

Sustained physical activity offers benefits beyond activity volume in chronic disease prevention

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Supplementary Table 1. Hazard ratios and 95% confidence intervals for major chronic diseases incidence and its components according to long-term cumulative average physical activity volume

	Cumulative average physical activity volume, MET-hours/week				Per increment of 15 MET-hours/week	P trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		
Major chronic diseases						
Median (IQR)	4 (2–6)	11 (9–14)	21 (17–26)	44 (34–60)		
Number of cases	20 286	19 213	17 755	15 394		
Person years	1 510 452	1 518 169	1 521 046	1 521 806		
Model 1 ^a	1	0.88 (0.86, 0.90)	0.81 (0.79, 0.82)	0.72 (0.70, 0.74)	0.89 (0.88, 0.90)	<0.0001
Model 2 ^b	1	0.91 (0.89, 0.92)	0.85 (0.83, 0.87)	0.78 (0.76, 0.80)	0.92 (0.91, 0.92)	<0.0001
Type 2 diabetes						
Median (IQR)	4 (2–6)	11 (9–14)	21 (17–26)	44 (33–59)		
Number of cases	7 856	6 338	5 081	3 759		
Person years	1 458 747	1 462 312	1 465 756	1 464 651		
Model 1 ^a	1	0.73 (0.71, 0.76)	0.58 (0.56, 0.60)	0.44 (0.43, 0.46)	0.73 (0.72, 0.74)	<0.0001
Model 2 ^b	1	0.79 (0.77, 0.82)	0.67 (0.65, 0.69)	0.55 (0.53, 0.57)	0.80 (0.79, 0.81)	<0.0001
Major cardiovascular disease						
Median (IQR)	4 (2–6)	11 (9–13)	20 (17–25)	43 (33–59)		
Number of cases	5 141	4 582	4 184	3 508		
Person years	1 594 576	1 602 573	1 604 931	1 605 962		
Model 1 ^a	1	0.80 (0.77, 0.84)	0.73 (0.70, 0.76)	0.63 (0.60, 0.66)	0.86 (0.84, 0.87)	<0.0001
Model 2 ^b	1	0.85 (0.82, 0.89)	0.80 (0.76, 0.83)	0.72 (0.69, 0.75)	0.90 (0.88, 0.91)	<0.0001
Cancer						
Median (IQR)	4 (2–6)	11 (9–14)	21 (17–25)	43 (33–59)		
Number of cases	10 253	10 695	10 640	9 937		

Person years	1 610 768	1 618 485	1 619 830	1 621 541		
Model 1 ^a	1	0.99 (0.96, 1.01)	0.97 (0.94, 1.00)	0.93 (0.90, 0.96)	0.97 (0.96, 0.98)	<0.0001
Model 2 ^b	1	0.99 (0.96, 1.02)	0.98 (0.95, 1.01)	0.95 (0.92, 0.98)	0.98 (0.97, 0.99)	<0.0001
Obesity-related cancer ^c						
Median (IQR)	4 (2–6)	11 (9–14)	21 (17–26)	43 (33–59)		
Number of cases	5 495	5 579	5 348	4 868		
Person years	1 655 898	1 663 346	1 665 567	1 667 351		
Model 1 ^a	1	0.98 (0.94, 1.01)	0.93 (0.90, 0.97)	0.88 (0.85, 0.92)	0.95 (0.93, 0.96)	<0.0001
Model 2 ^b	1	0.97 (0.93, 1.00)	0.92 (0.89, 0.96)	0.87 (0.84, 0.91)	0.94 (0.93, 0.96)	<0.0001

Abbreviation: IQR, interquartile range; MET, metabolic equivalent of task

^a Cox proportional hazards models were stratified by age (months), questionnaire cycle (two-year interval), and cohort. The 95% confidence intervals for the hazard ratios and P values were derived using two-sided Wald tests. No multiple comparisons were adjusted.

^b We further adjusted for covariates including race, smoking status and packyears, alcohol consumption, Alternative Healthy Eating Index-2010, regular aspirin use, regular NSAIDs use, multivitamin use, family history of diabetes mellitus, cardiovascular disease, or cancer; for females, also menopausal status and hormone use. The 95% confidence intervals for the hazard ratios and P values were derived using two-sided Wald tests. No multiple comparisons were adjusted.

^c Include cancers of esophagus, stomach, colon/rectum, liver, gallbladder, pancreas, postmenopausal breast, endometrium, ovary, kidney, meningioma, thyroid and multiple myeloma.

Supplementary Table 2. Characteristics of study participants at age 60 according to physical activity trajectories from ages 40 to 60

Characteristics	Trajectories of physical activity from ages 40 to 60 (N = 73 340) ^a				
	Consistently inactive	Consistently medium volume	High to medium volume	Medium to high volume	Consistently high volume
Female, %	91	85	74	69	55
White, %	95	96	95	96	95
BMI, mean (SD), kg/m²	29.1 (6.6)	27.5 (5.5)	26.5 (4.9)	25.7 (4.3)	25.0 (4.0)
Alcohol drinking, mean (SD), g/day	4.9 (9.2)	5.8 (8.9)	7.5 (9.9)	7.5 (9.6)	9.0 (10.6)
AHEI score, mean (SD)	47.8 (9.0)	52.4 (9.4)	56.5 (9.9)	56.3 (9.9)	59.0 (10.2)
Smoking status, %					
Never smoking	52	54	51	54	53
Former smoking	34	38	40	39	40
Current smoking	12	7	7	5	5
Missing	2	1	2	2	2
Pack-years of smoking, mean (SD)	11.8 (19.1)	8.9 (15.0)	7.9 (13.2)	7.5 (13.1)	6.6 (11.4)
Multivitamin use, %	54	62	65	66	65
Regular aspirin use, %	24	25	27	30	34
Regular NSAIDs use, %	36	39	39	38	38
Family history of cancer, %	57	61	59	59	56
Family history of CVD, %	50	51	48	48	43
Family history of diabetes, %	38	41	37	39	35
Menopause and hormone use, %					
Male or premenopausal	12	16	27	31	46
Never user, postmenopausal	30	26	24	22	18

Current user, postmenopausal	32	32	28	26	20
Past user, postmenopausal	26	26	21	21	16

Abbreviation: AHEI, Alternative Healthy Eating Index-2010; BMI, body mass index; CVD, cardiovascular disease; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation
^a 14 271 males from the HPFS, 27 221 females from the NHS and 31 848 females from the NHS II

Supplementary Table 3. Mean and 95% confidence intervals of physical activity volume (MET-hours/week) from ages 40 to 60 according to trajectories identified ^a

	Trajectory of physical activity from ages 40 to 60				
	Consistently inactive	Consistently medium volume	High to medium volume	Medium to high volume	Consistently high volume
Number of participants	6 888	45 499	5 880	11 022	4 051
Age 40	2.5 (2.5, 2.6)	13.4 (13.2, 13.6)	42.8 (42.0, 43.7)	18.5 (18.0, 19.0)	40.6 (39.9, 41.3)
Age 44	2.4 (2.3, 2.4)	12.6 (12.4, 12.7)	42.1 (41.6, 42.7)	19.5 (19.1, 19.9)	48.5 (48.0, 49.0)
Age 48	2.3 (2.3, 2.3)	12.7 (12.6, 12.9)	37.5 (37.1, 38.0)	25.1 (24.7, 25.4)	55.5 (55.0, 55.9)
Age 52	2.5 (2.4, 2.5)	13.5 (13.4, 13.6)	31.3 (30.9, 31.7)	33.0 (32.7, 33.4)	60.2 (59.8, 60.5)
Age 56	2.4 (2.4, 2.5)	14.5 (14.3, 14.6)	25.9 (25.4, 26.4)	40.7 (40.3, 41.0)	61.3 (60.8, 61.7)
Age 60	2.6 (2.6, 2.7)	15.3 (15.1, 15.5)	23.5 (22.9, 24.0)	45.3 (44.8, 45.8)	57.5 (56.9, 58.0)

Abbreviation: MET, metabolic equivalent of task

^aFor the “consistently inactive” group, means and CIs were calculated using SAS PROC MEANS, while for other groups they were derived from model-predicted values in SAS PROC TRAJ. 95% confidence intervals were derived from two-sided Wald tests.

Supplementary Table 4. Hazard ratios and 95% confidence intervals for major chronic diseases incidence and its components according to cumulative years meeting the recommended physical activity level

	Cumulative years meeting the recommended level				Per 10-year increment	P trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		
Major chronic diseases						
Median (IQR)	0 (0–2)	6 (4–8)	12 (10–14)	22 (20–28)		
Number of cases	18 218	15 795	20 905	17 730		
Person years	1 642 551	1 408 339	1 524 907	1 495 677		
Model 1 ^a	1	0.93 (0.90, 0.95)	0.81 (0.80, 0.83)	0.70 (0.68, 0.71)	0.84 (0.83, 0.85)	<0.0001
Model 2 ^b	1	0.93 (0.91, 0.95)	0.85 (0.83, 0.87)	0.77 (0.75, 0.79)	0.88 (0.87, 0.89)	<0.0001
Type 2 diabetes						
Median (IQR)	0 (0–2)	6 (4–8)	12 (10–14)	22 (18–26)		
Number of cases	6 430	5 308	6 244	5 052		
Person years	1 564 201	1 415 914	1 437 458	1 433 893		
Model 1 ^a	1	0.75 (0.72, 0.78)	0.57 (0.55, 0.60)	0.41 (0.39, 0.43)	0.64 (0.62, 0.65)	<0.0001
Model 2 ^b	1	0.79 (0.76, 0.82)	0.66 (0.64, 0.69)	0.52 (0.50, 0.55)	0.72 (0.70, 0.74)	<0.0001
Major cardiovascular disease						
Median (IQR)	0 (0–2)	6 (4–8)	12 (10–14)	22 (20–26)		
Number of cases	4 354	3 750	5 033	4 278		
Person years	1 722 963	1 495 973	1 669 750	1 519 355		
Model 1 ^a	1	0.86 (0.82, 0.90)	0.72 (0.68, 0.75)	0.59 (0.56, 0.62)	0.77 (0.75, 0.79)	<0.0001
Model 2 ^b	1	0.91 (0.86, 0.95)	0.79 (0.75, 0.83)	0.69 (0.65, 0.73)	0.83 (0.81, 0.85)	<0.0001
Cancer						
Median (IQR)	0 (0–2)	6 (4–8)	12 (10–14)	22 (20–28)		
Number of cases	9 383	8 591	11 990	11 561		

Person years	1 714 634	1 481 996	1 642 395	1 631 598		
Model 1 ^a	1	1.02 (0.99, 1.05)	0.98 (0.95, 1.01)	0.94 (0.91, 0.97)	0.96 (0.95, 0.97)	<0.0001
Model 2 ^b	1	1.01 (0.98, 1.04)	0.99 (0.95, 1.02)	0.96 (0.93, 0.99)	0.97 (0.96, 0.99)	<0.0001
Obesity-related cancer ^c						
Median (IQR)	0 (0–2)	6 (4–8)	12 (10–14)	22 (20–28)		
Number of cases	4 970	4 323	6 472	5 525		
Person years	1 737 678	1 511 818	1 693 511	1 709 155		
Model 1 ^a	1	1.00 (0.96, 1.04)	0.96 (0.92, 1.01)	0.88 (0.84, 0.92)	0.93 (0.91, 0.95)	<0.0001
Model 2 ^b	1	0.97 (0.93, 1.01)	0.94 (0.90, 0.98)	0.87 (0.83, 0.92)	0.93 (0.91, 0.95)	<0.0001

Abbreviation: IQR, interquartile range; MET, metabolic equivalent of task

^a Cox proportional hazards models were stratified by age (months), questionnaire cycle (two-year interval), and cohort. The 95% confidence intervals for the hazard ratios and P values were derived using two-sided Wald tests. No multiple comparisons were adjusted.

^b We further adjusted for covariates including race, smoking status and packyears, alcohol consumption, Alternative Healthy Eating Index-2010, regular aspirin use, regular NSAIDs use, multivitamin use, family history of diabetes mellitus, cardiovascular disease, or cancer; for females, also menopausal status and hormone use. The 95% confidence intervals for the hazard ratios and P values were derived using two-sided Wald tests. No multiple comparisons were adjusted.

^c Include cancers of esophagus, stomach, colon/rectum, liver, gallbladder, pancreas, postmenopausal breast, endometrium, ovary, kidney, meningioma, thyroid and multiple myeloma.

Supplementary Table 5. Multivariable hazard ratios and 95% confidence intervals for the association between physical activity volume (per increment of 15 MET-hours/week) and major chronic diseases incidence with different lag periods

	Lag period between assessment of exposure and outcome			
	No lag ^a	4 years ^b	8 years ^c	12 years ^d
Major chronic diseases	0.92 (0.91, 0.92)	0.93 (0.92, 0.94)	0.94 (0.94, 0.95)	0.95 (0.94, 0.96)
Type 2 diabetes	0.80 (0.79, 0.81)	0.82 (0.81, 0.83)	0.85 (0.83, 0.86)	0.88 (0.86, 0.89)
Major cardiovascular disease	0.90 (0.89, 0.91)	0.92 (0.90, 0.93)	0.94 (0.92, 0.95)	0.96 (0.94, 0.98)
Cancer	0.98 (0.97, 0.99)	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)
Obesity-related cancer	0.94 (0.93, 0.96)	0.96 (0.95, 0.98)	0.97 (0.96, 0.98)	0.97 (0.95, 0.98)

Abbreviation: MET, metabolic equivalent of task

^a The number of person years (number of cases) for major chronic diseases, type 2 diabetes, major cardiovascular disease, cancer, and obesity-related cancer were 6 071 473 (72 648), 5 851 466 (23 034), 6 408 042 (17 415), 6 470 624 (41 525), and 6 652 162 (21 290), respectively. The 95% confidence intervals for the hazard ratios were derived using two-sided Wald tests.

^b The number of person years (number of cases) for major chronic diseases, type 2 diabetes, major cardiovascular disease, cancer, and obesity-related cancer were 5 248 562 (65 019), 4 859 076 (20 783), 5 373 190 (14 623), 5 585 262 (36 936), and 5 730 570 (18 954), respectively. The 95% confidence intervals for the hazard ratios were derived using two-sided Wald tests.

^c The number of person years (number of cases) for major chronic diseases, type 2 diabetes, major cardiovascular disease, cancer, and obesity-related cancer were 4 310 766 (56 184), 3 892 734 (18 019), 4 286 884 (11 572), 4 522 760 (29 296), and 4 658 236 (16 382), respectively. The 95% confidence intervals for the hazard ratios were derived using two-sided Wald tests.

^d The number of person years (number of cases) for major chronic diseases, type 2 diabetes, major cardiovascular disease, cancer, and obesity-related cancer were 3 422 904 (45 314), 2 987 716 (14 185), 3 338 110 (9 149), 3 613 506 (25 611), and 3 690 608 (13 187), respectively. The 95% confidence intervals for the hazard ratios were derived using two-sided Wald tests.

Supplementary Table 6. Hazard ratios and 95% confidence intervals with additional BMI adjustment for major chronic diseases incidence and its components according to (A) long-term physical activity exposures; (B) trajectories of physical activity from ages 40 to 60

(A)

	Consistency (percentage of follow-up years) of physical activity meeting the recommended level				Per 50% increment	<i>P</i> trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		
Major chronic diseases						
Number of cases	20 245	22 999	7 403	22 001		
Person years	1 520 018	1 569 992	509 386	2 472 078		
HR (95% CI) ^a	1	0.99 (0.97, 1.01)	0.95 (0.93, 0.98)	0.88 (0.86, 0.90)	0.94 (0.93, 0.95)	<0.0001
Type 2 diabetes						
Number of cases	7 881	6 982	2 687	5 484		
Person years	1 460 485	1 426 439	620 403	2 344 139		
HR (95% CI) ^a	1	0.95 (0.92, 0.98)	0.94 (0.90, 0.98)	0.81 (0.78, 0.84)	0.90 (0.89, 0.92)	<0.0001
Major cardiovascular disease						
Number of cases	4 813	5 455	2 393	4 754		
Person years	1 635 753	1 568 590	667 630	2 536 068		
HR (95% CI) ^a	1	0.94 (0.90, 0.98)	0.83 (0.79, 0.88)	0.76 (0.73, 0.79)	0.86 (0.84, 0.88)	<0.0001
Cancer						
Number of cases	10 742	12 066	5 256	13 461		
Person years	1 637 301	1 588 761	691 374	2 553 187		
HR (95% CI) ^a	1	1.00 (0.97, 1.03)	0.98 (0.95, 1.02)	0.95 (0.93, 0.98)	0.98 (0.97, 0.99)	0.006
Obesity-related cancer						
Number of cases	5 945	6 347	2 535	6 463		

Person years	1 673 864	1 645 237	721 303	2 611 757		
HR (95% CI) ^a	1	0.98 (0.94, 1.02)	0.95 (0.90, 1.00)	0.91 (0.88, 0.75)	0.96 (0.94, 0.98)	<0.0001
Cumulative years meeting the recommended level						
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Per 10-year increment	<i>P</i> trend
Major chronic diseases						
Number of cases	18 218	15 795	20 905	17 730		
Person years	1 642 551	1 408 339	1 524 907	1 495 677		
HR (95% CI) ^a	1	0.98 (0.96, 1.00)	0.94 (0.92, 0.96)	0.91 (0.89, 0.94)	0.95 (0.94, 0.97)	<0.0001
Type 2 diabetes						
Number of cases	6 430	5 308	6 244	5 052		
Person years	1 564 201	1 415 914	1 437 458	1 433 893		
HR (95% CI) ^a	1	0.90 (0.87, 0.94)	0.85 (0.82, 0.89)	0.83 (0.80, 0.87)	0.91 (0.89, 0.93)	<0.0001
Major cardiovascular disease						
Number of cases	4 354	3 750	5 033	4 278		
Person years	1 722 963	1 495 973	1 669 750	1 519 355		
HR (95% CI) ^a	1	0.93 (0.89, 0.98)	0.83 (0.79, 0.87)	0.76 (0.72, 0.80)	0.87 (0.85, 0.89)	<0.0001
Cancer						
Number of cases	9 383	8 591	11 990	11 561		
Person years	1 714 634	1 481 996	1 642 395	1 631 598		
HR (95% CI) ^a	1	1.02 (0.98, 1.05)	1.01 (0.97, 1.04)	0.99 (0.96, 1.03)	0.99 (0.97, 1.00)	0.17
Obesity-related cancer						
Number of cases	4 970	4 323	6 472	5 525		
Person years	1 737 678	1 511 818	1 693 511	1 709 155		
HR (95% CI) ^a	1	0.99 (0.95, 1.03)	0.98 (0.94, 1.02)	0.94 (0.89, 0.98)	0.96 (0.94, 0.98)	0.0004

	Cumulative average physical activity volume, MET-hours/week				Per increment of 15 MET-hours/week	<i>P</i> trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		
Major chronic diseases						
Number of cases	20 286	19 213	17 755	15 394		
Person years	1 510 452	1 518 169	1 521 046	1 521 806		
HR (95% CI) ^a	1	0.96 (0.94, 0.98)	0.94 (0.92, 0.96)	0.90 (0.88, 0.92)	0.96 (0.95, 0.97)	<0.0001
Type 2 diabetes						
Number of cases	7 856	6 338	5 081	3 759		
Person years	1 458 747	1 462 312	1 465 756	1 464 651		
HR (95% CI) ^a	1	0.92 (0.89, 0.95)	0.87 (0.84, 0.90)	0.83 (0.79, 0.86)	0.92 (0.91, 0.94)	<0.0001
Major cardiovascular disease						
Number of cases	5 141	4 582	4 184	3 508		
Person years	1 594 576	1 602 573	1 604 931	1 605 962		
HR (95% CI) ^a	1	0.88 (0.84, 0.92)	0.84 (0.80, 0.87)	0.78 (0.74, 0.81)	0.92 (0.90, 0.93)	<0.0001
Cancer						
Number of cases	10 253	10 695	10 640	9 937		
Person years	1 610 768	1 618 485	1 619 830	1 621 541		
HR (95% CI) ^a	1	1.00 (0.98, 1.03)	1.00 (0.97, 1.03)	0.97 (0.95, 1.00)	0.99 (0.98, 1.00)	0.07
Obesity-related cancer						
Number of cases	5 495	5 579	5 348	4 868		
Person years	1 655 898	1 663 346	1 665 567	1 667 351		
HR (95% CI) ^a	1	0.99 (0.95, 1.03)	0.96 (0.92, 0.99)	0.92 (0.89, 0.96)	0.96 (0.95, 0.98)	<0.0001

Abbreviation: CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task

^a Cox proportional hazards models were stratified by age (months), questionnaire cycle (two-year interval), and cohort, and further adjusted for covariates including race, smoking status and packyears, alcohol consumption, Alternative Healthy Eating Index-2010, regular aspirin use, regular NSAIDs use, multivitamin use, family history of diabetes mellitus, cardiovascular disease, or cancer; for females, also menopausal status and hormone use. The 95% confidence intervals for the hazard ratios and P values were derived using two-sided Wald tests. No multiple comparisons were adjusted.

(B)

	Trajectories of physical activity from ages 40 to 60				
	Consistently inactive	Consistently medium volume	High to medium volume	Medium to high volume	Consistently high volume
Number of participants	6 888	45 499	5 880	11 022	4 051
Major chronic diseases					
HR (95% CI) ^a	1	0.95 (0.90, 1.01)	0.87 (0.80, 0.95)	0.87 (0.81, 0.93)	0.84 (0.76, 0.93)
P value ^b		Reference	0.01	0.0008	0.004
Type 2 diabetes					
HR (95% CI) ^a	1	0.86 (0.78, 0.93)	0.79 (0.68, 0.91)	0.72 (0.63, 0.81)	0.64 (0.53, 0.78)
P value ^b		Reference	0.17	0.0007	0.002
Major cardiovascular disease					
HR (95% CI) ^a	1	1.03 (0.90, 1.19)	0.86 (0.70, 1.07)	0.88 (0.74, 1.05)	0.81 (0.64, 1.03)
P value ^b		Reference	0.04	0.01	0.02
Cancer					
HR (95% CI) ^a	1	0.99 (0.92, 1.06)	0.93 (0.84, 1.04)	0.94 (0.86, 1.03)	0.95 (0.84, 1.07)
P value ^b		Reference	0.20	0.13	0.46
Obesity-related cancer					
HR (95% CI) ^a	1	0.92 (0.84, 1.02)	0.82 (0.71, 0.96)	0.84 (0.74, 0.95)	0.78 (0.65, 0.95)
P value ^b		Reference	0.07	0.06	0.06

Abbreviation: CI, confidence interval; HR, hazard ratio

^a The 95% confidence intervals for the hazard ratios were derived using two-sided Wald tests. No multiple comparisons were adjusted.

^b P values were derived using two-sided Wald tests comparing the hazard ratios for the other groups to the hazard ratio for the “consistently medium volume” group.

Supplementary Table 7. Hazard ratios and 95% confidence intervals by sex for major chronic diseases incidence according to long-term physical activity exposures

	Consistency (percentage of follow-up years) of physical activity meeting the recommended level				Per 50% increment	<i>P</i> trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		
Males						
Median (IQR)	24 (0–45)	80 (70–86)	93 (93–94)	100 (100–100)		
Number of cases	5 434	5 309	207	7 092		
Person years	263 603	265 418	21 108	515 884		
Model 1 ^a	1	0.87 (0.84, 0.91)	0.78 (0.67, 0.91)	0.71 (0.69, 0.74)	0.82 (0.80, 0.84)	<0.0001
Model 2 ^b	1	0.89 (0.86, 0.93)	0.82 (0.70, 0.95)	0.77 (0.74, 0.80)	0.85 (0.83, 0.87)	<0.0001
Females						
Median (IQR)	0 (0–18)	55 (45–67)	83 (75–88)	100 (100–100)		
Number of cases	15 120	15 773	8 804	14 909		
Person years	1 271 099	1 206 380	571 788	1 956 194		
Model 1 ^a	1	0.96 (0.94, 0.99)	0.85 (0.83, 0.87)	0.71 (0.69, 0.73)	0.84 (0.83, 0.85)	<0.0001
Model 2 ^b	1	0.96 (0.94, 0.98)	0.88 (0.86, 0.91)	0.78 (0.76, 0.80)	0.88 (0.87, 0.89)	<0.0001
	Cumulative years meeting the recommended level				Per 10-year increment	<i>P</i> trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		
Males						
Median (IQR)	2 (0–4)	8 (6–10)	14 (12–16)	24 (22–28)		
Number of cases	4 904	4 647	4 917	3 574		
Person years	303 976	254 684	252 773	254 579		
Model 1 ^a	1	0.86 (0.82, 0.91)	0.73 (0.69, 0.77)	0.63 (0.59, 0.67)	0.80 (0.78, 0.82)	<0.0001

Model 2 ^b	1	0.90 (0.86, 0.94)	0.78 (0.74, 0.82)	0.70 (0.66, 0.75)	0.84 (0.82, 0.86)	<0.0001
Females						
Median (IQR)	0 (0–2)	6 (4–8)	12 (10–14)	22 (20–26)		
Number of cases	13 314	11 148	15 988	14 156		
Person years	1 338 574	1 153 654	1 272 134	1 241 098		
Model 1 ^a	1	0.94 (0.92, 0.97)	0.84 (0.81, 0.86)	0.71 (0.69, 0.73)	0.84 (0.83, 0.85)	<0.0001
Model 2 ^b	1	0.94 (0.92, 0.97)	0.87 (0.84, 0.89)	0.78 (0.76, 0.80)	0.88 (0.87, 0.90)	<0.0001
Cumulative average physical activity volume, MET-hours/week					Per increment of 15	<i>P</i> trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	MET-hours/week	
Males						
Median (IQR)	6 (3–9)	17 (14–20)	31 (27–36)	57 (48–72)		
Number of cases	5 163	4 718	4 376	3 785		
Person years	262 966	266 615	267 640	268 793		
Model 1 ^a	1	0.86 (0.82, 0.89)	0.80 (0.77, 0.83)	0.71 (0.68, 0.74)	0.91 (0.90, 0.92)	<0.0001
Model 2 ^b	1	0.89 (0.86, 0.93)	0.84 (0.81, 0.88)	0.77 (0.74, 0.81)	0.93 (0.92, 0.94)	<0.0001
Females						
Median (IQR)	4 (2–5)	10 (9–12)	20 (17–23)	40 (32–55)		
Number of cases	15 123	14 495	13 379	11 609		
Person years	1 247 487	1 251 554	1 253 406	1 253 013		
Model 1 ^a	1	0.89 (0.87, 0.91)	0.81 (0.79, 0.83)	0.72 (0.71, 0.74)	0.88 (0.87, 0.88)	<0.0001
Model 2 ^b	1	0.91 (0.89, 0.93)	0.85 (0.83, 0.87)	0.79 (0.77, 0.81)	0.91 (0.90, 0.92)	<0.0001

Abbreviation: IQR, interquartile range; MET, metabolic equivalent of task

^a Cox proportional hazards models were stratified by age (months) and questionnaire cycle (two-year interval). The 95% confidence intervals for the hazard ratios and *P* values were derived using two-sided Wald tests. No multiple comparisons were adjusted.

^b We further adjusted for covariates including race, smoking status and packyears, alcohol consumption, Alternative Healthy Eating Index-2010, regular aspirin use, regular NSAIDs use, multivitamin use, family history of diabetes mellitus, cardiovascular disease, or cancer; for females, also menopausal status and hormone use. The 95% confidence intervals for the hazard ratios and *P* values were derived using two-sided Wald tests. No multiple comparisons were adjusted.

Supplementary Table 8. Specification and emulation of a target trial of guideline-based physical activity interventions and major chronic diseases risk using observational data from the Health Professionals Follow-up Study and Nurses' Health Study (1986–2018)

Protocol component	Target trial specification	Target trial emulation
Eligibility criteria	No history of cancer, CVD, or T2D at baseline	Same as the target trial. We also require complete baseline data on physical activity, birth date, diet (missing FFQ items <70, plausible energy intake reported [800 to 4200 kcal/d in males; 500 to 3500 kcal/d in females]) and other risk factors.
Physical activity intervention	Each individual is assigned to one of the following strategies at baseline: • Limit physical activity to <7.5 MET-hours/week • Maintain ≥ 7.5 MET-hours/week of physical activity • Maintain ≥ 15 MET-hours/week of physical activity • Maintain ≥ 30 MET-hours/week of physical activity	Same as the target trial.
Strategy assignment	Individuals are randomly assigned to a strategy at baseline and are aware of their assigned strategy.	We assumed randomization conditional on the following baseline covariates: age, race, smoking history, overweight/obesity status, alcohol consumption, alternative healthy eating index-2010, regular aspirin use, regular NSAIDs use, multivitamin use, family history of diabetes mellitus, cardiovascular disease, or cancer; for females, also menopausal status and hormone use.
Outcome	Major chronic disease, defined as the first occurrence of T2D, major CVD (coronary heart disease and stroke), or	Same as the target trial.

Follow-up	total cancer (excluding nonmelanoma skin cancer and nonfatal prostate cancer). For each eligible individual, follow-up starts at strategy assignment (baseline) and ends upon loss to follow-up, death, the outcome of interest, or cutoff date, whichever happens first. Intention to treat analysis.	Same as the target trial. Loss to follow-up was defined as questionnaire nonresponse.
Statistical analysis	Per protocol analysis: Parametric g-formula to compare 32-year risk under each strategy, with adjustment for pre- and postbaseline prognostic factors associated with adherence and loss to follow-up.	Same as the per-protocol analysis of the target trial.

Supplementary Fig. 1. Flow chart of study participants

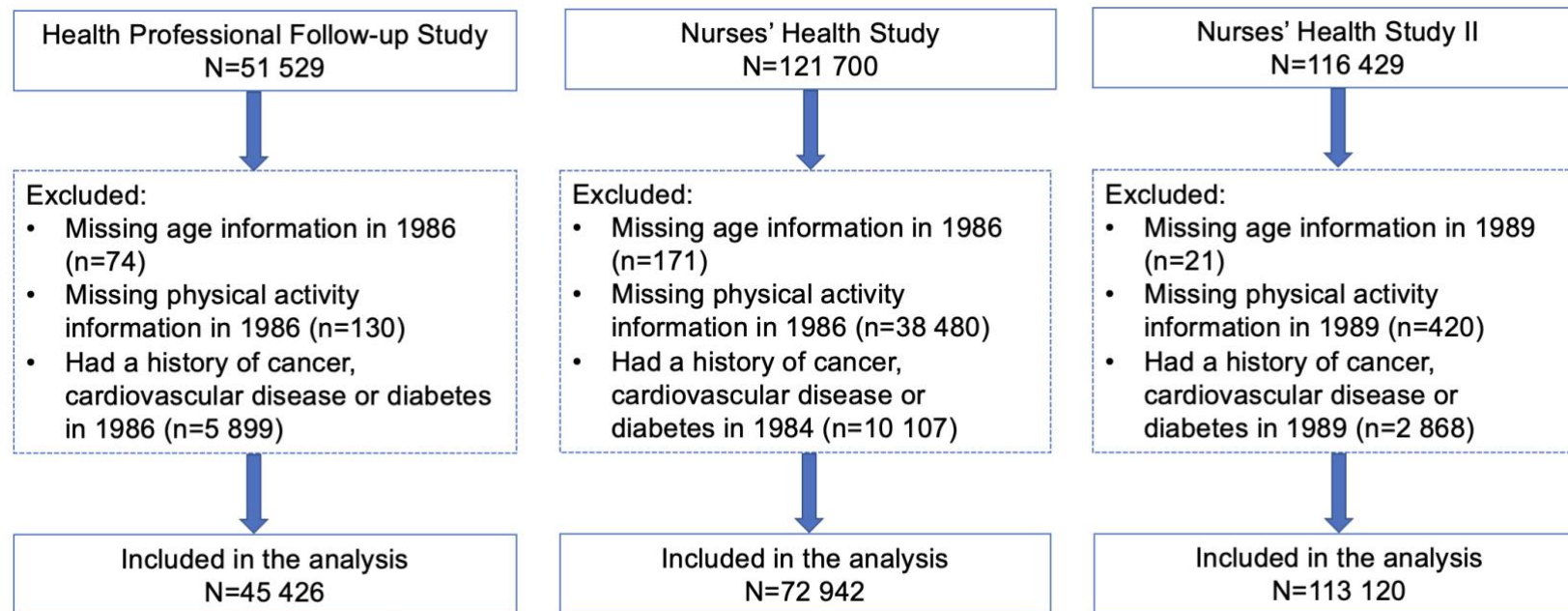
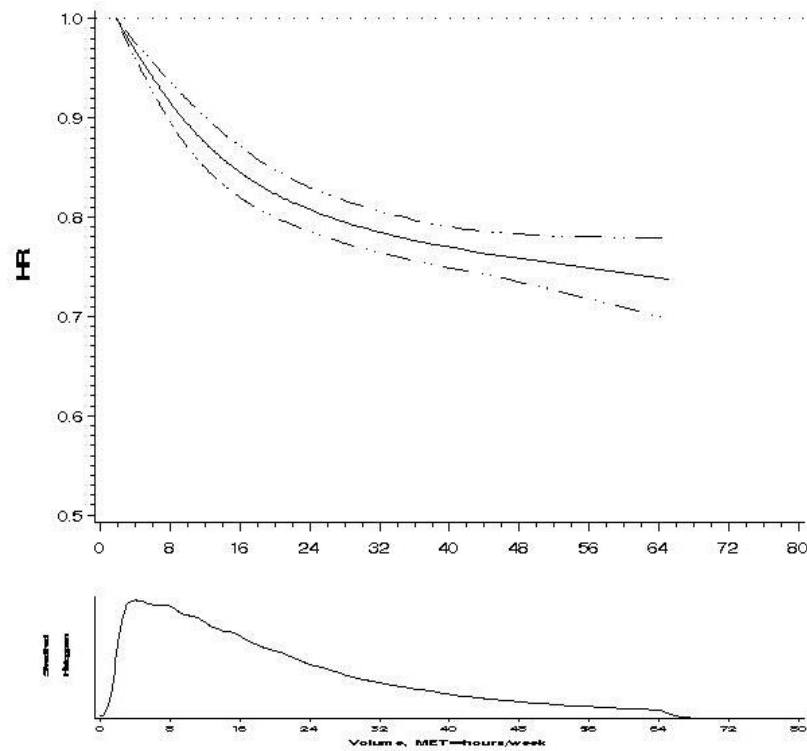


Figure legend:

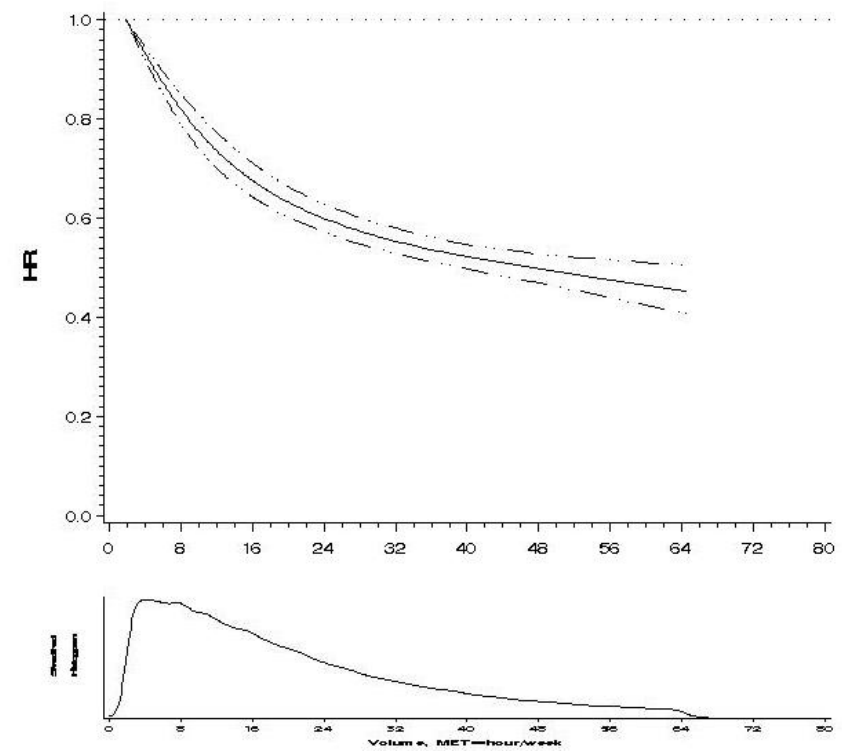
We drew data from three large prospective cohorts in the US: the Health Professional Follow-up Study (HPFS) began in 1986 and enrolled 51 529 male health professionals aged 40–75 years from all 50 states; the Nurses' Health Study (NHS) began in 1976 and included 121 700 female registered nurses aged 30–55 years from 11 states; the NHS II began in 1989 and enrolled 116 429 younger female registered nurses aged 25–42 years. Participants were excluded at baseline if they had reported a history of cancer, cardiovascular disease, or diabetes, or had missing data on age or physical activity. After exclusions, 45 426 males from the HPFS, 72 942 females from the NHS, and 113 120 females from the NHS II aged 25–75 years were included.

Supplementary Fig. 2. Restricted cubic spline analysis of cumulative average physical activity volume and major chronic diseases incidence

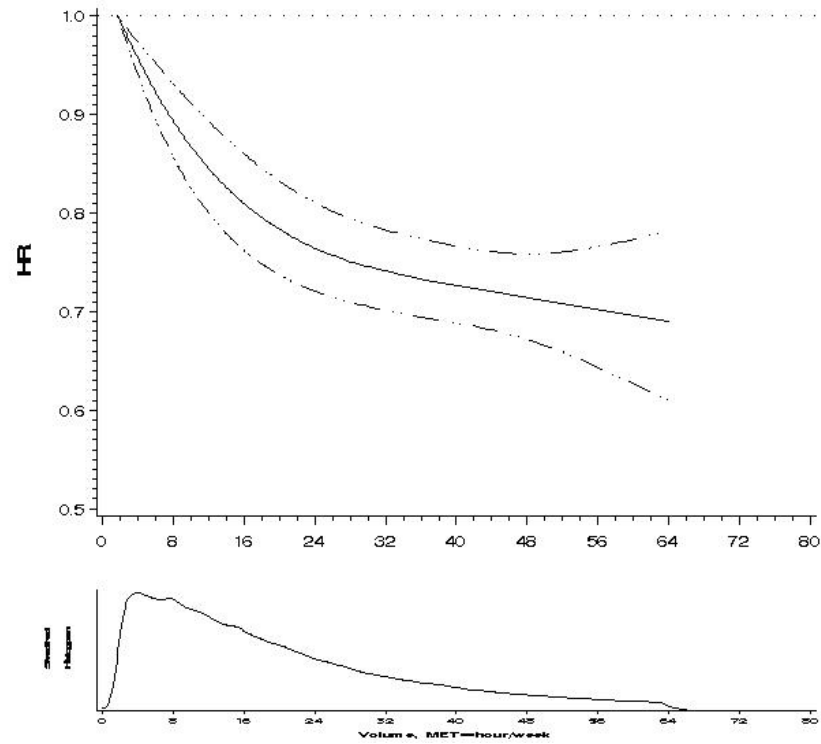
(A) Major chronic diseases, P for non-linearity <0.0001



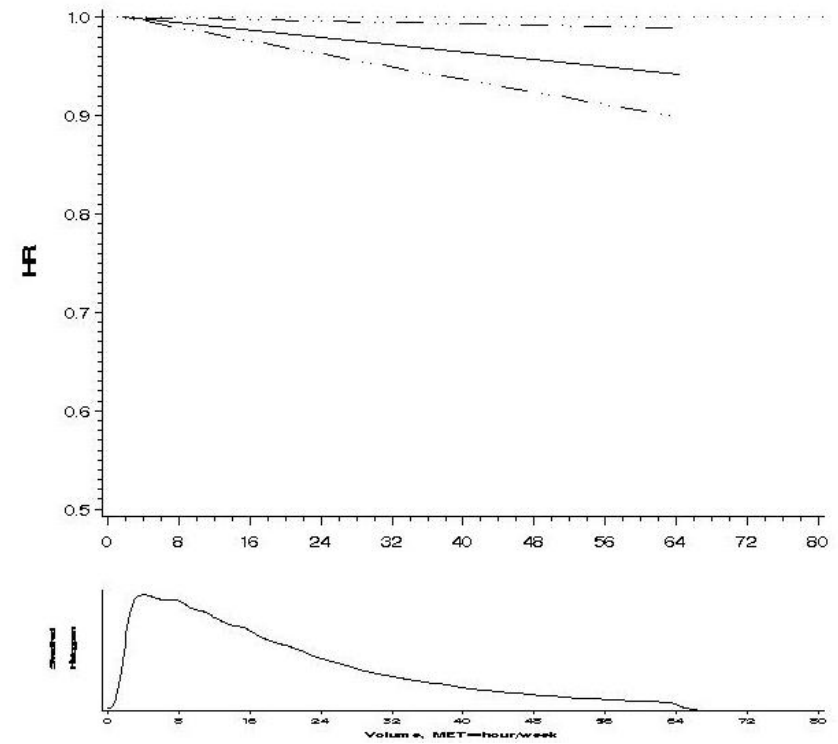
(B) Type 2 diabetes, P for non-linearity <0.0001



(C) Major cardiovascular disease, P for non-linearity <0.0001



(D) Cancer, P for non-linearity >0.99



(E) Obesity related cancer, P for non-linearity 0.04

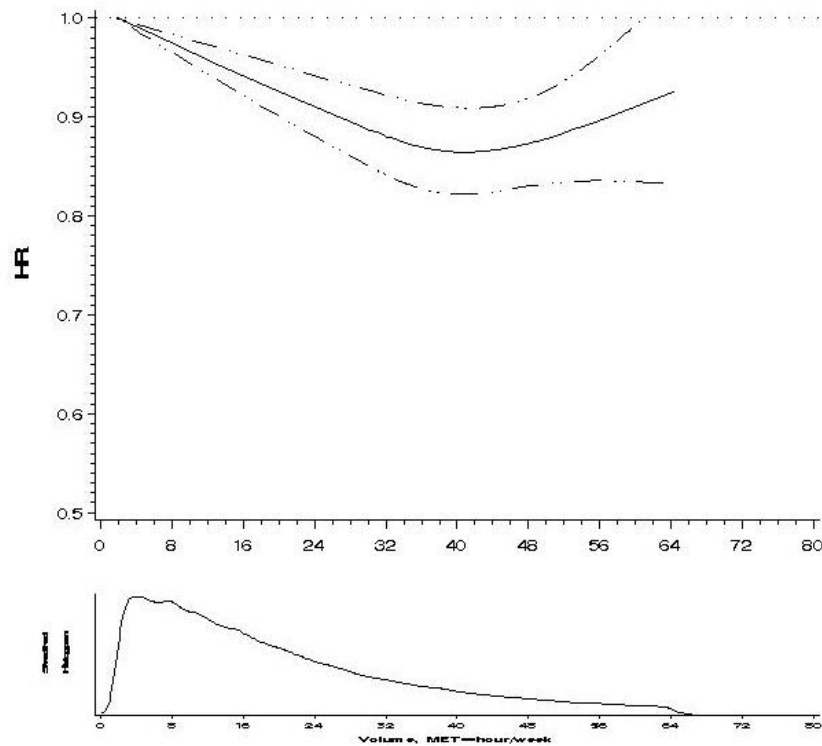


Figure legend:

Abbreviation: HR, hazard ratio; MET, metabolic equivalent of task

The number of person years (number of cases) for the analysis of major chronic diseases, type 2 diabetes, major cardiovascular disease, cancer, and obesity-related cancer were 6 071 473 (72 648), 5 851 466 (23 034), 6 408 042 (17 415), 6 470 624 (41 525), and 6 652 162 (21 290), respectively. Panels A, B, C, D, and E represent the results for major chronic diseases, type 2 diabetes, major cardiovascular disease, cancer, and obesity-related cancer, respectively.

We used Cox proportional hazards models stratified by age (months), questionnaire cycle (two-year interval), and cohort, and further adjusted for race, smoking status and packyears, alcohol consumption, Alternative Healthy Eating Index-2010, regular aspirin use, regular NSAIDs use, multivitamin use, family history of diabetes mellitus, cardiovascular disease, or cancer; for females, also menopausal status and hormone use.

The solid lines denote the hazard ratios, and the dotted lines denote 95% confidence intervals derived using two-sided Wald tests. P values for non-linearity were derived using two-sided likelihood ratio tests, comparing the model with only the linear term to the model with the linear and the cubic spline terms. P values smaller than 0.05 indicate a non-linear relationship.

Supplementary Fig. 3. Trend of physical activity volume throughout adulthood

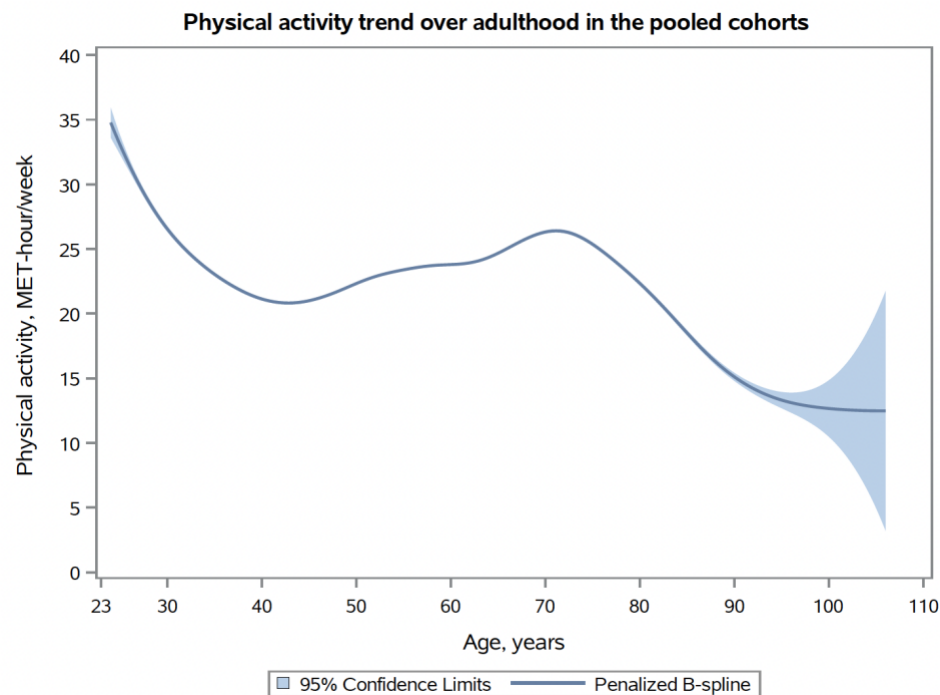


Figure legend:

Abbreviation: MET, metabolic equivalent of task

45 426 males from the HPFS, 72 942 females from the NHS, and 113 120 females from the NHS II were included. The curve represents the predicted mean physical activity volume (MET-hours/week) as a function of age, estimated using a penalized B-spline smoothing function (PBSPLINE) in SAS PROC SGPLOT. Shaded bands denote 95% confidence intervals for the mean, derived using two-sided Wald tests.

Supplementary Fig. 4. Flow chart of study participants in the trajectory analysis of physical activity from ages 40 to 60

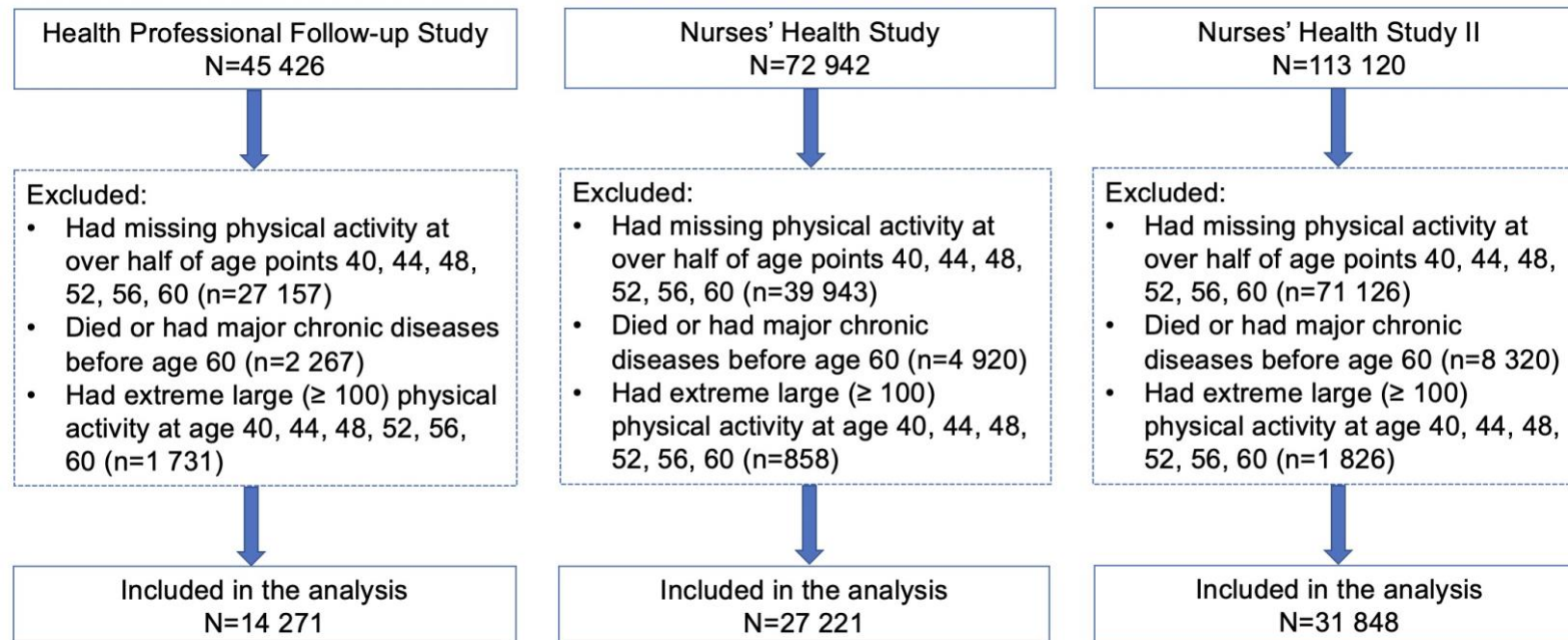
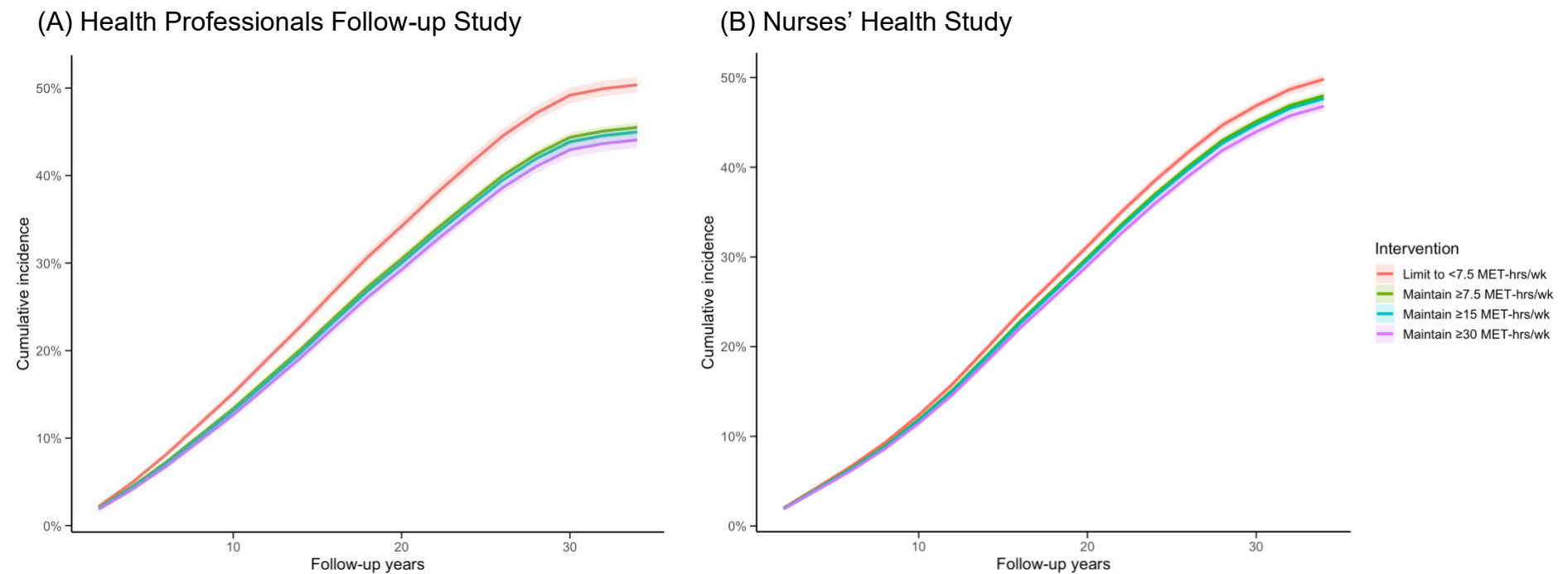


Figure legend:

We included participants who provided physical activity data for at least three different time points out of age 40, 44, 48, 52, 56, and 60, and excluded those who died or had major chronic diseases before age 60 or had extremely large physical activity over 100 MET-hours/week (95 percentile) at any of those age points. A total of 14 271 males from the HPFS, 27 221 females from the NHS, and 31 848 females from the NHS II were included in the trajectory analysis.

Supplementary Fig. 5. Estimated 32-year risk of major chronic diseases under physical activity interventions in the Health Professionals Follow-up Study and Nurses' Health Study (1986-2018)



Intervention strategy	32-year risk, %	
	HPFS	NHS
Limit to < 7.5 MET-hours/week	50.3 (49.5, 51.3)	49.3 (48.5, 50.2)
Maintain ≥ 7.5 MET-hours/week	45.4 (44.7, 46.1)	46.9 (46.3, 47.5)

Maintain $\geq$ 15 MET-hours/week	45.0 (44.1, 45.6)	46.5 (45.7, 47.2)
Maintain $\geq$ 30 MET-hours/week	44.0 (43.1, 44.8)	45.7 (44.9, 46.5)

Figure legend:

Abbreviation: MET, metabolic equivalent of task

The study population for target trial emulation consisted of 40 729 males from the HPFS and 67 768 females from the NHS who had no baseline history of cancer, cardiovascular disease, or diabetes, and had no missing data on physical activity or covariates at baseline. Panels A and B represent the results for the HPFS (males) and NHS (females), respectively.

Estimates were based on the parametric g-formula, adjusted for age, race, smoking packyears, alcohol consumption, body mass index, Alternative Healthy Eating Index-2010, regular aspirin use, regular NSAIDs use, multivitamin use, family history of diabetes mellitus, cardiovascular disease, or cancer; for females, also menopausal status and hormone use.

Shaded bands denote the 95% confidence intervals of major chronic diseases incidence. A nonparametric bootstrapping procedure with 200 iterations was used to calculate percentile-based 95% confidence intervals for all estimates.