Preplanned Studies

Physical Activity and Different Recommendations Associated with the Dynamic Trajectory of Cardiometabolic Diseases — UK, 2006–2021

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Summary

What is already known about this topic?

Previous studies have illustrated the benefits of physical activity on cardiometabolic multimorbidity (CMM), while limited studies have concentrated on the trajectory of CMM progression.

What is added by this report?

Through multi-stage regression analysis, we found that physical activity could reduce the risk of CMM incidence. Participants initially free of cardiometabolic diseases (CMDs) may benefit more from engaging in recommended physical activity.

What are the implications for public health practice?

Adults, especially those initially free of CMDs, should engage in WHO-recommended physical activity as early as possible to prevent CMD incidence and further progression.

While many studies have investigated the associations between physical activity and cardiometabolic diseases (CMDs), evidence remains scarce regarding the relationship between physical activity and different stages of cardiometabolic multimorbidity (CMM) progression. Using data from the United Kingdom (UK) Biobank study from 2006 to 2021, we adopted traditional Cox proportional hazard regression models and multi-state regression models to examine the associations between physical activity and CMM progression (Supplementary Figure S1, available in http://weekly.chinacdc.cn/). CMD was defined as any of the following three diseases, including ischemic heart disease (IHD) (I20 to I25), stroke (I60 to I64), and type 2 diabetes (T2D), (E11, and E14), which were determined via the International Classification of Diseases (10th Revision) (*1*). Incidence of the first CMD (FCMD) was identified as the earliest occurrence of any of these three diseases (IHD, stroke, and T2D), and incident of CMM was defined as the subsequent occurrence of any of the remaining CMDs. Inverse associations were observed between physical activity and almost all phases of CMM progression, albeit to different extents. The associations were stronger in transitions from baseline to FCMD [hazard ratio (HR): 0.880, 95% confidence intervals (*CI*): 0.853, 0.908 and HR: 0.892, 95% *CI*: 0.864, 0.920 for moderate and high physical activity levels]. Adults, especially those free of CMDs, showed the most conspicuous health benefits when meeting the World Health Organization (WHO) Guidelines.

UK Biobank (UKB), an ongoing cohort study, recruited over half a million participants across the UK between 2006 and 2010. Data from the UK Biobank are available upon reasonable request (https://www.ukbiobank.ac.uk/). The study was approved by the Northwest Multi-Centre Research Ethics Committee (06/MRE08/65). Informed consent was obtained, and detailed information on the study protocols has been described elsewhere (*2*). All participants were followed up from recruitment to study until they were deceased, lost of subsequent follow-up from the health record, or March 31, 2021, whichever came first. A group of potential confounders were selected as presented in Table 1, and 307,411 participants were included in the final analysis (Supplementary Figure S2, available in http://weekly.chinacdc.cn/).

Self-reported physical activity was categorized as low, moderate, and high levels according to widely-used criteria of the International Physical Activity Questionnaire (IPAQ). This criterion corresponds to <150 minutes/week, 150–750 minutes/week, and ≥ 750 minutes per week of moderate-intensity physical activity. The cut-off value of 600 MET-min/week is set by the WHO physical activity recommendations (*3*). Considering the more physically active cohort, four recommendations (Guideline Low, 2017 Physical Activity Guidelines, Guideline 300, and Guideline 450) were further defined to examine whether participants would harvest more benefits if they take

higher-level physical activity (details of definitions of physical activity seen in Supplementary Methods, available in http://weekly.chinacdc.cn/) (*4*).

Two incrementally adjusted Cox proportional hazard regression models were constructed to examine the associations between physical activity, FCMD, CMM, and all-cause death. The model plotted the data against follow-up time. Multi-state regression models (*5*) were used to assess the relationships between physical activity and the different phases of CMM progression, resulting in 5 transitions in trajectory pattern A (Supplementary Figure S1). Considering participants might enter the stages of FCMD/CMM or all-cause death simultaneously, we determined the entering date of the theoretically prior stage as the entering date of the theoretically latter stage minus 0.5 days (*1*). Several sensitivity analyses were conducted to examine the robustness of our results (Supplementary Methods) (*6*).

All statistical analyses were conducted using R software (version 3.3.2, R Foundation for Statistical Computing, Vienna, Austria). A two-sided *P* value of <0.05 was considered statistically significant.

A total of 307,411 participants with an average age of 55.46 [standard deviation (SD): 8.09] years at baseline were included (Table 1). During a mean follow-up of 11.92 years, 29,373 (9.56%) participants developed at least one CMD (3.67% were self-reported cases); among them, 7.13% developed CMM later, and 22.67% died from CMM eventually (Supplementary Figure S1).

In traditional Cox regression analysis, higher physical activity levels were associated with lower FCMD, CMM, and all-cause mortality incidence (Table 2). For moderate physical activity level, the fully adjusted HRs [95% confidence intervals (*CI*)] relative to low physical activity level were 0.880 (0.853, 0.908) for FCDM, 0.840 (0.749, 0.942) for CMM, and

TABLE 1. Baseline characteristics of the participants by incident disease status during follow-up*.

Levels	Total	FCMD survivor	CMM survivor	Death with FCMD	Death with CMM†	Death without CMD†	Non-cases
Number of participants	307,411	23,273	1,620	4,005	475	9,772	268,266
Age at recruitment (years)	55.46 (8.09)	58.60 (7.34)	59.92 (6.85)	61.48 (6.46)	63.08 (5.49)	60.46 (6.89)	54.87 (8.05)
Years of follow-up	11.92 (1.47)	12.18 (0.83)	12.22 (0.81)	8.16 (3.19)	9.45 (2.54)	7.57 (3.26)	12.12 (0.94)
Sex							
Female	164,962 (53.66)	9,247 (39.73)	568 (35.06)	1,312 (32.76)	140 (29.47)	4,341 (44.42)	149,354 (55.67)
Male	142,449 (46.34)	14,026 (60.27)	1,052 (64.94)	2,693 (67.24)	335 (70.53)	5,431 (55.58)	118,912 (44.33)
Ethnicity							
White	292,433 (95.13)	21,980 (94.44)	1,494 (92.22)	3,880 (96.88)	451 (94.95)	9,512 (97.34)	255,116 (95.10)
Non-white	14,173 (4.61)	1,221 (5.25)	119 (7.35)	114 (2.85)	24 (5.05)	230 (2.35)	12,465 (4.65)
Unknown	805 (0.26)	72 (0.31)	7 (0.43)	11 (0.27)	0 (0.00)	30 (0.31)	685 (0.26)
BMI, kg/m^2							
Normal	106,760 (34.73)	4,939 (21.22)	200 (12.35)	1,006 (25.12)	84 (17.68)	3,142 (32.15)	97,389 (36.30)
Underweight	1,512 (0.49)	67 (0.29)	2 (0.12)	29 (0.72)	3 (0.63)	100 (1.02)	1,311 (0.49)
Overweight	134,015 (43.59)	10,389 (44.64)	688 (42.47)	1,838 (45.89)	207 (43.58)	4,255 (43.54)	116,638 (43.48)
Obese	65,124 (21.18)	7,878 (33.85)	730 (45.06)	1,132 (28.26)	181 (38.11)	2,275 (23.28)	52,928 (19.73)
Education							
Higher degree	159,486 (51.88)	1,0492 (45.08)	615 (37.96)	1,632 (40.75)	147 (30.95)	4,338 (44.39)	142,262 (53.03)
School degree	91,542 (29.78)	6,367 (27.36)	449 (27.72)	1,018 (25.42)	114 (24.00)	2,551 (26.11)	81,043 (30.21)
Vocational degree	17,332 (5.64)	1,818 (7.81)	122 (7.53)	306 (7.64)	41 (8.63)	713 (7.30)	14,332 (5.34)
Other	39,051 (12.70)	4,596 (19.75)	434 (26.79)	1,049 (26.19)	173 (36.42)	2,170 (22.21)	30,629 (11.42)
Employment							
Paid	195,130 (63.48)	12,180 (52.34)	735 (45.37)	1,453 (36.28)	137 (28.84)	4,012 (41.06)	176,613 (65.84)
Retired	23,384 (7.61)	1,906 (8.19)	189 (11.67)	383 (9.56)	56 (11.79)	888 (9.09)	19,962 (7.44)
Unpaid	88,897 (28.92)	9,187 (39.47)	696 (42.96)	2,169 (54.16)	282 (59.37)	4,872 (49.86)	71,691 (26.72)

TABLE 1. (Continued)

Levels	Total	FCMD survivor	CMM survivor	Death with FCMD	Death with CMM†	Death without CMD†	Non-cases
Smoking status							
Never	174,910 (56.90)	11,544 (49.60)	722 (44.57)	1,616 (40.35)	152 (32.00)	4,258 (43.57)	156,618 (58.38)
Previous	102,212 (33.25)	8,837 (37.97)	655 (40.43)	1,564 (39.05)	217 (45.68)	3,770 (38.58)	87,169 (32.49)
Current	30,289 (9.85)	2,892 (12.43)	243 (15.00)	825 (20.60)	106 (22.32)	1,744 (17.85)	24,479 (9.12)
Alcohol intake							
Never	20,073 (6.53)	1,951 (8.38)	173 (10.68)	350 (8.74)	52 (10.95)	789 (8.07)	16,758 (6.25)
Occasional	64,093 (20.85)	5,252 (22.57)	423 (26.11)	805 (20.10)	100 (21.05)	1,977 (20.23)	55,536 (20.70)
Moderate	156,506 (50.91)	11,025 (47.37)	686 (42.35)	1,781 (44.47)	209 (44.00)	4,416 (45.19)	138,389 (51.59)
Heavy	66,739 (21.71)	5,045 (21.68)	338 (20.86)	1,069 (26.69)	114 (24.00)	2,590 (26.50)	57,583 (21.46)
Household income							
Low	50,701 (16.49)	5,241 (22.52)	452 (27.90)	1,311 (32.73)	185 (38.95)	2,688 (27.51)	40,824 (15.22)
Moderate	207,405 (67.47)	14,522 (62.40)	915 (56.48)	2,118 (52.88)	214 (45.05)	5,592 (57.22)	184,044 (68.61)
High	18,066 (5.88)	869 (3.73)	31 (1.91)	108 (2.70)	8 (1.68)	293 (3.00)	16,757 (6.25)
Unknown	31,239 (10.16)	2,641 (11.35)	222 (13.70)	468 (11.69)	68 (14.32)	1,199 (12.27)	26,641 (9.93)
Fruit & vegetable intake							
Low	87,443 (28.44)	7,193 (30.91)	490 (30.25)	1,356 (33.86)	151 (31.79)	3,011 (30.81)	75,242 (28.05)
Moderate	156,342 (50.86)	11,360 (48.81)	791 (48.83)	1,859 (46.42)	227 (47.79)	4,807 (49.19)	137,298 (51.18)
High	63,626 (20.70)	4,720 (20.28)	339 (20.93)	790 (19.73)	97 (20.42)	1,954 (20.00)	55,726 (20.77)
Family history of CMM							
No	240,798 (78.33)	16,832 (72.32)	1,089 (67.22)	3,076 (76.80)	344 (72.42)	7,780 (79.62)	211,677 (78.91)
Yes	66,613 (21.67)	6,441 (27.68)	531 (32.78)	929 (23.20)	131 (27.58)	1,992 (20.38)	56,589 (21.09)
Physical activity level							
Low	55,116 (17.93)	4,721 (20.29)	360 (22.22)	841 (21.00)	108 (22.74)	1,920 (19.65)	47,166 (17.58)
Moderate	125,837 (40.93)	9,148 (39.31)	630 (38.89)	1,561 (38.98)	179 (37.68)	4,049 (41.43)	110,270 (41.10)
High	126,458 (41.14)	9,404 (40.41)	630 (38.89)	1,603 (40.02)	188 (39.58)	3,803 (38.92)	110,830 (41.31)
Meeting the 2017 physical activity guidelines§							
No	54,427 (17.70)	4,518 (19.41)	328 (20.25)	797 (19.90)	100 (21.05)	1,800 (18.42)	46,884 (17.48)
Yes	252,984 (82.30)	18,755 (80.59)	1,292 (79.75)	3,208 (80.10)	375 (78.95)	7,972 (81.58)	221,382 (82.52)
Meeting the WHO guidelines§							
No	54,590 (17.76)	4,651 (19.98)	343 (21.17)	821 (20.50)	105 (22.11)	1,908 (19.53)	46,762 (17.43)
Yes	252,821 (82.24)	18,622 (80.02)	1,277 (78.83)	3,184 (79.50)	370 (77.89)	7,864 (80.47)	221,504 (82.57)

Abbreviation: BMI=Body mass index; CMD=Cardiometabolic diseases; FCMD=First cardiometabolic disease; CMM=Cardiometabolic multimorbidity; 2017 Physical Activity Guidelines=the 2017 UK Physical Activity Guidelines; IHD=Ischemic heart disease; T2D=Type 2 diabetes.

* Results are presented as mean (standard deviation) for continuous variables or number (percentage) for categorical variables.

† CMD include IHD, stroke, and T2D. CMM is defined as the co-occurrence of two or more diseases mentioned above.

§ Meeting the 2017 Physical Activity Guidelines means participants take 150 minutes of walking or moderate-intensity activity, 75 minutes of vigorous-intensity activity per week. WHO Guidelines mean participants take 150 minutes of moderate-intensity physical activity, 75 minutes of vigorous-intensity physical activity, or an equivalent combination of moderate- and vigorous-intensity physical activity.

0.872 (0.833, 0.912) for all-cause mortality, respectively.

Multi-state regression analyses generated similar results regarding the results yielded by traditional Cox regression models (Table 3). The inverse associations were found between physical activity and almost all transitions in CMM progression, as the HRs (95% *CIs*) of transition from baseline to death were 0.886 (0.838, 0.936) and 0.815 (0.771, 0.862) for moderate and high level of physical activity. Meeting the WHO Guidelines showed the most conspicuous benefits among all five transitions (Supplementary Table S2,

TABLE 2. Associations between physical activity and FCMD, CMM, and all-cause death among 307,411 participants in the UK Biobank.

Outcomes*	Physical activity	No. of cases (total number)	Model 1†		Model 2†	
			HR (95% *CI*)	*P*	HR (95% *CI*)	*P*
FCMD	Physical activity level					
	Low	6,030 (55,116)	1.000	–	1.000	–
	Moderate	11,518 (125,837)	0.800 (0.775, 0.825)	<0.001	0.880 (0.853, 0.908)	<0.001
	High	11,825 (126,458)	0.798 (0.773, 0.823)	<0.001	0.890 (0.862, 0.919)	<0.001
	Meeting the 2017 PA guidelines					
	No	5,743 (54,427)	1.000	–	1.000	–
	Yes	23,630 (252,984)	0.826 (0.803, 0.851)	<0.001	0.906 (0.880, 0.933)	<0.001
	Meeting the WHO guidelines§					
	No	5,920 (54,590)	1.000	–	1.000	–
	Yes	23,453 (252,821)	0.805 (0.783, 0.829)	<0.001	0.895 (0.869, 0.921)	<0.001
CMM	Physical activity level					
	Low	468 (55,116)	1.000	–	1.000	–
	Moderate	809 (125,837)	0.718 (0.641, 0.805)	<0.001	0.840 (0.749, 0.942)	<0.001
	High	818 (126,458)	0.702 (0.627, 0.787)	<0.001	0.824 (0.734, 0.926)	<0.001
	Meeting the 2017 PA guidelines					
	No	428 (54,427)	1.000	–	1.000	–
	Yes	1,667 (252,984)	0.770 (0.692, 0.856)	<0.001	0.887 (0.796, 0.988)	0.029
	Meeting the WHO guidelines§					
	No	448 (54,590)	1.000	–	1.000	–
	Yes	1,647 (252,821)	0.738 (0.665, 0.819)	<0.001	0.869 (0.781, 0.966)	0.009
All-cause death	Physical activity level					
	Low	2,869 (55,116)	1.000	–	1.000	–
	Moderate	5,789 (125,837)	0.825 (0.789, 0.863)	<0.001	0.872 (0.833, 0.912)	<0.001
	High	5,594 (126,458)	0.782 (0.747, 0.818)	<0.001	0.819 (0.782, 0.857)	<0.001
	Meeting the 2017 PA guidelines					
	No	2,697 (54,427)	1.000	–	1.000	–
	Yes	11,555 (252,984)	0.974 (0.958, 0.990)	0.002	0.961 (0.945, 0.977)	<0.001
	Meeting the WHO guidelines§					
	No	2,834 (54,590)	1.000	–	1.000	–
	Yes	11,418 (252,821)	0.803 (0.771, 0.837)	<0.001	0.851 (0.816, 0.887)	<0.001

Note: "–" means not applicable.
Abbreviation: FCMD=First cardiometabolic disease; CMM=Cardiometabolic multimorbidity; CMD=Cardiometabolic diseases; PA=Physical activity; No.=Number; HR=Hazard ratio; *CI*=Confidence interval; IHD=Ischemic heart disease; T2D=Type 2 diabetes.
* CMD include IHD, stroke, and T2D. CMM is defined as the co-occurrence of two or more diseases mentioned above.
† Model 1 was adjusted for age (per 5-year interval), sex, and ethnicity; Model 2 was further adjusted for body mass index, total household income, employment, education, smoking status, alcohol intake, fruit and vegetable intake, and family history of CMM. All results were calculated by the traditional Cox proportional hazard regression models.
§ Meeting the 2017 Physical Activity Guidelines means participants take 150 minutes of walking or moderate-intensity activity or 75 minutes of vigorous-intensity activity per week. WHO Guidelines means participants take 150 minutes of moderate-intensity physical activity, 75 minutes of vigorous-intensity physical activity, or an equivalent combination of moderate- and vigorous-intensity physical activity.

available in http://weekly.chinacdc.cn/). All our findings remained substantially stable after conducting several sensitivity analyses (Supplementary Tables S2–S3, available in http://weekly.chinacdc.cn/).

DISCUSSION

Our study investigated the impact of physical activity levels and recommendations on different

TABLE 3. Associations between 5 transitions of CMM progression and physical activity levels among 307,411 participants in the UK Biobank.

Transition*	Physical activity level	No. of cases (total number)	HR (95% *CI*)†	*P*
Baseline → FCMD	Low	6,030 (55,116)	1.000	
	Moderate	11,518 (125,837)	0.880 (0.853, 0.908)	<0.001
	High	11,825 (126,458)	0.892 (0.864, 0.920)	<0.001
Baseline → Death	Low	1,920 (55,116)	1.000	
	Moderate	4,049 (125,837)	0.886 (0.838, 0.936)	<0.001
	High	3,803 (126,458)	0.815 (0.771, 0.862)	<0.001
FCMD → CMM	Low	468 (6,030)	1.000	
	Moderate	809 (11,518)	0.951 (0.848, 1.068)	0.398
	High	818 (11,825)	0.942 (0.838, 1.059)	0.315
FCMD → Death	Low	841 (6,030)	1.000	
	Moderate	1,561 (11,518)	0.908 (0.834, 0.988)	0.026
	High	1,603 (11,825)	0.916 (0.841, 0.998)	0.045
CMM → Death	Low	108 (468)	1.000	
	Moderate	179 (809)	0.882 (0.690, 1.127)	0.314
	High	188 (818)	1.009 (0.790, 1.288)	0.943

Abbreviation: FCMD=First cardiometabolic disease; CMM=Cardiometabolic multimorbidity; HR=Hazard ratio; *CI*=Confidence interval; IHD=Ischemic heart disease; T2D=Type 2 diabetes; BMI=Body mass index.

* CMD include IHD, stroke, and T2D. CMM is defined as co-occurrence of two or more diseases mentioned above. Trajectory pattern A consists of 5 transitions, including transitions from baseline to FCMD and all-cause death, transitions from FCMD to CMM and all-cause death, and to transition from CMM to all-cause death.

† Multivariable models were adjusted by age at recruitment (5-year interval) to sex, ethnicity, BMI, total household income, employment, education, smoking status, alcohol intake, fruit and vegetable intake, and family history of CMM.

trajectories of CMM progression. The results of both traditional Cox regression and multi-state regression analyses yielded the inverse associations between physical activity and CMD incidence and further progression, albeit to different degrees. More substantial impacts of physical activity were found on transitions from baseline to FCMD and all-cause death. The WHO Guidelines seemed to possess more pronounced health benefits than the other four recommendations.

In traditional Cox regression analyses, increasing physical activity levels were associated with lower FCMD, CMM, and death incidence. A stronger association was found in transition from the baseline to CMM. The findings differed from previous studies reporting a more beneficial role physical activity played in the transition from the baseline to single CMD than CMM (*7*). The heterogeneity might be due to multiple factors, albeit largely unclear. First, CMM incidence in traditional Cox regression models consisted of several transitions in multi-state regression models. Different transitions might have reshaped the characteristics of the study population, consequently leading to different effect estimates. Second, as Albrecht et al. suggested (*8*), the disability paradox might largely influence the fundamental relationship between life quality and diseases. The influence of physical activity might thus be exaggerated as adults may be influenced to have higher levels of physical activity after being diagnosed with CMDs. Notably, such speculation seemed contradictory to the findings in multi-state regression models, where stronger associations were observed in the transition from the baseline to FCMD than in the transition from FCMD to CMM. Further studies are warranted to confirm our findings and to investigate the underlying mechanisms.

Inverse relationships between physical activity and almost all the transition incidences were observed in multi-state regression models, with stronger associations observed in transitions from baseline to FCMD/death. In contrast, a recent study of the China Kadoorie Biobank (CKB) found that physical inactivity significantly impacted the transition from FCMD to death/CMM (*1*). Foremost, the percentage of low physical activity levels was relatively more prominent in the CKB (about 50%) than UKB (about 20%) (*1*), indicating the Chinese adults were more physically inactive, albeit the CKB participants might

not represent the general Chinese population well. Physical activity has been well-confirmed to be associated with lower risks of numerous chronic diseases (*9*). The relatively low percentage of taking physical activity in China would therefore imply more significant health benefits if Chinese adults could take more physical activity. Furthermore, a higher prevalence of CMDs in CKB (19%) than in UKB (9.55%) indicated that the Chinese population was more sensitive to adverse health outcomes, such as CMM. Physical activity could play a more notable role in CMM progression in CKB than UKB, considering the more vulnerable group of Chinese adults. Therefore, Chinese policymakers should encourage adults to take physical activity actively to help lower the risks of CMM in the Chinese population.

Meeting the WHO Guidelines showed the most notable benefits on almost all transitions compared with other higher-level recommendations. It was different from the current physical activity recommendations suggesting that adults already with chronic diseases should take more physical activity. The difference could be interpreted by the fact that the health benefits of increasing physical activity tend to hit a plateau when adults have met the WHO Guidelines (*10*).

Several limitations should be noted. First, we only adopted information at baseline levels. Changes in physical activity and other covariates over the follow-up may influence the estimates. However, we further conducted an additional analysis in a sub-sample of participants (n=15,894), finding most participants (63%) maintained their physical activity level. The distribution of physical activity levels among participants with or without CMDs was similar (Supplementary Table S1), indicating the changes were non-differentially distributed, our results would not be substantially affected. Second, for those diagnosed with two or more CMDs on the same date, we determined the entering date as the entering date of the theoretically latter stage minus 0.5 days, which may lead to a biased estimate. However, considering the small proportion [1,304 (0.4%)] and robust results of sensitivity analyses (Supplementary Table S3), the bias may not influence the results substantially. Third, almost 20% of the population was excluded at baseline, which may cause selection bias inevitably. However, we compared baseline characteristics between included and excluded participants, finding that the distribution of baseline characteristics was comparable between the two groups (data not shown). Furthermore, we conducted a multivariate imputation, and no substantial changes in results were found (data not shown).

In summary, our study suggested that physical activity could reduce CMD incidence and further progression, albeit to different extents. Adults should engage in physical activity, meeting the WHO Guidelines as early as possible, especially those initially free of CMDs.

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SUPPLEMENTARY MATERIALS

Supplementary Methods

Changes in Physical Activity between Baseline and Resurvey

We calculated the difference in total physical activity level (measured based on the criteria of the short form of IPAQ) between the 2006–10 baseline and 2014+ resurvey (*1*). The number (proportion) of change in physical activity by cardiometabolic disease status at 2014+ resurvey was calculated.

Definitions of Different Physical Activity Recommendations

Guideline low means participants take at least 150 minutes of walking each week, but fail to meet the WHO Guidelines. 2017 Physical Activity Guidelines mean participants take 150 minutes of walking or moderate-intensity activity, or 75 minutes of vigorous-intensity activity per week, or an equivalent combination of these activities. The WHO Guidelines mean participants take 150 minutes of moderate-intensity physical activity, or 75 minutes of vigorous-intensity physical activity, or an equivalent combination of both intensities (*2*). Guideline 300 means participants take 300 minutes of moderate-intensity physical activity, or 150 minutes of vigorous-intensity physical activity, or an equivalent combination of both intensities. And Guideline 450 means participants take 450 minutes of moderate-intensity physical activity, or 225 minutes of vigorous-intensity physical activity, or an equivalent combination of both intensities.

Analytical Protocol

We constructed two incrementally-adjusted models: Model 1 was adjusted for age at recruitment, sex, and ethnicity; Model 2 was further adjusted for BMI, household income, employment status, education, lifestyle factors (smoking status, alcohol consumption, and fruit and vegetable intake), and family history of cardiometabolic multimorbidity (CMM). Several sensitivity analyses were performed for the multi-state analyses on the trajectory pattern A, including: 1) determining the entering date of theoretically prior stage with different time intervals (0.5 year, 1 year, and 1.5 years) for participants entering different disease stages on the same date; 2) excluding participants entering different stages on the same date; 3) excluding cardiometabolic disease (CMD) cases occurring in the first two years of follow-up; 4) further adjusting for the history of hypertension; 5) in addition to the predefined 5 transitions, adding another transition directly from the baseline to CMM. Considering the fact that we excluded a relatively large number of participants due to missing baseline covariates, we additionally conducted a multivariate imputation via chained equation (MICE) (the number of imputations was five) to make sure that the representativeness of the cohort was not substantially affected by exclusion of participants (data not shown) (*3*).

SUPPLEMENTARY TABLE S1. Changes in physical activity levels between 2006–2010 baseline and resurvey between 2014 and 2020 by cardiometabolic disease status among 15,894 participants.

Change in physical activity level[*†]	Overall	Free of CMD	FCMD/CMM
Total number	15,894	15,554	340
Upward	3,652 (22.98)	3,586 (23.06)	66 (19.41)
Downward	2,154 (13.55)	2,111 (13.57)	43 (12.65)
Stable	10,088 (63.47)	9,857 (63.37)	231 (67.94)

Abbreviation: FCMD=First cardiometabolic disease; CMM=Cardiometabolic multimorbidity; CMD=Cardiometabolic diseases.
Cardiometabolic diseases include ischemic heart disease (IHD), stroke, and type 2 diabetes (T2D). Cardiometabolic multimorbidity is defined as co-occurrence of two or more diseases mentioned above.
* Results are presented as number (percentage) for categorical variables.
† Changes in physical activity between baseline and resurvey were classified into stable (at the same level), upward (from low level to moderate/high level, or from moderate level to high level), and downward (from high level to moderate/low level, or from moderate level to low level). The number (proportion) of change in physical activity by cardiometabolic disease status at 2014+ resurvey was calculated.

SUPPLEMENTARY TABLE S2. Associations between different physical activity recommendations and 5 transitions of CMM progression.

5 transitions in trajectory pattern A[†]	Physical activity recommendations[*§]				
	Guideline low	2017 UK physical activity guideline	WHO guidelines	Guideline 300	Guideline 450
Baseline → FCMD	0.935 (0.904, 0.968)[¶]	0.907 (0.880, 0.934)[¶]	0.894 (0.868, 0.920)[¶]	0.933 (0.911, 0.955)[¶]	0.963 (0.940, 0.985)[¶]
Baseline → Death	0.946 (0.891, 1.004)	0.884 (0.839, 0.931)[¶]	0.849 (0.807, 0.893)[¶]	0.891 (0.855, 0.930)[¶]	0.880 (0.845, 0.916)[¶]
FCMD → CMM	0.982 (0.865, 1.116)	1.000 (0.897, 1.114)	0.986 (0.886, 1.097)	0.997 (0.911, 1.090)	1.039 (0.952, 1.134)
FCMD → Death	0.950 (0.867, 1.042)	0.925 (0.854, 1.001)	0.934 (0.863, 1.010)	0.923 (0.865, 0.985)[¶]	0.972 (0.913, 1.035)
CMM → Death	0.800 (0.611, 1.051)	0.914 (0.729, 1.148)	0.916 (0.732, 1.145)	0.982 (0.813, 1.186)	1.084 (0.903, 1.301)

Abbreviation: FCMD=First cardiometabolic disease; CMM=Cardiometabolic multimorbidity; HR=Hazard ratio; *CI*=Confidence interval; CMD=Cardiometabolic diseases; IHD=Ischemic heart disease; T2D=Type 2 diabetes; UK=United Kingdom; WHO=World Health Organization.
* Multivariable models were adjusted for age (per 5-year interval), sex, ethnicity, body mass index, total household income, employment, education, smoking status, alcohol intake, fruit and vegetables intake, and family history of CMM. Estimates were presented as HRs and their 95% *CI*s with the reference group of not meeting corresponding guidelines.
† CMD include IHD, stroke, and T2D. CMM is defined as co-occurrence of two or more diseases mentioned above. Five transitions in trajectory pattern A consist of transitions from baseline to FCMD and all-cause death, transitions from FCMD to CMM and all-cause death, and transition from CMM to all-cause death.
§ Guideline low means participants take at least 150 minutes of walking each week, but fail to meet WHO Guidelines. 2017 UK Physical Activity Guidelines mean participants meet its standards. WHO Guidelines mean participants take 150 minutes of moderate-intensity physical activity; or 75 minutes of vigorous-intensity physical activity; or an equivalent combination of moderate- and vigorous-intensity physical activity. Guideline 300 means participants take 300 minutes of moderate-intensity physical activity; or 150 minutes of vigorous-intensity physical activity; or an equivalent combination of moderate- and vigorous-intensity physical activity. And guideline 450 means participants take 450 minutes of moderate-intensity physical activity; or 225 minutes of vigorous-intensity physical activity; or an equivalent combination of moderate- and vigorous-intensity physical activity.
¶ The statistically significant differences (P<0.05).

SUPPLEMENTARY TABLE S3. Sensitivity analysis of the associations between physical activity levels and 5 phases of CMM trajectory among 307,411 participants in the UK Biobank.

Physical activity levels	Time interval	Different trajectory phases of CMM progression[†]					
		Baseline → FCMD	Baseline → Death	FCMD → CMM	FCMD → Death	CMM → Death	Baseline → CMM
Low level	–	1.000	1.000	1.000	1.000	1.000	1.000
Moderate level	**Different time intervals**						
	0.5 days	0.880 (0.853, 0.908)[§]	0.886 (0.838, 0.936)[§]	0.951 (0.848, 1.068)[§]	0.908 (0.834, 0.988)[§]	0.882 (0.690, 1.127)[§]	–
	0.5 years	0.880 (0.852, 0.908)[§]	0.886 (0.838, 0.936)[§]	0.967 (0.861, 1.086)[§]	0.900 (0.827, 0.980)[§]	0.948 (0.736, 1.220)[§]	–
	1 year	0.880 (0.853, 0.908)[§]	0.886 (0.838, 0.936)[§]	0.967 (0.861, 1.086)[§]	0.900 (0.827, 0.980)[§]	0.948 (0.736, 1.220)[§]	–
	3 years	0.880 (0.853, 0.908)[§]	0.886 (0.838, 0.936)[§]	0.967 (0.861, 1.086)[§]	0.900 (0.827, 0.980)[§]	0.948 (0.736, 1.220)[§]	–
	5 years	0.880 (0.853, 0.908)[§]	0.886 (0.838, 0.936)[§]	0.967 (0.861, 1.086)[§]	0.900 (0.827, 0.980)[§]	0.948 (0.736, 1.220)[§]	–
	Excluding participants who entered different stages on the same date						
	–	0.879 (0.851, 0.908)[§]	0.886 (0.839, 0.936)[§]	0.953 (0.847, 1.073)	0.868 (0.786, 0.960)[§]	0.863 (0.655, 1.135)	–
	Additionally adjusted for whether having the history of hypertension						
	–	0.878 (0.851, 0.906)[§]	0.885 (0.838, 0.935)[§]	0.949 (0.845, 1.065)	0.908 (0.834, 0.989)[§]	0.881 (0.689, 1.128)	–
	Excluding events occurred in the first two-year of follow-up						
	–	0.878 (0.850, 0.908)[§]	0.896 (0.847, 0.949)[§]	1.039 (0.892, 1.212)	0.857 (0.732, 1.004)	0.712 (0.457, 1.110)	–
	Adding a transition from free of CMD to CMM directly						
	–	0.881 (0.853, 0.909)[§]	0.742 (0.604, 0.911)[§]	0.886 (0.839, 0.936)[§]	0.957 (0.853, 1.073)	0.908 (0.834, 0.988)[§]	0.946 (0.759, 1.179)
High level	**Different time intervals**						
	0.5 days	0.892 (0.864, 0.920)[§]	0.815 (0.771, 0.862)[§]	0.942 (0.838, 1.059)[§]	0.916 (0.841, 0.998)[§]	1.009 (0.790, 1.288)[§]	–
	0.5 years	0.892 (0.864, 0.920)[§]	0.815 (0.771, 0.862)[§]	0.950 (0.844, 1.069)[§]	0.910 (0.835, 0.991)[§]	1.046 (0.812, 1.346)[§]	–
	1 year	0.892 (0.864, 0.92)[§]	0.815 (0.771, 0.862)[§]	0.950 (0.844, 1.069)[§]	0.910 (0.835, 0.991)[§]	1.046 (0.812, 1.346)[§]	–
	3 years	0.892 (0.864, 0.920)[§]	0.815 (0.771, 0.862)[§]	0.950 (0.844, 1.069)[§]	0.910 (0.835, 0.991)[§]	1.046 (0.812, 1.346)[§]	–
	5 years	0.892 (0.864, 0.920)[§]	0.815 (0.771, 0.862)[§]	0.950 (0.844, 1.069)[§]	0.910 (0.835, 0.991)[§]	1.046 (0.812, 1.346)[§]	–
	Excluding participants who entered different stages on the same date						
	–	0.889 (0.861, 0.918)[§]	0.815 (0.771, 0.863)[§]	0.925 (0.820, 1.042)	0.854 (0.772, 0.946)[§]	0.899 (0.680, 1.187)	–
	Additionally adjusted for whether having the history of hypertension						
	–	0.891 (0.863, 0.92)[§]	0.815 (0.770, 0.862)[§]	0.942 (0.838, 1.058)	0.916 (0.841, 0.998)[§]	1.008 (0.789, 1.289)	–
	Excluding events occurred in the first two-year of follow-up						
	–	0.898 (0.868, 0.928)[§]	0.836 (0.789, 0.886)[§]	0.934 (0.798, 1.094)	0.819 (0.697, 0.962)[§]	0.657 (0.413, 1.045)	–
	Adding a transition from free of CMD to CMM directly						
	–	0.892 (0.865, 0.921)[§]	0.704 (0.571, 0.869)[§]	0.816 (0.771, 0.863)[§]	0.947 (0.843, 1.064)	0.916 (0.841, 0.998)[§]	1.044 (0.835, 1.304)

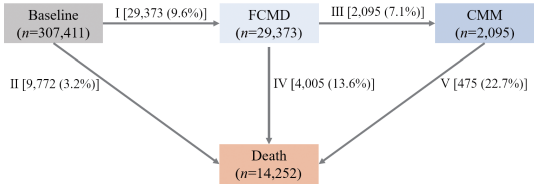
Note: "–" means not applicable.

Abbreviation: FCMD=First cardiometabolic disease; CMM=Cardiometabolic multimorbidity; CMD=Cardiometabolic diseases; *CI*=Confidence interval; HR=Hazard ratio; IHD=Ischemic heart disease; T2D=Type 2 diabetes; UK=United Kingdom.

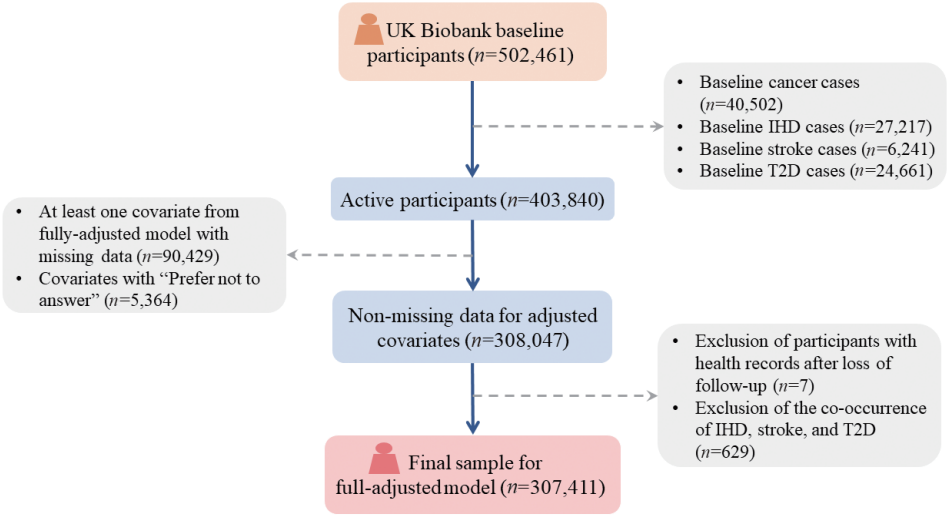
* Multivariable models were adjusted for age (per 5-year interval), sex, ethnicity, body mass index, total household income, employment, education, smoking status, alcohol intake, fruit and vegetables intake, and family history of CMM. Estimates were presented as HRs and their 95% *CI*s.

[†] CMD include IHD, stroke, and T2D. Cardiometabolic multimorbidity is defined as co-occurrence of two or more diseases mentioned above.

[§] The statistically significant differences ($P<0.05$).



SUPPLEMENTARY FIGURE S1. Numbers (percentages) of participants in trajectory pattern A from baseline to the first cardiometabolic diseases (FCMD) to cardiometabolic multimorbidity (CMM), and to death.
Note: FCMD was identified as the earliest occurrence of any of these three diseases (ischemic heart disease, stroke, and type 2 diabetes). CMM is defined as subsequent occurrence of any of the remaining CMDs.
Abbreviation: FCMD=First cardiometabolic disease; CMD=Cardiometabolic diseases.



SUPPLEMENTARY FIGURE S2. Flowchart of selection of participants.
Abbreviation: IHD=Ischemic heart disease; T2D=Type 2 disease.

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