Lee J, Song RJ, Musa Yola I, et al. Association of estimated cardiorespiratory fitness in midlife with cardiometabolic outcomes and mortality. *JAMA Netw Open.* 2021;4(10):e2131284. doi:10.1001/jamanetworkopen.2021.31284

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**eMETHODS.** Detailed methods

**Study sample**

Overall, analyses were conducted based on two large subsamples of the Framingham Offspring Study (FOS). First, 3,539 participants who attended the seventh examination cycle (1998-2001) were eligible (**Sample 1.1 – Sample 1.8**). Of these 3,539 participants, we excluded those aged beyond the limits for which estimated cardiorespiratory fitness (eCRF) algorithms were developed (<20 years of age, as well as, women >76 and men >86 years of age), body mass index (BMI) \(\leq 18.5\) kg/m\(^2\), and/or those with unavailable data for calculation eCRF and covariates at baseline (n=577) to examine the association of eCRF at the seventh examination (eCRF\(_{\text{exam7}}\)) with all-cause mortality (**Sample 1.1; n=2,962**). To investigate the relation of eCRF\(_{\text{exam7}}\) with incident cardiometabolic diseases (hypertension, diabetes, chronic kidney disease [CKD], and cardiovascular disease [CVD]), we then excluded participants with prevalent cardiometabolic disease or unavailable data on cardiometabolic disease status at the seventh examination, resulting in final sample sizes of 1,506 (**Sample 1.2; hypertension**), 2,268 (**Sample 1.3; diabetes**), 2,343 (**Sample 1.4; CKD**), and 2,608 (**Sample 1.5; CVD**), respectively. We examined the cross-sectional associations of eCRF\(_{\text{exam7}}\) with carotid-femoral pulse wave velocity (CFPWV, **Sample 1.6; n=2,041**), carotid intima-media thickness (CIMT, **Sample 1.7; n=2,106**), and coronary artery calcium score (CAC, **Sample 1.8; n=1,172**).

Additionally, 2,820 participants who attended the second (1979-1983), fourth (1987-1991), fifth (1991-1995), and seventh (1998-2001) examination cycles were eligible to examine associations of the trajectories of eCRF (eCRF\(_{\text{trajectories}}\)) and the standardized average of eCRF (eCRF\(_{\text{average}}\)) between second and seventh examinations with outcomes (**Sample 2.1 – Sample 2.8**). After excluding those aged beyond the range for which eCRF algorithms were developed, BMI \(\leq 18.5\) kg/m\(^2\), and/or with unavailable data for eCRF calculation, outcomes, and covariates.
at the seventh examination, we examined the associations of midlife eCRF trajectories and eCRF_average with the incidence of all-cause mortality (Sample 2.1; n=2,247), hypertension (Sample 2.2; n=1,159), diabetes (Sample 2.3; n=1,770), CKD (Sample 2.4; n=1,817), and CVD (Sample 2.5; n=1,970). The cross-sectional associations of eCRF trajectories and eCRF_average with prevalent subclinical atherosclerosis were examined using subsamples of Sample 2.1 (CFPWV [Sample 2.6; n=1,498], CIMT [Sample 2.7; n=1,699], and CAC score [Sample 2.8; n=970]).

**eCRF assessment**

During each Heart Study examination, data for eCRF calculations were obtained. Data on age and sex were collected using a medical history questionnaire. Height and weight were measured via a standardized scale, and BMI was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured by a trained professional applying anthropometric tape at the level of the umbilicus and recording the reading at midrespiration and rounding to the nearest 0.25 of an inch. Resting heart rate was measured using standard supine 12-lead electrocardiography performed after approximately 5 minutes of resting quietly. Physical activity was measured using the Physical Activity Index (PAI), which measures self-reported intensity, frequency, and duration of physical activity during leisure time and is categorized as active (yes) or insufficiently active (no) based on the median values of PAI as previously described. Participants who self-reported smoking ≥1 cigarette/day during the year before each examination cycle were classified as current smokers.
Indicators of arterial stiffness and subclinical atherosclerosis

To quantify CFPWV, applanation tonometry was performed after participants rested for 5 minutes in the supine position using a commercially available tonometer (SPT-301, Millar Instruments, Houston, TX).² For each participant, the transit distances from the suprasternal notch to carotid and femoral sites were measured, and the difference between the two lengths was divided by the delay in time between the bottom of the carotid and femoral waveforms, as previously described.³ All measures were stored digitally in a core (Cardiovascular Engineering, Inc, Norwood, MA) and blinded to clinical information for subsequent analyses.²

Standard coronary computed tomography angiography was performed to calculate the standardized CAC score in which a calcified lesion was defined per the following standards: an area ≥3 connected pixels, an attenuation >130 Hounsfield units. An Agatston score was calculated as previously described.⁴ Results were evaluated by a certified clinician.

Lastly, ultrasound of the carotid arteries was performed during the eighth examination cycle to quantify CIMT. The common carotid arteries (CCA) were imaged with a 7.5-MHz transducer while the carotid bulb and internal carotid arteries (ICA) were imaged with a 5-MHz transducer (3-dB point: 6.2 MHz). Color Doppler and Doppler spectral analyzer software (model SSH140A; Toshiba America Medical Systems) were applied.⁵,⁶ Gated diastolic images were obtained of the left and right carotid arteries at the level of the distal CCA, the carotid artery bulb, and the proximal 2 cm of the ICA. Assessment by two independent interpreters (replicate readings, n=25) for the mean ICA and CCA IMT showed intraclass correlation coefficients of 0.74 and 0.90, respectively.⁷
Covariates

Baseline blood pressure was measured twice at rest in a seated position by a physician using a mercury column sphygmomanometer and measurements were averaged. Fasting plasma glucose, total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) concentrations were measured using standard enzymatic methods. Serum creatinine was measured using the modified Jaffé method and adjusted by a two-step serum creatinine calibration process as previously described. The CKD-Epidemiology Collaboration (CKD-EPI) equation was used to estimate the glomerular filtration rate (eGFR). Information on cardiovascular disease was collected by a medical history questionnaire, physical examination, and hospitalization records.

Statistical analysis

For analyses of eCRF trajectories, we limited the number of trajectory groups to ≤5, using the Bayesian Information Criterion to assess the best model fit. We accounted for the uncertainty of eCRF group membership by simulating 50 imputed datasets of trajectory group assignment re-classifying participants using the participant’s posterior group probability. We then combined estimates from the 50 datasets using PROC MIANALYZE.
eReferences

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eTable 1. Characteristics of participants included and excluded from the analysis.

| Variable                                | Included (n=2,962) | Excluded (n=577) |
|-----------------------------------------|--------------------|------------------|
| Age, years                              | 61 (9)             | 66 (11)          |
| Women, n (%)                            | 1562 (52.7)        | 352 (61.0)       |
| Body mass index, kg/m²                  | 28.2 (5.2)         | 27.7 (6.2)       |
| Waist circumference, cm                 | 100.1 (14.0)       | 98.3 (15.0)      |
| Resting heart rate, beats/minute        | 65 (11)            | 67 (12)          |
| Physical activity index                 | 38 (6.4)           | 35.7 (5.1)       |
| SBP, mmHg                               | 127 (19)           | 131 (20)         |
| DBP, mmHg                               | 74 (10)            | 73 (11)          |
| Hypertension, n (%)                     | 1308 (44.2)        | 326 (57.6)       |
| Antihypertensive medication, n (%)      | 972 (32.8)         | 246 (43.4)       |
| Fasting glucose, mg/dL                  | 104 (25)           | 109 (36)         |
| Diabetes, n (%)                         | 320 (10.8)         | 75 (19.6)        |
| Diabetes medication, n (%)              | 188 (6.4)          | 59 (10.3)        |
| Total cholesterol, mg/dL                | 200 (37)           | 200 (39)         |
| HDL-C, mg/dL                            | 54 (17)            | 55 (19)          |
| Lipid-lowering medication, n (%)        | 603 (20.4)         | 139 (24.2)       |
| eGFR, ml/min/1.73m²                     | 83.8 (16.3)        | 79 (19)          |
| Internal carotid artery IMT, mm         | 2.3 (1.1)          | 2.5 (1.2)        |
| Common carotid artery IMT, mm           | 0.7 (0.2)          | 0.8 (0.2)        |
| CFPWV, m/s                              | 10.0 (3.4)         | 11.4 (4.5)       |
| CAC, AU, median (Q1, Q3)                | 34.1 (0, 237.7)    | 81.7 (1.4, 316.2) |
| Prevalent CKD, n (%)                    | 242 (8.2)          | 53 (14.9)        |
| Prevalent CVD, n (%)                    | 354 (12.0)         | 125 (21.7)       |
| eCRF, METs                              | 9.3 (2.0)          | 7.7 (2.4)        |

**Abbreviations:** SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration; IMT, intima-media thickness; CFPWV, carotid-femoral pulse wave velocity; CAC, coronary artery calcium; AU, Agatston unit; CKD, chronic kidney disease; CVD, cardiovascular disease; eCRF, non-exercise estimated cardiorespiratory fitness; METs, metabolic equivalent of tasks.

**Note:** Values are mean (standard deviation) unless otherwise indicated.
eTable 2. Age- and sex-specific Spearman correlations between midlife eCRF and its components

| eCRFexam7 (N=2,692) | eCRFexam7 | BMI   | WC   | Resting HR | PAI   | Smoking |
|---------------------|----------|-------|------|------------|-------|---------|
| eCRFexam7           | 1        | -0.85*| -0.82*| -0.46*     | 0.28* | -0.08*  |
| BMI                 | 1        | 0.88* | 0.19*| -0.08*     | -0.03 |
| WC                  | 1        | 0.19* | 0.19*| -0.13*     | -0.01 |
| Resting HR          | 1        |       |       | -0.06†     | 0.10* |
| PAI                 | 1        |       |       | 0.01       |       |
| Smoking             | 1        |       |       |            |       |

| eCRFtrajectories (N=2,247) | eCRFtrajectories | BMI   | WC   | Resting HR | PAI   | Smoking |
|---------------------------|------------------|-------|------|------------|-------|---------|
| eCRFtrajectories         | 1                | -0.72*| 0.70*| -0.32*     | 0.14* | -0.07†  |
| BMI                       | 1                | 0.88* | 0.19*| -0.06†     | -0.02 |
| WC                        | 1                | 0.19* | 0.19*| -0.12*     | 0.003 |
| Resting HR               | 1                |       |       | -0.06†     | 0.09* |
| PAI                       | 1                |       |       | 0.01       |       |
| Smoking                   | 1                |       |       |            |       |

| eCRFaverage (N=2,247) | eCRFaverage | BMI   | WC   | Resting HR | PAI   | Smoking |
|-----------------------|-------------|-------|------|------------|-------|---------|
| eCRFaverage           | 1           | -0.81*| -0.78*| -0.36*     | 0.16* | -0.09*  |
| BMI                   | 1           | 0.88* | 0.19*| -0.06†     | -0.02 |
| WC                    | 1           | 0.19* | 0.19*| -0.12*     | -0.003|
| Resting HR            | 1           |       |       | -0.06†     | 0.09* |
| PAI                   | 1           |       |       | 0.03       |       |
| Smoking               | 1           |       |       |            |       |

**Abbreviations:** eCRF, non-exercise estimated cardiorespiratory fitness; BMI, body mass index; WC, waist circumference; HR, heart rate; PAI, physical activity index.

**Note:** Sex-specific eCRF at the seventh examinations were converted into z-score with mean of 0 and standard deviation of 1 (eCRFexam7); Sex-specific eCRF trajectories between second and seventh examinations were determined using group based modeling strategy (SAS PROC TRAJ, eCRFtrajectories); Sex-specific average of eCRF between second and seventh examinations were converted into z-score with mean of 0 and standard deviation of 1 (eCRFaverage).

*P<0.001; †P<0.01; ‡P<0.05.
**eTable 3.** Association of midlife eCRF with subclinical atherosclerosis in participants without CVD at baseline.

| -1000/CFPWV (ms/m) | eCRF<sub>exam7</sub> (n=1,792) | eCRF<sub>trajectories</sub> (n=1,304) | eCRF<sub>average</sub> (n=1,304) |
|---------------------|-----------------------------|---------------------------------|-----------------------------|
|                     | N   | β est. | SE  | P value | N   | β est. | SE  | P value | N   | β est. | SE  | P value |
| eCRF (per 1 SD increment) | 1,792 | -5.84  | 0.63 | <.001 | 1,304 | --    | --  | --     | 1,498 | -5.51  | 0.74 | <.001 |
| Low eCRF            | 458 | Referent | 153 | Referent | 427 | Referent | 427 | Referent |
| Moderate eCRF       | 618 | -6.37  | 1.18 | <.001 | 598 | -6.60  | 1.75 | <.001 | 521 | -6.00  | 1.40 | <.001 |
| High eCRF           | 716 | -12.27 | 1.41 | <.001 | 553 | -13.08 | 2.05 | <.001 | 550 | -10.55 | 1.65 | <.001 |

| CIMT (mm) | eCRF<sub>exam7</sub> (n=1,889) | eCRF<sub>trajectories</sub> (n=1,518) | eCRF<sub>average</sub> (n=1,518) |
|-----------|-----------------------------|---------------------------------|-----------------------------|
|           | N   | β est. | SE  | P value | N   | β est. | SE  | P value | N   | β est. | SE  | P value |
| eCRF (per 1 SD increment) | 1,889 | -0.05  | 0.02 | <.001 | 1,518 | --    | --  | --     | 1,518 | -0.07  | 0.02 | <.001 |
| Low eCRF  | 510 | Referent | 205 | Referent | 407 | Referent | 407 | Referent |
| Moderate eCRF | 657 | -0.03  | 0.04 | .44   | 680 | -0.11  | 0.06 | .06    | 518 | -0.05  | 0.05 | .24   |
| High eCRF | 722 | -0.10  | 0.05 | .03   | 633 | -0.18  | 0.06 | .005   | 593 | -0.13  | 0.05 | .02   |

| CAC (AU) | eCRF<sub>exam7</sub> (n=1,076) | eCRF<sub>trajectories</sub> (n=886) | eCRF<sub>average</sub> (n=886) |
|----------|-----------------------------|---------------------------------|-----------------------------|
|          | N   | β est. | SE  | P value | N   | β est. | SE  | P value | N   | β est. | SE  | P value |
| eCRF (per 1 SD increment) | 1,076 | -0.16  | 0.09 | .04   | 886 | --    | --  | --     | 886 | -0.28  | 0.09 | .02   |
| Low eCRF | 282 | Referent | 104 | Referent | 211 | Referent | 211 | Referent |
| Moderate eCRF | 381 | -0.04  | 0.17 | .81   | 388 | -0.19  | 0.25 | .45    | 308 | -0.32  | 0.19 | .09   |
| High eCRF | 413 | -0.27  | 0.20 | .17   | 394 | -0.65  | 0.27 | .02    | 367 | -0.65  | 0.21 | .002  |

**Abbreviations:** eCRF, non-exercise estimated cardiorespiratory fitness; CVD, cardiovascular disease; CFPWV, carotid femoral pulse wave velocity; est., estimate; SE, standard error; SD, standard deviation; CIMT, carotid intima-media thickness; CAC, coronary artery calcium; AU, Agatston unit.

**Note:** Models were adjusted for age, sex, systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes, total cholesterol/high-density lipoprotein cholesterol, and lipid-lowering medication at exam 7; SDs are equal to 2.0 MET for all models.
### eTable 4. Associations of midlife eCRF with the incidence of cardiometabolic diseases and mortality.

| Hypertension | eCRF<sub>exam7</sub> (n=1,506) | eCRF<sub>trajectories</sub> (n=1,159) | eCRF<sub>average</sub> (n=1,159) |
|--------------|---------------------------------|--------------------------------------|---------------------------------|
|              | # events/ # at risk | HR (95% CI) | P value | # events/ # at risk | HR (95% CI) | P value | # events/ # at risk | HR (95% CI) | P value |
| eCRF (per 1 SD increment) | 728/1,506 | 0.82 (0.72-0.94) | .004 | 580/1,159 | -- | -- | 580/1,159 | 0.74 (0.64-0.86) | <.001 |
| Low eCRF     | 196/292 | Referent | 67/100 | Referent | 147/212 | Referent |
| Moderate eCRF | 273/488 | 0.83 (0.63-1.09) | .18 | 282/451 | 0.81 (0.53-1.26) | .35 | 224/381 | 0.69 (0.50-0.94) | .02 |
| High eCRF    | 259/726 | 0.63 (0.46-0.85) | .003 | 231/608 | 0.54 (0.34-0.87) | .01 | 209/566 | 0.48 (0.34-0.68) | <.001 |

| Diabetes | eCRF<sub>exam7</sub> (n=2,268) | eCRF<sub>trajectories</sub> (n=1,170) | eCRF<sub>average</sub> (n=1,170) |
|----------|---------------------------------|--------------------------------------|---------------------------------|
| eCRF (per 1 SD increment) | 214/2,268 | 0.67 (0.56-0.82) | <.001 | 169/1,770 | -- | -- | 169/1,770 | 0.64 (0.52-0.79) | <.001 |
| Low eCRF | 95/573 | Referent | 55/206 | Referent | 86/443 | Referent |
| Moderate eCRF | 89/801 | 0.74 (0.52-1.04) | .08 | 86/807 | 0.46 (0.29-0.72) | <.001 | 57/617 | 0.51 (0.34-0.76) | .001 |
| High eCRF | 30/894 | 0.38 (0.23-0.62) | <.001 | 28/757 | 0.27 (0.15-0.48) | <.001 | 26/710 | 0.31 (0.18-0.54) | <.001 |

| CKD | eCRF<sub>exam7</sub> (n=2,343) | eCRF<sub>trajectories</sub> (n=1,817) | eCRF<sub>average</sub> (n=1,817) |
|-----|---------------------------------|--------------------------------------|---------------------------------|
| eCRF (per 1 SD increment) | 439/2,343 | 0.87 (0.75-1.01) | .07 | 358/1,817 | -- | -- | 358/1,817 | 0.84 (0.72-0.98) | .03 |
| Low eCRF | 189/632 | Referent | 81/249 | Referent | 147/484 | Referent |
| Moderate eCRF | 150/810 | 0.69 (0.53-0.89) | .005 | 192/815 | 0.68 (0.47-0.98) | .04 | 134/629 | 0.75 (0.56-1.00) | .049 |
| High eCRF | 100/901 | 0.89 (0.63-1.25) | .49 | 85/753 | 0.63 (0.40-0.97) | .04 | 77/704 | 0.64 (0.44-0.94) | .02 |

| CVD | eCRF<sub>exam7</sub> (n=2,608) | eCRF<sub>trajectories</sub> (n=1,970) | eCRF<sub>average</sub> (n=1,970) |
|-----|---------------------------------|--------------------------------------|---------------------------------|
| eCRF (per 1 SD increment) | 500/2,608 | 0.83 (0.75-0.93) | <.001 | 392/1,970 | -- | -- | 392/1,970 | 0.75 (0.67-0.84) | <.001 |
| Low eCRF | 230/784 | Referent | 101/298 | Referent | 195/583 | Referent |
| Moderate eCRF | 176/882 | 0.85 (0.69-1.04) | .12 | 227/900 | 0.87 (0.66-1.14) | .30 | 137/667 | 0.75 (0.59-0.94) | .01 |
| High eCRF | 94/942 | 0.71 (0.53-0.95) | .02 | 64/772 | 0.46 (0.31-0.68) | <.001 | 60/720 | 0.43 (0.30-0.60) | <.001 |

| All-cause mortality | eCRF<sub>exam7</sub> (n=2,962) | eCRF<sub>trajectories</sub> (n=2,247) | eCRF<sub>average</sub> (n=2,247) |
|---------------------|---------------------------------|--------------------------------------|---------------------------------|
| eCRF (per 1 SD increment) | -- | -- | -- | -- | -- | -- | -- | -- | -- |

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|                  | # events / # at risk | HR (95% CI)   | P value | # events / # at risk | HR (HR-95% CI) | P value | # events / # at risk | HR (95% CI) | P value |
|------------------|----------------------|---------------|---------|----------------------|----------------|---------|----------------------|---------------|---------|
| **eCRF**         |                      |               |         |                      |                |         |                      |               |         |
| (per 1 SD increment) | 770/2,962           | 0.84 (0.77-0.92) | <.001   | 600/2,247            | --             | --      | 600/2,247            | 0.81 (0.73-0.89) | <.001   |
| Low eCRF         | 404/961              | Referent      |         | 201/384              | Referent       |         | 316/727              | Referent       |         |
| Moderate eCRF    | 240/1,003            | 0.82 (0.69-0.97) | .02     | 290/1,046            | 0.67 (0.56-0.82) | <.001   | 182/757              | 0.77 (0.64-0.94) | .009    |
| High eCRF        | 126/998              | 0.83 (0.65-1.06) | .13     | 109/817              | 0.69 (0.50-0.95) | .03     | 102/763              | 0.80 (0.61-1.05) | .11     |

**Abbreviations:** eCRF, non-exercise estimated cardiorespiratory fitness; HR, hazard ratio; CI, confidence interval; SD, standard deviation; CKD, chronic kidney disease; CVD, cardiovascular disease.

**Note:** Models were adjusted for age, sex, systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes, total cholesterol/high-density lipoprotein cholesterol, lipid-lowering medication, and prevalence of CVD; Antihypertensive medication was not adjusted in the model using hypertension as an outcome; Fasting blood glucose was adjusted instead of diabetes in the model using diabetes as an outcome; estimated glomerular filtration rate was further adjusted in the model using CKD as an outcome; Prevalence of CVD was excluded in the model using CVD as an outcome; SDs are equal to 1.9 MET for hypertension, diabetes, and CKD samples and 2.0 MET for CVD and all-cause mortality sample.
eTable 5. Associations of midlife eCRF with the incidence of cardiometabolic diseases and mortality among participants not on antihypertensive treatment.

| Hypertension | eCRF<sub>exam7</sub> (n=1,506) | eCRF<sub>trajectories</sub> (n=1,159) | eCRF<sub>average</sub> (n=1,159) |
|--------------|-------------------------------|--------------------------------------|-----------------------------|
|              | #events/#at risk | HR (95% CI) | P value | #events/#at risk | HR (95% CI) | P value | #events/#at risk | HR (95% CI) | P value |
| eCRF (per 1 SD increment) | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Low eCRF | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Moderate eCRF | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| High eCRF | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Diabetes | eCRF<sub>exam7</sub> (n=1,506) | eCRF<sub>trajectories</sub> (n=1,159) | eCRF<sub>average</sub> (n=1,159) |
|              | # events/#at risk | HR (95% CI) | P value | # events/#at risk | HR (95% CI) | P value | # events/#at risk | HR (95% CI) | P value |
| eCRF (per 1 SD increment) | 120/1,657 | 0.72 (0.55-0.93) | .01 | 93/1,281 | -- | -- | 93/1,281 | 0.70 (0.53-0.93) | .01 |
| Low eCRF | 46/332 | Referent | | 22/115 | Referent | | 36/244 | Referent | |
| Moderate eCRF | 50/561 | 0.69 (0.43-1.14) | .15 | 47/511 | 0.59 (0.31-1.11) | .10 | 36/421 | 0.59 (0.34-1.04) | .07 |
| High eCRF | 24/764 | 0.44 (0.23-0.84) | .01 | 24/655 | 0.36 (0.17-0.77) | .008 | 21/616 | 0.36 (0.18-0.72) | .004 |
| CKD | eCRF<sub>exam7</sub> (n=1,506) | eCRF<sub>trajectories</sub> (n=1,159) | eCRF<sub>average</sub> (n=1,159) |
|              | # events/#at risk | HR (95% CI) | P value | # events/#at risk | HR (95% CI) | P value | # events/#at risk | HR (95% CI) | P value |
| eCRF (per 1 SD increment) | 254/1,686 | 0.91 (0.75-1.11) | .36 | 210/1,299 | -- | -- | 210/1,299 | 0.86 (0.69-1.06) | .15 |
| Low eCRF | 92/353 | Referent | | 36/129 | Referent | | 71/258 | Referent | |
| Moderate eCRF | 85/562 | 0.67 (0.46-0.95) | .03 | 108/516 | 0.72 (0.44-1.19) | .20 | 78/427 | 0.68 (0.46-1.01) | .06 |
| High eCRF | 77/771 | 0.92 (0.60-1.43) | .71 | 66/654 | 0.65 (0.36-1.15) | .14 | 61/614 | 0.60 (0.37-0.96) | .03 |
| CVD | eCRF<sub>exam7</sub> (n=1,506) | eCRF<sub>trajectories</sub> (n=1,159) | eCRF<sub>average</sub> (n=1,159) |
|              | # events/#at risk | HR (95% CI) | P value | # events/#at risk | HR (95% CI) | P value | # events/#at risk | HR (95% CI) | P value |
| eCRF (per 1 SD increment) | 293/1,865 | 0.85 (0.73-0.97) | .02 | 229/1,402 | -- | -- | 229/1,402 | 0.72 (0.62-0.84) | <.001 |
| Low eCRF | 120/443 | Referent | | 49/157 | Referent | | 96/314 | Referent | |
| Moderate eCRF | 100/606 | 0.86 (0.65-1.14) | .29 | 132/570 | 0.84 (0.59-1.21) | .36 | 87/454 | 0.75 (0.55-1.01) | .06 |
| High eCRF | 73/816 | 0.73 (0.51-1.04) | .08 | 48/675 | 0.43 (0.26-0.69) | <.001 | 46/634 | 0.40 (0.27-0.61) | <.001 |

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| All-cause mortality | eCRF<sub>exam7</sub> (n=1,506) | eCRF<sub>trajectories</sub> (n=1,159) | eCRF<sub>average</sub> (n=1,159) |
|---------------------|-----------------------------|-------------------------------|-----------------------------|
|                     | # events / #at risk | HR (95% CI) | P value | # events / #at risk | HR (HR - 95% CI) | P value | # events / #at risk | HR (95% CI) | P value |
| eCRF (per 1 SD increment) | 397/1,990 | 0.85 (0.75-0.97) | .02 | 311/1,494 | -- | -- | 311/1,494 | 0.79 (0.69-0.91) | .001 |
| Low eCRF | 181/498 | Referent | | 82/182 | Referent | | 133/349 | Referent |
| Moderate eCRF | 127/651 | 0.82 (0.64-1.04) | .11 | 148/615 | 0.64 (0.48-0.86) | .003 | 101/490 | 0.71 (0.54-0.93) | .01 |
| High eCRF | 89/841 | 0.82 (0.60-1.13) | .23 | 81/697 | 0.66 (0.44-0.99) | .047 | 77/655 | 0.75 (0.54-1.06) | .11 |

**Abbreviations:** eCRF, non-exercise estimated cardiorespiratory fitness; HR, hazard ratio; CI, confidence interval; SD, standard deviation; CKD, chronic kidney disease; CVD, cardiovascular disease.

**Note:** Models were adjusted for age, sex, systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes, total cholesterol/high-density lipoprotein cholesterol, lipid-lowering medication, and prevalence of CVD; No results were reported regarding the relation between eCRF and incident hypertension because the definition of hypertension include patients on antihypertensive treatment; Fasting blood glucose was adjusted instead of diabetes in the model using diabetes as an outcome; Estimated glomerular filtration rate was further adjusted in the model using CKD as an outcome; Prevalence of CVD was excluded in the model using CVD as an outcome; SDs are equal to 1.9 MET for diabetes and CKD samples and 2.0 MET for CVD and all-cause mortality sample.
### eTable 6. Association of midlife eCRF with the incidence of hypertension based on the 2017 AHA/ACC guidelines for hypertension.

| Hypertension | eCRF<sub>exam7</sub> (n=1,076) | eCRF<sub>trajectories</sub> (n=832) | eCRF<sub>average</sub> (n=832) |
|--------------|-------------------------------|-----------------------------------|--------------------------------|
|              | #events/#at risk | HR (95% CI) | P value | #events/#at risk | HR (95% CI) | P value | #events/#at risk | HR (95% CI) | P value |
| eCRF (per 1 SD increment) | 630/1,076 | 0.85 (0.72-1.01) | .06 | 495/832 | -- | -- | 495/832 | 0.78 (0.65-0.93) | .006 |
| Low eCRF | 128/175 | Referent | | 42/61 | Referent | | 98/135 | Referent | |
| Moderate eCRF | 221/334 | 0.93 (0.65-1.31) | .66 | 207/300 | 1.12 (0.65-1.92) | .68 | 170/254 | 0.81 (0.55-1.19) | .28 |
| High eCRF | 281/567 | 0.75 (0.51-1.09) | .13 | 246/471 | 0.85 (0.49-1.49) | .57 | 227/443 | 0.68 (0.46-1.03) | .07 |

**Abbreviations:** eCRF, non-exercise estimated cardiorespiratory fitness; AHA, American Heart Association; ACC, American College of Cardiology; HR, hazard ratio; CI, confidence interval; SD, standard deviation

**Note:** Models were adjusted for age, sex, systolic blood pressure, diastolic blood pressure, diabetes, total cholesterol/high-density lipoprotein cholesterol, lipid-lowering medication, and prevalence of CVD.
eTable 7. Associations of midlife eCRF with subclinical atherosclerosis and the incidence of cardiometabolic diseases and mortality, additionally adjusting for eCRF slope.

| -1000/CFPWV (ms/m) | eCRF<sub>exam7</sub> (n=2,041) |  |  |  |
|---------|-------------------------------|---|---|---|
|         | N    | β est. | SE  | P value |
| eCRF (per 1 SD increment) | 2,041 | -4.90  | 0.70 | <.001 |

| CIMT (mm) | eCRF<sub>exam7</sub> (n=2,106) |  |  |  |
|----------|-------------------------------|---|---|---|
|          | N    | β est. | SE  | P value |
| eCRF (per 1 SD increment) | 2,106 | -0.08  | 0.02 | <.001 |

| CAC (AU) | eCRF<sub>exam7</sub> (n=1,172) |  |  |  |
|----------|-------------------------------|---|---|---|
|          | N    | β est. | SE  | P value |
| eCRF (per 1 SD increment) | 1,172 | -0.34  | 0.09 | 0.20  |

| Hypertension | eCRF<sub>exam7</sub> (n=1,506) |  |  |  |
|--------------|-------------------------------|---|---|---|
| #events/#at risk | HR (95% CI) | P value |
| eCRF (per 1 SD increment) | 728/1,506 | 0.72 (0.61-0.84) | <.001 |

| Diabetes | eCRF<sub>exam7</sub> (n=2,268) |  |  |  |
|----------|-------------------------------|---|---|---|
| # events/#at risk | HR (95% CI) | P value |
| eCRF (per 1 SD increment) | 214/2,268 | 0.67 (0.53-0.82) | <.001 |

| CKD | eCRF<sub>exam7</sub> (n=2,343) |  |  |  |
|-----|-------------------------------|---|---|---|
| # events/#at risk | HR (95% CI) | P value |
| eCRF (per 1 SD increment) | 439/2,343 | 0.81 (0.69-0.95) | .011 |

| CVD | eCRF<sub>exam7</sub> (n=2,608) |  |  |  |
|-----|-------------------------------|---|---|---|
| # events/#at risk | HR (95% CI) | P value |
| eCRF (per 1 SD increment) | 500/2,608 | 0.73 (0.65-0.82) | <.001 |

| All-cause mortality | eCRF<sub>exam7</sub> (n=2,962) |  |  |  |
|---------------------|-------------------------------|---|---|---|
| # events/#at risk | HR (95% CI) | P value |
| eCRF (per 1 SD increment) | 770/2,962 | 0.80 (0.72-0.89) | <.001 |

Abbreviations: eCRF, non-exercise estimated cardiorespiratory fitness; HR, hazard ratio; CI, confidence interval; SD, standard deviation; CIMT, carotid intima-media thickness; CAC, coronary artery calcium; AU, Agatston units; CKD, chronic kidney disease; CVD, cardiovascular disease.

Note: Models were adjusted for age, sex, systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes, total cholesterol/high-density lipoprotein cholesterol, lipid-lowering medication, and prevalence of CVD; Antihypertensive medication was not adjusted in the model using hypertension as an outcome; Fasting blood glucose was adjusted instead of diabetes in the model using diabetes as an outcome; estimated glomerular filtration rate was further adjusted in the model using CKD as an outcome; Prevalence of CVD was excluded in the model using CVD as an outcome; SDs are equal to 1.9 MET for hypertension, diabetes, and CKD samples and 2.0 MET for CVD and all-cause mortality sample.
**eTable 8.** Associations of midlife eCRF with incidence of cardiometabolic diseases and mortality, using eCRF defined by Nes et al.

| Hypertension | eCRF exams7 (n=1,506) | # events/# at risk | HR (95% CI) | P value |
|--------------|-----------------------|--------------------|-------------|---------|
| eCRF, original (per 1 SD increment) | 728/1,506 | 0.82 (0.72-0.94) | .004 |
| eCRF, Nes et al. (per 1 SD increment) | 728/1,506 | 0.84 (0.74-0.95) | .006 |

| Diabetes | eCRF exams7 (n=2,268) | # events/# at risk | HR (95% CI) | P value |
|----------|-----------------------|--------------------|-------------|---------|
| eCRF, original (per 1 SD increment) | 214/2,268 | 0.67 (0.56-0.82) | <.001 |
| eCRF, Nes et al. (per 1 SD increment) | 214/2,268 | 0.68 (0.57-0.81) | .001 |

| CKD | eCRF exams7 (n=2,343) | # events/# at risk | HR (95% CI) | P value |
|-----|-----------------------|--------------------|-------------|---------|
| eCRF, original (per 1 SD increment) | 439/2,343 | 0.87 (0.75-1.01) | .07 |
| eCRF, Nes et al. (per 1 SD increment) | 439/2,343 | 0.90 (0.78-1.03) | .11 |

| CVD | eCRF exams7 (n=2,608) | # events/# at risk | HR (95% CI) | P value |
|-----|-----------------------|--------------------|-------------|---------|
| eCRF, original (per 1 SD increment) | 500/2,608 | 0.83 (0.75-0.93) | <.001 |
| eCRF, Nes et al. (per 1 SD increment) | 500/2,608 | 0.86 (0.78-0.95) | .004 |

| All-cause mortality | eCRF exams7 (n=2,962) | # events/# at risk | HR (95% CI) | P value |
|---------------------|-----------------------|--------------------|-------------|---------|
| eCRF, original (per 1 SD increment) | 770/2,962 | 0.84 (0.77-0.92) | <.001 |
| eCRF, Nes et al. (per 1 SD increment) | 770/2,962 | 0.92 (0.84-0.996) | .040 |

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**eFigure.** Trajectories of midlife eCRF.

**Abbreviations:** eCRF, non-exercise estimated cardiorespiratory fitness; MET, metabolic equivalent of task.