, body mass index, total cholesterol to high-density lipoprotein cholesterol ratio, SBP, diastolic blood pressure, blood glucose level, diabetes, and use of antihypertensive and lipid-lowering medications; HR_{peak} was additionally included in the model evaluating the association between impaired HR recovery and CKD incidence.

[c] Defined as HR_{peak} less than (220 − age) × 0.85

[d] Hazard ratios are expressed in terms of 1-SD increment of Exercise SBP.

TABLE 4.

Conjoint Associations Between All the Exercise Test Variables and CKD Incidence: Results From Stepwise Cox Proportional Hazards Regression Model[a,b]

	All participants			Participants not on β-blocker therapy			Participants not on antihypertensive treatment		
Exercise variable	**Events/at risk (No.)**	**Hazard ratio (95% CI)**	***P* value**	**Events/at risk (No.)**	**Hazard ratio (95% CI)**	***P* value**	**Events/at risk (No.)**	**Hazard ratio (95% CI)**	***P* value**
CRF tertile 1	224/820	Referent		212/795	Referent		190/747	Referent	
CRF tertile 2	464/1895	0.78 (0.65–0.93)	.007	446/1843	0.79 (0.66–0.95)	.01	414/1761	0.80 (0.66–0.97)	.02
Chronotropic competence	598/2461	Referent		588/2424	Referent		NA[c]	NA[c]	
Chronotropic incompetence[d]	90/254	1.35 (1.05–1.74)	.02	70/214	1.28 (0.96–1.69)	.09	NA[c]	NA[c]	NA[c]
Exercise SBP[e]	688/2715	1.15 (1.05–1.26)	.003	658/2638	1.14 (1.04–1.26)	.004	604/2508	1.16 (1.06–1.28)	.002
ΔHR_1 ≥12 beats/min	636/2591	Referent		607/2516	Referent		556/2398	Referent	
ΔHR_1 <12 beats/min	52/124	1.61 (1.16–2.21)	.004	51/122	1.59 (1.15–2.20)	.005	48/110	1.76 (1.25–2.47)	.001

[a]CI = confidence interval; CKD = chronic kidney disease (defined as estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m^2); CRF = cardiorespiratory fitness (categorized into tertiles of age- and sex-specific duration of submaximal treadmill test and second and third tertiles of CRF were combined); Exercise SBP = systolic blood pressure measured during the second stage of exercise (2.5 miles/h at a 12% grade); HR = heart rate; $\Delta HR_1 = HR_{peak} - HR$ after 1 minute of exercise; NA, not available.

[b]CRF (combined), chronotropic incompetence, Exercise SBP, ΔHR_1 (≥12 beats/min vs <12 beats/min), age, sex, eGFR, resting HR, HR_{peak}, current smoking status, body mass index, total cholesterol to high-density lipoprotein cholesterol (TC:HDL-C) ratio, resting SBP, resting DBP, blood glucose level, diabetes, and antihypertensive and lipid-lowering medications were included in the stepwise Cox proportional hazards regression model; CRF (combined), chronotropic incompetence, Exercise SBP, ΔHR_1 (≥12 beats/min vs <12 beats/min), age, sex, eGFR, TC:HDL-C ratio, and diabetes were retained in the final model.

[c]The measure of association between chronotropic incompetence and incident CKD among participants with no antihypertensive treatment was not available because chronotropic incompetence was excluded from the stepwise Cox proportional hazards model.

[d]Defined as HR_{peak} less than (220 − age) × 0.85.

[e]Hazard ratios are expressed in terms of 1-SD increments of Exercise SBP.

TABLE 5.

Association Between Composite Exercise Test Scores and Incident CKD[a]

Exercise variable	All participants			Participants not on β-blocker therapy			Participants not on antihypertensive treatment		
	Events/at risk (No.)	Hazard ratio (95% CI)	*P* value	Events/at risk (No.)	Hazard ratio (95% CI)	*P* value	Events/at risk (No.)	Hazard ratio (95% CI)	*P* value
Composite exercise test score[b]									
Excellent (score=0)	161/924	Referent		158/912	Referent		155/908	Referent	
Moderate (score=1–2)	479/1676	1.45 (1.18–1.79)	<.001	460/1625	1.42 (1.15–1.75)	.001	413/1512	1.44 (1.16–1.79)	<.001
Poor (score=3–4)	48/115	2.04 (1.38–3.00)	<.001	40/101	1.87 (1.24–2.83)	.003	36/88	1.96 (1.27–3.02)	.002
Standardized exercise test score[c]									
First tertile	148/882	Referent		146/877	Referent		NA[d]	NA[d]	NA[d]
Second tertile	246/929	1.34 (1.07–1.68)	.01	235/888	1.31 (1.04–1.66)	.02	NA[d]	NA[d]	NA[d]
Third tertile	294/904	1.85 (1.45–2.36)	<.001	277/873	1.77 (1.38–2.27)	<.001	NA[d]	NA[d]	NA[d]

[a] CI = confidence interval; CKD = chronic kidney disease; NA = not available.

[b] Each primary exercise test component, including tertiles of cardiorespiratory fitness (CRF), chronotropic incompetence, systolic blood pressure measured during the second stage of exercise (Exercise SBP), and change in heart rate 1 minute after exercise from peak exercise heart rate (ΔHR_1), is dichotomized into normal (0 points) or abnormal (1 point) and summed to create an exercise test score ranging from 0 to 4.

[c] Primary exercise test variables were weighted by their regression coefficients of the stepwise Cox proportional hazards regression model to calculate a standardized exercise test score as follows: standardized exercise test score (all) = $-0.24999 \times CRF + 0.29918 \times$ chronotropic incompetence $+ 0.13953 \times$ Exercise SBP $+ 0.47296 \times \Delta HR_1$; standardized exercise test score (no β-blocker use) = $-0.23337 \times CRF + 0.24323 \times$ chronotropic incompetence $+ 0.13466 \times$ Exercise SBP $+ 0.46424 \times \Delta HR_1$.

[d] A standardized exercise test score was not available among participants with no antihypertensive treatment because chronotropic incompetence was excluded from the stepwise Cox proportional hazards model.