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Supplementary Material

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Table S1: *Categories* cohort, participants flow

Initial sample		95,153
Excluded participants without a pre-defined category test	17,197	77,956

Table S2: Missing data for participants included in the *categories* cohort analyses

Variable	Missing	Total	Percent Missing
Age	0	77,956	0
Sex	0	77,956	0
Systolic blood pressure	459	77,956	0.59
Body mass index	278	77,956	0.36
Smoking status	539	77,956	0.69
High cholesterol [^]	0	77,956	0
Number of medications	2	77,956	<0.01
Maximum working load	1	77,956	<0.01
Prevalent cancer	2	77,956	<0.01
Prevalent cardiovascular disease [#]	415	77,956	0.53
Prevalent diabetes	514	77,956	0.66

Number of participants with missing data on age, sex, systolic blood pressure, body mass index, smoking status, high cholesterol, number of medications, maximum working load, and prevalent cancer, cardiovascular disease, or diabetes at baseline

[^] Defined using data field 20002 (Non-cancer illness code, self-reported Medical conditions), code 1473
[\[http://biobank.ctsu.ox.ac.uk/crystal/coding.cgi?id=6\]](http://biobank.ctsu.ox.ac.uk/crystal/coding.cgi?id=6)

[#] "Heart attack", "Angina", or "Stroke" in data field 6150

Table S3: *Fitness* cohort, participants flow

Initial sample		95,153
Excluded participants without a pre-defined category test	17,197	77,956
Excluded participants who did not complete the test	6,298	71,658
Excluded participants with at-rest measurement (Category 4)	8,245	63,413
Excluded participants with missing data on variables* to estimate cardiorespiratory fitness	2,479	60,934
Excluded participants with (max HR – baseline HR) = 0 or (max WL – baseline WL) = 0	1,170	59,764
Excluded participants with (max HR – baseline HR) / (max WL – baseline WL) ≤ 0	1	59,763

HR, heart rate

WL, working load

* Age, body weight, baseline and maximum heart rate, baseline and maximum working load

Table S4: Missing data for participants included in the *fitness* cohort analyses

Variable	Missing	Total	Percent Missing
Age	0	59,763	0
Sex	0	59,763	0
Systolic blood pressure	291	59,763	0.49
Body mass index	32	59,763	0.05
Smoking status	312	59,763	0.52
High cholesterol [^]	0	59,763	<0.01
Number of medications	2	59,763	<0.01
Prevalent cancer	2	59,763	<0.01
Prevalent cardiovascular disease [#]	234	59,763	0.39
Prevalent diabetes	285	59,763	0.48

Number of participants with missing data on age, sex, systolic blood pressure, body mass index, smoking status, high cholesterol, number of medications, and prevalent cancer, cardiovascular disease, or diabetes at baseline.

[^] Defined using data field 20002 (Non-cancer illness code, self-reported Medical conditions), code 1473 [<http://biobank.ctsu.ox.ac.uk/crystal/coding.cgi?id=6>]

[#] "Heart attack", "Angina", or "Stroke" in data field 6150

Table S5: Baseline characteristics of participants in the *categories* cohort

Variable	Category 1, cycle rising to 50% level	Category 2, cycle rising to 35% level	Category 3, cycle at constant level	Category 4, at-rest measurement	Total
	N=57484	N=8773	N=2222	N=7822	N=76301
Age, years	57.8 (49.9-63.4)	61.6 (54.8-65.6)	61.0 (53.8-65.3)	61.4 (54.4-65.8)	58.8 (50.9-64.0)
Sex					
Females	31828 (55.4%)	3880 (44.2%)	1257 (56.6%)	4657 (59.5%)	41622 (54.5%)
Males	25656 (44.6%)	4893 (55.8%)	965 (43.4%)	3165 (40.5%)	34679 (45.5%)
Systolic blood pressure, mmHg	135.0 (124.0-147.0)	164.0 (152.0-174.0)	140.0 (127.0-153.0)	144.0 (130.0-162.0)	138.0 (126.0-152.0)
Body mass index, kg/m ²	26.3 (23.8-29.3)	27.8 (25.2-30.9)	28.2 (25.2-31.7)	28.4 (25.3-32.5)	26.7 (24.1-29.9)
Smoking status					
Never	32565 (56.7%)	4783 (54.5%)	1129 (50.8%)	3970 (50.8%)	42447 (55.6%)
Former	19636 (34.2%)	3297 (37.6%)	824 (37.1%)	2799 (35.8%)	26556 (34.8%)
Current	5283 (9.2%)	693 (7.9%)	269 (12.1%)	1053 (13.5%)	7298 (9.6%)
High cholesterol [^]					
No	51115 (88.9%)	7214 (82.2%)	1767 (79.5%)	6302 (80.6%)	66398 (87.0%)
Yes	6369 (11.1%)	1559 (17.8%)	455 (20.5%)	1520 (19.4%)	9903 (13.0%)
Number of medications	1.0 (0.0-3.0)	2.0 (1.0-4.0)	3.0 (1.0-6.0)	3.0 (1.0-6.0)	2.0 (0.0-3.0)
Prevalent cancer					
No	52451 (91.2%)	7976 (90.9%)	2029 (91.3%)	6910 (88.3%)	69366 (90.9%)
Yes	5033 (8.8%)	797 (9.1%)	193 (8.7%)	912 (11.7%)	6935 (9.1%)
Prevalent CVD [#]					
No	55914 (97.3%)	7942 (90.5%)	1734 (78.0%)	6677 (85.4%)	72267 (94.7%)
Yes	1570 (2.7%)	831 (9.5%)	488 (22.0%)	1145 (14.6%)	4034 (5.3%)
Prevalent diabetes					
No	54789 (95.3%)	8261 (94.2%)	2013 (90.6%)	6974 (89.2%)	72037 (94.4%)
Yes	2695 (4.7%)	512 (5.8%)	209 (9.4%)	848 (10.8%)	4264 (5.6%)
All cause death					
No	56600 (98.5%)	8555 (97.5%)	2159 (97.2%)	7505 (95.9%)	74819 (98.1%)
Yes	884 (1.5%)	218 (2.5%)	63 (2.8%)	317 (4.1%)	1482 (1.9%)
Cancer death					
No	56898 (99.0%)	8653 (98.6%)	2191 (98.6%)	7664 (98.0%)	75406 (98.8%)
Yes	586 (1.0%)	120 (1.4%)	31 (1.4%)	158 (2.0%)	895 (1.2%)
CVD death					
No	57337 (99.7%)	8720 (99.4%)	2207 (99.3%)	7743 (99.0%)	76007 (99.6%)
Yes	147 (0.3%)	53 (0.6%)	15 (0.7%)	79 (1.0%)	294 (0.4%)

Data are n (%) or median (interquartile range)

[^] Defined using data field 20002 (Non-cancer illness code, self-reported Medical conditions), code 1473 [<http://biobank.ctsu.ox.ac.uk/crystal/coding.cgi?id=6>]

[#] CVD (cardiovascular): "Heart attack", "Angina", or "Stroke" in data field 6150

Cancer death: ICD-10 codes C00-C97; CVD death: ICD-10 codes I00-I79

Table S6: Hazard ratio of mortality by category of bicycle test

Category	Hazard ratio (95% CI)
Category 1, cycle rising to 50% level	1 (Ref)
Category 2, cycle rising to 35% level	1.23 (1.04, 1.44)
Category 3, cycle at constant level	1.24 (0.95, 1.61)
Category 4, at-rest measurement	1.63 (1.41, 1.88)

Estimates adjusted for age, sex, systolic blood pressure, body mass index (nonlinear spline), smoking status, high cholesterol, number of medications, and prevalent cancer, cardiovascular disease, or diabetes at baseline.

Category 1, minimal risk; **Category 2**, small risk; **Category 3**, medium risk; **Category 4**, high risk

Table S7: C-index change on addition of cardiorespiratory fitness to risk factors

Model	c-index	Difference	p-value
Age	0.6910 (0.6752, 0.7069)		
Age + CRF	0.6910 (0.6752, 0.7068)	-0.0001 (-0.0004, 0.0003)	0.717
Age, Sex, SBP, Smoking, High cholesterol	0.7160 (0.7002, 0.7319)		
Age, Sex, SBP, Smoking, High cholesterol + CRF	0.7172 (0.7013, 0.7331)	0.0012 (-0.0021, 0.0044)	0.487
Age, Sex, SBP, Smoking, High cholesterol, BMI, No. of medications	0.7264 (0.7107, 0.7421)		
Age, Sex, SBP, Smoking, High cholesterol, BMI, No. of medications + CRF	0.7264 (0.7106, 0.7422)	-0.0000 (-0.0027, 0.0027)	0.997
Age, Sex, SBP, Smoking, High cholesterol, BMI, No. of medications, Prevalent cancer, cardiovascular disease, or diabetes	0.7493 (0.7342, 0.7645)		
Age, Sex, SBP, Smoking, High cholesterol, BMI, No. of medications, Prevalent cancer, cardiovascular disease, or diabetes + CRF	0.7488 (0.7335, 0.7641)	-0.0005 (-0.0033, 0.0022)	0.710

BMI, body mass index

CRF, cardiorespiratory fitness

SBP, systolic blood pressure

Table S8: Reclassification indices on addition of cardiorespiratory fitness to risk factors

Variable	Index	Estimate	Lb, 95%	Ub, 95%	p-value
Age + CRF	NRI	-0.0003	-0.0056	0.0049	0.898
Age + CRF	IDI	0.0000	0.0000	0.0000	0.265
Age, Sex, SBP, Smoking, High cholesterol + CRF	NRI	0.0361	0.0107	0.0615	0.005
Age, Sex, SBP, Smoking, High cholesterol + CRF	IDI	0.0005	0.0003	0.0008	<0.001
Age, Sex, SBP, Smoking, High cholesterol, BMI, No. of medications + CRF	NRI	0.0075	-0.0154	0.0305	0.520
Age, Sex, SBP, Smoking, High cholesterol, BMI, No. of medications + CRF	IDI	0.0006	0.0002	0.0009	<0.001
Age, Sex, SBP, Smoking, High cholesterol, BMI, No. of medications, Prevalent cancer, cardiovascular disease, or diabetes + CRF	NRI	0.0203	0.0000	0.0406	0.050
Age, Sex, SBP, Smoking, High cholesterol, BMI, No. of medications, Prevalent cancer, cardiovascular disease, or diabetes + CRF	IDI	0.0009	0.0005	0.0014	<0.001

BMI, body mass index

CRF, cardiorespiratory fitness

SBP, systolic blood pressure

NRI, net-reclassification-improvement

IDI, integrated-discrimination-improvement

Lb, Lower bound 95% confidence interval

Ub, Upper bound 95% confidence interval

Risk groups (<2.5%; 2.5% to 3.75%; 3.75% to 5.0%; >5.0%) [Cut off points defined for 5-year risk: *Journal of the American College of Cardiology* 2016; 67: 2118-2130]

Table S9: Other indices of added value of cardiorespiratory fitness

Index	Formula	Value
Pre AIC	-	9916.194
Post AIC	-	9904.095
Pre BIC	-	10122.81
Post BIC	-	10119.7
Likelihood ratio test Pre vs Post (p-value)	-	0.0001734
Pre Wald-chi2 (k)	-	819.9195
Post Wald-chi2 (j)	-	835.6071
Adequacy of base model	k/j	0.9812261
Fraction of new information from cardiorespiratory fitness	1-(k/j)	0.0187739
Pre R ²	-	0.4603337
Post R ²	-	0.4667152
Pre R ² _D	-	0.3501704
Post R ² _D	-	0.3550087
Pre variance of 5-year survival probabilities (z)	-	0.000213
Post variance of 5-year survival probabilities (t)	-	0.0002196
Relative explained variation	z/t	0.9697616
Fraction of new information from cardiorespiratory fitness	1-(z/t)	0.0302385

AIC, Akaike Information Criterion (lower values indicate “better” model)

BIC, Bayesian Information Criterion (lower values indicate “better” model)

Pre indicates model with age, sex, systolic blood pressure, body mass index (nonlinear spline), smoking status, high cholesterol, number of medications, and prevalent cancer, cardiovascular disease, or diabetes at baseline.

Post indicates model **Pre** + cardiorespiratory fitness.

R² and R²_D have been calculated as reported in *The Stata Journal*, vol. 6, 1: pp. 83-96.

Table S10: Patients exclusion in sensitivity analysis

		Baseline CVD		Total
		No	Yes	
Baseline cancer	No	51,635	2,223	53,858
	Yes	4,803	231	5,034
	Total	56,438	2,454	58,892

CVD, cardiovascular disease; Participants without baseline CVD or cancer: 51,635.

Table S11: Participants and events in sensitivity analysis

	Death		
	All-cause	Cancer	CVD
Participants	51,635	51,635	51,635
Events (%)	637 (1.23)	370 (0.72)	125 (0.24)

CVD, cardiovascular disease

Table S12: C-index change on addition of cardiorespiratory fitness to risk factors in sensitivity analysis

Model	c-index	Difference	p-value
Age	0.6929 (0.6737, 0.7121)		
Age + CRF	0.6938 (0.6746, 0.7131)	0.0009 (-0.0009, 0.0027)	0.325
Age, Sex, SBP, Smoking, High cholesterol	0.7260 (0.7070, 0.7450)		
Age, Sex, SBP, Smoking, High cholesterol + CRF	0.7260 (0.7070, 0.7450)	-0.0000 (-0.0018, 0.0018)	0.993
Age, Sex, SBP, Smoking, High cholesterol, BMI, No. of medications	0.7308 (0.7119, 0.7496)		
Age, Sex, SBP, Smoking, High cholesterol, BMI, No. of medications + CRF	0.7305 (0.7116, 0.7494)	-0.0003 (-0.0016, 0.0010)	0.650
Age, Sex, SBP, Smoking, High cholesterol, BMI, No. of medications, Prevalent diabetes	0.7308 (0.7119, 0.7496)		
Age, Sex, SBP, Smoking, High cholesterol, BMI, No. of medications, Prevalent diabetes + CRF	0.7305 (0.7116, 0.7493)	-0.0003 (-0.0017, 0.0010)	0.629

BMI, body mass index

CRF, cardiorespiratory fitness

SBP, systolic blood pressure

Table S13: Reclassification indices on addition of cardiorespiratory fitness to risk factors in sensitivity analysis

Variable	Index	Estimate	Lb, 95%	Ub, 95%	p-value
Age + CRF	NRI	-0.0023	-0.0163	0.0118	0.753
Age + CRF	IDI	0.0001	0.0000	0.0002	0.147
Age, Sex, SBP, Smoking, High cholesterol + CRF	NRI	0.0002	-0.0176	0.0180	0.981
Age, Sex, SBP, Smoking, High cholesterol + CRF	IDI	0.0001	0.0000	0.0002	0.063
Age, Sex, SBP, Smoking, High cholesterol, BMI, No. of medications + CRF	NRI	-0.0060	-0.0211	0.0091	0.435
Age, Sex, SBP, Smoking, High cholesterol, BMI, No. of medications + CRF	IDI	0.0000	-0.0001	0.0001	0.409
Age, Sex, SBP, Smoking, High cholesterol, BMI, No. of medications, Prevalent diabetes + CRF	NRI	-0.0028	-0.0178	0.0123	0.717
Age, Sex, SBP, Smoking, High cholesterol, BMI, No. of medications, Prevalent diabetes + CRF	IDI	0.0001	0.0000	0.0002	0.182

BMI, body mass index

CRF, cardiorespiratory fitness

SBP, systolic blood pressure

NRI, net-reclassification-improvement

IDI, integrated-discrimination-improvement

Lb, Lower bound 95% confidence interval

Ub, Upper bound 95% confidence interval

Risk groups (<2.5%; 2.5% to 3.75%; 3.75% to 5.0%; >5.0%) [Cut off points defined for 5-year risk: *Journal of the American College of Cardiology* 2016; 67: 2118-2130]

Table S14: Other indices of added value of cardiorespiratory fitness in sensitivity analysis

Index	Formula	Value
Pre AIC	-	7096.81
Post AIC	-	7097.476
Pre BIC	-	7282.701
Post BIC	-	7292.219
Likelihood ratio test Pre vs Post (p-value)	-	0.2480897
Pre Wald- χ^2 (k)	-	406.7929
Post Wald- χ^2 (j)	-	408.9189
Adequacy of base model	k/j	0.994801
Fraction of new information from cardiorespiratory fitness	1-(k/j)	0.005199
Pre R^2	-	0.3875926
Post R^2	-	0.3885666
Pre R^2_D	-	0.3021776
Post R^2_D	-	0.3031909
Pre variance of 5-year survival probabilities (z)	-	0.0000842
Post variance of 5-year survival probabilities (t)	-	0.0000848
Relative explained variation	z/t	0.99289
Fraction of new information from cardiorespiratory fitness	1-(z/t)	0.00711

AIC, Akaike Information Criterion (lower values indicate “better” model)

BIC, Bayesian Information Criterion (lower values indicate “better” model)

Pre indicates model with age, sex, systolic blood pressure, body mass index (nonlinear spline), smoking status, high cholesterol, number of medications, and prevalent diabetes at baseline.

Post indicates model **Pre** + cardiorespiratory fitness.

R^2 and R^2_D have been calculated as reported in *The Stata Journal*, vol. 6, 1: pp. 83-96.

Figure S1: Individual Post-Pre difference in 5-year survival by levels of risk factors

Pre indicates model with age, sex, systolic blood pressure, body mass index (nonlinear spline), smoking status, high cholesterol, number of medications, and prevalent cancer, cardiovascular disease, or diabetes at baseline.

Post indicates model **Pre** + cardiorespiratory fitness.

Figure S2: 5-year standardized survival by cardiorespiratory fitness and levels of risk factors

5-year survival estimates across MET ($\text{kcal} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) levels adjusted for age, sex, systolic blood pressure, body mass index (nonlinear spline), smoking status, high cholesterol, number of medications, and prevalent cancer, cardiovascular disease, or diabetes at baseline. For predictions for continuous risk factors, range values are based on their respective distributions.

Age (years): Green, 45; Gold, 50; Orange, 55; Purple, 60; Red, 65. **Systolic blood pressure (mmHg):** Green, 130; Gold, 140; Orange, 150; Purple, 160; Red, 170. **Body mass index (kg/m^2):** Green, 20; Gold, 22.5; Orange, 25; Purple, 30; Red, 32.5; Black, 35. **Number of drugs:** Green, 0; Gold, 1; Orange, 2; Purple, 3; Red, 4; Grey, 5; Black, 6. **Smoking:** Green, Never; Gold, Former; Red, Active. **High cholesterol:** Green, No; Red, Yes. **Sex:** Pink, Women; Blue, Men.

Areas indicate 95% confidence intervals, shown for first and last level of risk factors.

Figure S3: 5-year standardized survival difference by cardiorespiratory fitness and levels of risk factors

5-year adjusted survival differences, per 1000 persons, comparing 20 vs 5 metabolic equivalent of task (METs, kcal·kg⁻¹·h⁻¹) of cardiorespiratory fitness (y-axis) across levels of risk factors (x-axis).

Estimates adjusted for age, sex, systolic blood pressure, body mass index (nonlinear spline), smoking status, high cholesterol, number of medications, and prevalent cancer, cardiovascular disease, or diabetes at baseline.

Colours for levels of risk factors are the same shown in **Figure S2**.

Figure S4: Individual Post vs Pre 5-year survival in sensitivity analysis

Pre indicates model with age, sex, systolic blood pressure, body mass index (nonlinear spline), smoking status, high cholesterol, number of medications, and prevalent diabetes at baseline.

Post indicates model **Pre** + cardiorespiratory fitness.

The range of x- and y-axis is the same shown for the main analysis (**Figure 3**) to facilitate the comparison.

Figure S5: Individual Post-Pre difference in 5-year survival by levels of risk factors in sensitivity analysis

Pre indicates model with age, sex, systolic blood pressure, body mass index (nonlinear spline), smoking status, high cholesterol, number of medications, and prevalent diabetes at baseline. **Post** indicates model **Pre** + cardiorespiratory fitness.

Figure S6: 5-year standardised survival by cardiorespiratory fitness and levels of risk factors in sensitivity analysis

5-year survival estimates adjusted for age, sex, systolic blood pressure, body mass index (nonlinear spline), smoking status, high cholesterol, number of medications, and prevalent diabetes at baseline. For predictions for continuous risk factors, range values are based on their respective distributions.

Age: Green, 45 years; Gold, 50 years; Orange, 55 years; Purple, 60 years; Red, 65 years. **SBP:** Green, 130 mmHg; Gold, 140 mmHg; Orange, 150 mmHg; Purple, 160 mmHg; Red, 170 mmHg. **Body mass index:** Green, 20 kg/m²; Gold, 22.5 kg/m²; Orange, 25 kg/m²; Purple, 30 kg/m²; Red, 32.5 kg/m²; Black, 35 kg/m². **Number of drugs:** Green, 0; Gold, 1; Orange, 2; Purple, 3; Red, 4; Grey, 5; Black, 6. **Smoking:** Green, never; Gold, former; Red, active. **High cholesterol:** Green, no; Red, yes. **Sex:** Pink, Women; Blue, Men.

Areas indicate 95% confidence intervals, shown for first and last level of risk factors.

Figure S7: 5-year standardised survival difference by cardiorespiratory fitness and levels of risk factors in sensitivity analysis

5-year adjusted survival differences (Δ), per 1000 persons, comparing 20 vs 5 metabolic equivalent of task (METs, $\text{kcal}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$) of cardiorespiratory fitness (y-axis) across levels of risk factors (x-axis). Estimates adjusted for age, sex, systolic blood pressure, body mass index (nonlinear spline), smoking status, high cholesterol, number of medications, and prevalent diabetes at baseline. For predictions for continuous risk factors, range values are based on their respective distributions. Colours for levels of risk factors are the same shown in **Figure S6**. Y-axis range from 0 to 16 to facilitate the comparison with the results of the main analysis (**Figure S3**).