R1 Leisure-time Physical Activity and Life Expectancy in people with Cardiometabolic Multimorbidity and Depression

Running title: Physical activity and survival in UK Biobank participants

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ABSTRACT

Background: Whether and to what extent leisure-time physical activity at the recommended levels of 150 minutes moderate activity is associated with survival in people with cardiometabolic multimorbidity and depression is unknown.

Methods: UK Biobank participants were classified into groups: (1) no disease; (2) diabetes; (3) cardiovascular disease (CVD); (4) depression; (5) diabetes and CVD; (6) diabetes and depression; (7) CVD and depression; (8) diabetes, CVD and depression. Leisure-time physical activity was categorised as active (meeting recommendations) or inactive. Survival models were applied to estimate life expectancy.

Results: 480,940 participants were included (median age, 58 years; 46% men; 95% white), of whom 74% with cardiometabolic multimorbidity and depression were inactive. During a mean follow-up of 7 years, 11006 deaths occurred. At age of 45 years, being physically active was associated with 2.34 (95% confidence interval: 0.93, 3.54) additional years of life compared to being inactive in participants with diabetes; corresponding estimate were 2.28 (1.40, 3.16) for CVD; 2.15 (0.05, 4.26) for diabetes and CVD; and 1.58 (1.27, 1.89) for no disease. Participants with a combination of diabetes, CVD and depression, being active was associated with 6.81 (-1.50, 15.31) additional years compared to being inactive; corresponding estimates were 3.07 (-2.46, 8.59) for diabetes and depression; 2.34 (-1.24, 5.91) for CVD and depression; and 0.80 (-0.46, 2.05) for depression. A similar pattern was found at 65 years.

Conclusions: Meeting the recommended level of physical activity was associated with a longer life expectancy in people with cardiometabolic multimorbidity but not in those with depression.

Key words: Cardiometabolic multimorbidity, depression, leisure-time physical activity, life expectancy, UK biobank.

INTRODUCTION

In recent years, there has been an increasing prevalence of multimorbidity, with patterns across the globe mainly evidenced for cardiometabolic conditions.[1-3] Data from the UK indicate that the combination of diabetes and cardiovascular diseases is the most common multimorbidity combination.[4] Similarly, a study in the elderly, aged 65 years and older, ranked cardiovascular and metabolic disorders to be the most prominent pattern amongst other clusters.[5] Cardiometabolic conditions may also coexist with mental health illnesses, such as depression.[6] More than 300 million people worldwide are affected by depression, whose symptoms are continuous low mood, loss of interest, poor concentration, low self-esteem, feeling anxious or worried and, in the severe forms, self-harm or suicidal thoughts. [7] People with multimorbidity have the highest prevalence of depression,[8] and the link between cardiometabolic multimorbidity and depression is well recognised, but it is often overlooked, since single diseases are given more priority.[9] The leading top ten causes of mortality are cardiometabolic conditions;[10] while there is evidence of a reduced life expectancy in people with cardiometabolic multimorbidity,[2] little is known about the impact on survival of depression in combination with cardiometabolic multimorbidity.

Evidence exists about the benefits of overall physical activity on longevity in people diagnosed with a single medical condition.[11] Conversely, research on leisure-time physical activity, which refers to recreation that is not related to regular work, housework, or transport activities, is more limited.[12] A pooled cohort study found that participants who met the minimum recommended levels of leisure-time physical activity had a life expectancy 3.4 years longer at the age of 40 compared to those who did not (*Table S1*).[13] Similarly, another study in Taiwan reported a gain of 4.2 years for men and 3.7 for women at the age of 30,[14] while in the United States meeting recommended activity levels was associated with a gain of 5.5 years at age 20 years in non-Hispanic black women.[15] However, all these studies did not clarify whether and to what extent the benefits of leisure-time physical activity are associated with survival differences in people with multimorbidities, in particular cardiometabolic multimorbidity and depression. This gap of knowledge is noteworthy, as

discretionary leisure time is important for the promotion of physical activity as the prevalence of multimorbidity will continue to rise during the coming years.[16, 17]

In this context, we aimed to explore the association between leisure-time physical activity and life expectancy in a contemporary large cohort of middle-aged people with cardiometabolic multimorbidity and depression.

METHODS

Data Source and Study Population

We used UK Biobank data (Application Number 14146), one of the world's largest Biobank cohorts, designed to improve the prevention, diagnosis and treatment of chronic diseases in middle-aged (38-73 years) adults, recruited from 22 sites across England, Wales and Scotland. This longitudinal study included 502,629 participants with baseline measures collected between 2006 and 2010 with data linked to mortality records.[18] Written informed consent was obtained prior to data collection and ethics was approved by the North-West Research Ethics Committee. To minimise reverse causality (i.e., undiagnosed, subclinical disease(s) leading to lower inactivity and mortality), we excluded participants who died within the first two years of follow-up (n=2,516).[19] Participants who withdrew from the study (n=91), their age during follow-up was less than 45 years (n=30), with no leisure-time physical activity data (n=11,517) or with missing covariate data (n=7,535) were excluded from the analysis (*Figure S1*).

Cardiometabolic Multimorbidity and Depression Definition

As part of the baseline assessment, participants were asked whether a physician had diagnosed them with long-term conditions including diabetes, cardiovascular disease (CVD: stroke, myocardial infarction, heart failure, angina, or peripheral vascular disease), or mild to moderate depression. We classified participants into eight mutually exclusive groups: (1) no disease (reference group); (2) diabetes; (3) CVD; (4) depression; (5) diabetes and CVD; (6) diabetes and depression; (7) CVD and depression; (8) diabetes and CVD and depression (*Table S2*).

Outcome

Mortality data were obtained from the National Health Service (NHS) Information Centre for participants from England and Wales and the NHS Central Register for participants from Scotland. Data for survivors were censored on 31st January 2016 for England and Wales and 30th November 2015 for Scotland.

Assessment of Leisure-time Physical Activity

Information on the primary exposure, leisure-time physical activity, was collected from an in-person baseline interview at the centre (Data-Field 6164). Participants were asked "In the last four weeks did you spend any time doing the following: walking for pleasure, light DIY (do-it-yourself, i.e. home maintenance and improvement and gardening activities), heavy DIY (e.g. using heavy tools, weeding, lawn mowing, digging, carpentry), strenuous sports (i.e. sports that make you sweat or breathe hard), other exercises (e.g. swimming, cycling, keep fit, bowling); none of the above". Participants were able to select more than one activity and were asked to quantify their participation by frequency (i.e. number of times) and duration (i.e. time in minutes/ hours). The intensity was expressed in terms of standardised metabolic equivalent of task (MET) values: 3.5 METs for walking for pleasure; 5.5 METs for heavy DIY; 8.0 METs for strenuous sports; 4.0 METs for other activities.[20] We did not include light DIY within our definition, since we were specifically investigating moderate to vigorous intensity physical activities. The total weekly leisure-time physical activity (METs-mins/week) was calculated by multiplying the frequency, duration, and the MET values.[20] We classified the sample into two groups: inactive (<500 METs-minutes/week) and active (≥500 METs-minutes/week); this threshold is equivalent to the current global health recommendations for physical activity (150 minutes of moderate activity or 75 minutes of vigorous activity or an equivalent combination).[21]

Other Covariates

Baseline confounding covariates that could potentially affect the association between leisure-time physical activity and all-cause mortality included: history of cancer, sociodemographic (sex, ethnicity, socioeconomic status, employment status) and lifestyle (body mass index, smoking status, alcohol intake, fruit and vegetable intake, sedentary behaviour) factors (*Table S2* and *Methods S1*).

Statistical Analysis

Participants were categorised according to the eight multimorbidity groups and leisure-time physical activity (active and inactive). Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of all-cause death were calculated in complete-case analysis using flexible parametric survival

models, with age as the time scale. Flexible parametric models has been shown to perform better than Cox models, in particular estimating life expectancy for smaller grouped samples.[22] HR estimates were firstly obtained for different disease groups, compared to no disease, and then by leisure-time physical activity (active vs inactive) in each disease group. The calculation of years of life lost (i.e., difference in average life expectancy) involved a two-step process. First, residual life expectancy was estimated as the area under the survival curve up to 100 years old, conditional on surviving at ages 45 to 100 years old (1-year intervals); survival curves were predicted for each individual and averaged over individuals. Second, years of life lost were calculated as the difference between the areas under two survival curves. Similarly to HR, survival curves were obtained averaging individual curves with each disease group and compared to no disease; and, for each disease group, within the active compared to inactive group. Analyses were unadjusted (model 1); and adjusted for potential confounders: history of cancer and sociodemographic factors (model 2); and additionally for lifestyle factors (model 3). For sensitivity analysis, we imputed missing covariate data (***Methods S2***). Stata version 15.0 was used to manipulate data and proportional hazards survival analyses were conducted with the stpm2 command which uses restricted cubic splines to model the baseline cumulative hazard.[23] A p-value <0.05 was considered indicative of statistical significance.

RESULTS

Baseline Characteristics

A total of 480,940 participants (median (range) age 58 (38-73) years; 46% men; 95% white) with complete data were included (**Table 1**): at baseline, 15213 (3.2%) participants had diabetes, 21403 (4.5%) CVD, 23835 (5.0%) depression, 3508 (0.7%) diabetes and CVD, 1011 (0.2%) diabetes and depression, 1619 (0.3%) CVD and depression, 296 (0.1%) diabetes, CVD and depression. Compared to participants with no diseases, we observed a higher number of non-white participants with diabetes (13.7%) and diabetes and CVD (11.2%). Also, participants with depression were younger (median age 55 years), mainly female (31.8% male) and currently working. Participants with the combination of diabetes, CVD and depression were found to live in the most deprived areas, to have higher BMI, and spent more sedentary time than those with no diseases. When comparing leisure-time physical activity groups, participants with baseline diseases were more inactive: we found 74% of participants with combination of diabetes, CVD and depression were inactive.

Life Expectancy

During a mean follow-up of 7 (range 2-9) years and 3.35 million person-years, 11006 deaths were recorded. Compared to the reference group (no disease), the HRs of mortality was significantly higher for those with baseline cardiometabolic conditions and depression (**Table 2**), ranging from HR 1.13 to 3.33 in the fully adjusted model. At the age of 45 years, participants with the combination of diabetes, CVD and depression had a significantly reduced life expectancy of 9.06 (95% CI 6.5, 11.7) years compared to participants with no disease (**Figure 1**); corresponding values were 7.18 (95% CI 6.27, 8.10) years for diabetes and CVD; 5.11 (95% CI 3.66, 6.56) for CVD and depression; 4.09 (95% CI 2.00, 6.21) for diabetes and depression; 3.25 (95% CI 2.65, 3.86) for diabetes; 2.92 (95% CI 2.45, 3.40) for CVD; and 0.86 (95% CI 0.24, 1.48) for depression. At the age of 65 years, participants with the combination of diabetes, CVD and depression had a significantly reduced life expectancy of 7.73 (95% CI 5.63, 9.83) years compared to participants with no disease; corresponding values were 6.19 (95% CI 5.42, 6.97) years for diabetes and CVD; 4.45 (95% CI 3.22, 5.69) for CVD and depression;

3.58 (95% CI 1.76, 5.40) for diabetes and depression; 2.86 (95% CI 2.33, 3.38) for diabetes; 2.57 (95% CI 2.15, 2.98) for CVD; and 0.76 (95% CI 0.21, 1.31) for depression.

Compared to the inactive group, participants in the active group with the combination of diabetes, CVD and depression had a lower risk of mortality (fully adjusted model HR: 0.45; 95% CI 0.19, 1.09); similarly, active participants with all other diseases and no disease had a lower risk of mortality, ranging from HR 0.70 to 0.89 (**Table 3**). **Figure 2** shows the years of life gained by leisure-time physical activity by baseline disease status. In the fully adjusted model, at the age of 45 years being physically active was associated with 2.34 (95% CI 0.93, 3.54) additional years of life compared to being inactive in participants with diabetes; corresponding estimates were 2.28 (95% CI 1.40, 3.16) for CVD; 2.15 (95% CI 0.05, 4.26) for diabetes and CVD; and 1.58 (95% CI 1.27, 1.89) for no disease. In participants with a combination of diabetes, CVD and depression who were active, the life expectancy was 6.81 (95% CI -1.50, 15.31) years longer compared to participants who were inactive; corresponding estimates were 3.07 (95% CI -2.46, 8.59) for diabetes and depression; 2.34 (95% CI -1.24, 5.91) for CVD and depression; and 0.80 (95% CI -0.46, 2.05) for depression. A similar pattern was found at the age of 65 years, where being active was significantly associated with 1.97 (95% CI 1.21, 2.73) additional years for participants with CVD; corresponding estimates were 1.85 (95% CI 0.76, 2.93) for diabetes; 1.78 (0.03, 3.52) for diabetes and CVD; 1.41 (95% CI 1.13, 1.68) for no disease; and non-significantly associated with 5.26 (95% CI -1.13, 11.64) additional years for participants with diabetes, CVD and depression; 2.36 (95% CI -1.98, 6.70) for diabetes and depression; 2.06 (95% CI -1.11, 5.24) for CVD and depression; and 0.70 (95% CI -0.41, 1.80) for depression (**Table 3**). In sensitivity analyses, the same pattern was identified when imputing missing data (*Table S3* and *Figure S2*).

DISCUSSION

Our analysis found that participants with the combination of diabetes, CVD and depression had the largest reduction of life expectancy: compared to participants with no disease, the presence of these three conditions resulted in a life expectancy which was 9.1 years shorter at the age of 45 years and 7.7 years shorter at the age of 65 years. Leisure-time physical activity, based on the recommended activity level, resulted in an increased life expectancy particularly in people with diabetes alone, CVD alone, or the combination of diabetes and CVD (i.e., cardiometabolic diseases). Conversely, the associations were no longer present in participants with depression alone or depression combined with cardiometabolic conditions. This difference suggests that people with cardiometabolic multimorbidity would benefit the most from physical activity while people with depression may require additional interventions, beyond meeting activity guidelines, to increase life expectancy.

To our knowledge, this is the first study to investigate the impact on survival of cardiometabolic conditions combined with mental ill-health. Our findings have important implications, as currently there is limited research about the most commonly occurring clusters of conditions and on their impact on life expectancy to quantify their burden.[17] In addition, this is the first study to estimate the association between leisure-time physical activity and life expectancy in people with cardiometabolic multimorbidity and depression. As previous studies are all based on the general population (*Table S1*), we were unable to directly compare our findings with the available evidence. A pooled analysis including a total of 654,827 participants across six studies reported that leisure-time activity at the minimum recommended equivalent to 150–299 minutes of brisk walking per week was associated with a gain in life expectancy: accounting for potential confounders, the risk of mortality was lower (HR 0.68) and, at the age of 40 years, the gain in life expectancy was 3.4 years.[13] A study in Taiwan showed that leisure-time activity at or above the minimum recommended level (7.5 METs-hour/week) was associated with a gain of 3.7 to 4.2 years of life expectancy compared to inactivity (<3.75 METs-hour/week).[24] These findings were consistent with the present study since the gain in life expectancy ranged from 0.8 to 6.8 years. A study from the United States indicated that leisure-time activity at the recommended levels was associated with life expectancy only in the non-

Hispanic population, where non-Hispanic black women could gain as high as 5.5 years at the age of 20 years; this study, however, was limited to a small sample size of non-Hispanics blacks and Hispanics.[15] The Copenhagen City Heart Study reported a gain in life expectancy associated with leisure-time physical activity; yet, the estimates were based on the type of leisure-time activity. When compared with the sedentary group, the gain in life expectancy ranged from a maximum of 9.7 years for tennis to a minimum of 1.5 years for health club activities.[25]

The use of self-reported leisure-time activities is a limitation, as the measurements could be inaccurate and overestimated;[26] however, most large epidemiological studies relied on self-reported questionnaires as it is efficient way to assess physical activity including leisure-time activities and there is a moderate correlation between self-reported and accelerometry measures.[27] Another limitation is the small number of participants with the combination of both cardiometabolic multimorbidity and depression compared to the other groups. Also, different levels of occupational activity and socioeconomic status participants could result in bias;[28] nevertheless, we accounted for several factors to reduce the risk of confounding bias. Although participants who died within the first two years of follow-up were excluded to reduce the risk of reverse causation,[19] it is still possible that participants with cardiometabolic multimorbidity may generally be less well, which could result in a lower leisure-time physical activity and a higher mortality rate. Moreover, the effect of leisure-time physical activity was assessed at a single time point and the study was limited to mortality end point; as such, further research is required to investigate how the bi-directional association of physical activity and depression would impact on mortality and other outcomes, including improvement of depression symptoms or remission of depression. In addition, participants without cardiometabolic and depression conditions (no disease group) may potentially have other diseases which have not been accounted for. Mental health comprises a broad range of symptoms with different levels of severity but we have included mild to moderate depression as this is the most prevalent condition globally[7, 29] and because depression is currently the only mental health disorder in which physical activity is recommended as an evidence-based treatment.[30] Our findings showed that 5.6% of participants had depression or depression with a cardiometabolic condition: this estimate is lower than the recent

Quality and Outcomes Framework (QOF) assessment, which showed a prevalence of depression of 9.9%.[31] Such difference may be due to the recruitment in UK Biobank of participants healthier than the general population, or depression not reported during data collection. Nevertheless, the characteristics of participants with depression were similar to previous studies; i.e. mainly women, at a younger age and currently working.[7] This was an observational study and causality cannot be demonstrated, therefore the results should be interpreted with caution. Strengths of this study include the large sample size and the number of deaths, which allowed enough data to allow the life expectancy to be estimated by disease groups. Lastly, we based our cut point for leisure-time physical activity on the global recommended levels.[21]

In conclusion, leisure-time physical activity at the recommended levels was associated with a longer life expectancy, especially in people with cardiometabolic multimorbidity. While changing lifestyle behaviours is not easy for those dealing with diabetes and CVD, moderate to vigorous intensity leisure-time physical activity could provide a safe opportunity to engage in enjoyable, sociable, and low-cost therapy, which may positively influence patients. For those dealing with depression, or depression combined with cardiometabolic multimorbidity, further research is required to identify strategies to increase life expectancy. Given the rising challenges of multimorbidity, our study has important implications for the public health and for the future research in people with both physical and mental health illnesses.

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Table 1 Baseline characteristics by disease status and leisure-time physical activity group

Characteristics	Disease status at baseline							
	None	**Diabetes**	**CVD**	**Depression**	**Diabetes + CVD**	**Diabetes + Depression**	**CVD + Depression**	**Diabetes + CVD + Depression**
Total (480,940 participants)								
No. (%)	414,055 (86.1)	15,213 (3.2)	21,403 (4.5)	23,835 (5.0)	3,508 (0.7)	1,011 (0.2)	1,619 (0.3)	296 (0.1)
Age in years, median [IQR]	57 [50-63]	61 [55-65]	63 [59-66]	55 [49-61]	63 [59-67]	58 [52-63]	61 [55-65]	61 [55-65]
Cancer	33,289 (8.0)	1,354 (8.9)	2,020 (9.4)	2,066 (8.7)	304 (8.7)	92 (9.1)	160 (9.9)	31 (10.5)
Male sex	183,381 (44.3)	9,290 (61.1)	14,413 (67.3)	7,575 (31.8)	2,643 (75.3)	482 (47.7)	849 (52.4)	195 (65.9)
Non-white ethnicity	20,491 (5.0)	2,086 (13.7)	908 (4.2)	791 (3.3)	394 (11.2)	83 (8.2)	64 (4.0)	26 (8.8)
Most deprived areas in UK	201,021 (48.6)	9,044 (59.5)	11,810 (55.2)	13,316 (55.9)	2,259 (64.4)	644 (63.7)	1,072 (66.2)	233 (78.7)
Working	250,932 (60.6)	6,735 (44.3)	6,885 (32.2)	12,237 (51.3)	836 (23.8)	312 (30.9)	367 (22.7)	44 (14.9)
Retired	130,854 (31.6)	6,683 (43.9)	11,872 (55.5)	6,676 (28.0)	2,002 (57.1)	393 (38.9)	738 (45.6)	140 (47.3)
Body mass index (kg/m^2), mean [SD]	27.1 [4.6]	31.1 [5.8]	28.7 [4.7]	28.1 [5.4]	31.7 [5.5]	32.9 [6.5]	29.8 [5.9]	33.4 [6.3]
Previous smoker	139,112 (33.6)	6,333 (41.6)	10,253 (47.9)	8,063 (33.8)	1,881 (53.6)	399 (39.5)	711 (43.9)	155 (52.4)
Current smoker	40,720 (9.8)	1,541 (10.1)	2,687 (12.6)	3,901 (16.4)	417 (11.9)	148 (14.6)	345 (21.3)	49 (16.6)
Excess alcohol (≥14 units/wk)	158,009 (38.2)	4,572 (30.1)	8,292 (38.7)	7,742 (32.5)	999 (28.5)	245 (24.2)	499 (30.8)	66 (22.3)
Meet fruit/ vegetable guidelines (5/day)	157,335 (38.0)	6,363 (41.8)	7,874 (36.8)	8,623 (36.2)	1,438 (41.0)	390 (38.6)	536 (33.1)	121 (40.9)
Sedentary (hours/day), mean [SD]	5.0 [2.3]	5.8 [2.7]	5.5 [2.5]	5.1 [2.5]	6.0 [2.8]	5.9 [3.0]	5.7 [2.9]	6.4 [3.2]
Inactive (229,945 participants)								
No. (%)	192,431 (46.5)	8,870 (58.3)	11,086 (51.8)	13,331 (55.9)	2,221 (63.3)	695 (68.7)	1,093 (67.5)	218 (73.7)
Age in years, median [IQR]	57 [49-63]	61 [54-65]	63 [58-66]	55 [48-61]	63 [59-67]	57 [51-63]	60 [54-65]	60 [55-65]
Cancer	15,842 (8.2)	826 (9.3)	1,068 (9.6)	1,190 (8.9)	192 (8.6)	63 (9.1)	120 (11.0)	25 (11.5)
Male sex	74,503 (38.7)	5,006 (56.4)	6,827 (61.6)	3,711 (27.8)	1,586 (71.4)	301 (43.3)	540 (49.4)	123 (65.6)
Non-white ethnicity	13,119 (6.8)	1,403 (15.8)	589 (5.3)	549 (4.1)	272 (12.3)	67 (9.6)	52 (4.8)	22 (10.1)
Most deprived areas in UK	102,880 (53.5)	5,640 (63.6)	6,807 (61.4)	7,991 (59.9)	1,520 (68.4)	467 (67.2)	766 (70.1)	178 (81.7)
Working	122,784 (63.8)	4,199 (47.3)	3,709 (33.5)	6,760 (50.7)	524 (23.6)	226 (32.5)	231 (21.1)	27 (12.4)
Retired	52,697 (27.4)	3,508 (39.6)	5,602 (50.5)	3,416 (25.6)	1,199 (54.0)	244 (35.1)	470 (43.0)	101 (46.3)
Body mass index (kg/m^2), mean [SD]	27.7 [5.0]	31.9 [6.1]	29.3 [5.1]	28.8 [5.8]	32.5 [5.8]	33.7 [6.6]	30.2 [6.2]	33.9 [6.4]
Previous smoker	62,118 (32.3)	3,543 (40.0)	5,073 (45.8)	4,334 (32.5)	1,151 (51.8)	263 (37.8)	480 (43.9)	108 (49.5)
Current smoker	22,730 (11.8)	1,005 (11.3)	1,796 (16.2)	2,473 (18.6)	312 (14.1)	108 (15.5)	262 (24.0)	40 (18.4)
Excess alcohol (≥14 units/wk)	64,877 (33.7)	2,383 (26.9)	3,812 (34.4)	3,963 (29.7)	557 (25.1)	139 (20.0)	324 (29.6)	43 (19.7)
Meet fruit/ vegetable guidelines (5/day)	61,995 (32.2)	3,377 (38.1)	3,520 (31.8)	4,084 (30.6)	836 (37.6)	235 (33.8)	328 (30.0)	78 (35.8)
Sedentary (hours/day), mean [SD]	5.2 [2.4]	5.9 [2.8]	5.7 [2.7]	5.3 [2.6]	6.2 [2.9]	6.1 [3.1]	5.9 [3.1]	6.6 [3.4]
Active (250,995 participants)								
No. (%)	221,624 (53.5)	6,343 (41.7)	10,317 (48.2)	10,504 (44.1)	1,287 (36.7)	316 (31.3)	526 (32.5)	78 (26.4)
Age in years, median [IQR]	58 [50-63]	61 [55-65]	64 [59-67]	56 [49-61]	64 [60-67]	60 [53-64]	61 [56-65]	62 [58-65]
Cancer	17,447 (7.9)	528 (8.3)	952 (9.2)	876 (8.3)	112 (8.7)	29 (9.2)	40 (7.6)	6 (7.7)
Male sex	108,878 (49.1)	4,284 (67.5)	7,586 (73.5)	3,864 (36.8)	1,057 (82.1)	181 (57.3)	309 (58.8)	52 (66.7)
Non-white ethnicity	7,372 (3.3)	683 (10.8)	319 (3.1)	242 (2.3)	122 (9.5)	16 (5.1)	12 (2.3)	4 (5.1)
Most deprived areas in UK	98,141 (44.3)	3,404 (53.7)	5,003 (48.5)	5,325 (50.7)	739 (57.4)	177 (56.0)	306 (58.2)	55 (70.5)
Working	128,148 (57.8)	2,536 (40.0)	3,176 (30.8)	5,477 (52.1)	312 (24.2)	86 (27.2)	136 (25.9)	17 (21.8)
Retired	78,157 (35.3)	3,175 (50.1)	6,270 (60.8)	3,260 (31.0)	803 (62.4)	149 (47.2)	268 (51.0)	39 (50.0)
Body mass index (kg/m^2), mean [SD]	26.5 [4.1]	30.0 [5.1]	28.0 [4.2]	27.1 [4.7]	30.4 [4.7]	31.1 [6.0]	29.0 [5.1]	32.1 [5.7]
Previous smoker	76,994 (34.7)	2,790 (44.0)	5,180 (50.2)	3,729 (35.5)	730 (56.7)	136 (43.0)	231 (43.9)	47 (60.3)
Current smoker	17,990 (8.1)	536 (8.5)	891 (8.6)	1,428 (13.6)	105 (8.2)	40 (12.7)	83 (15.8)	9 (11.5)
Excess alcohol (≥14 units/wk)	93,132 (42.0)	2,189 (34.5)	4,480 (43.4)	3,779 (36.0)	442 (34.3)	106 (33.5)	175 (33.3)	23 (29.5)
Meet fruit/ vegetable guidelines (5/day)	95,340 (43.0)	2,986 (47.1)	4,354 (42.2)	4,539 (43.2)	602 (46.8)	155 (49.1)	208 (39.5)	43 (55.1)
Sedentary (hours/day), mean [SD]	4.9 [2.1]	5.5 [2.5]	5.3 [2.2]	4.9 [2.2]	5.7 [2.4]	5.5 [2.7]	5.3 [2.5]	5.7 [2.8]

Shown are numbers (%) unless stated otherwise. CVD=cardiovascular disease [stroke (4,725), myocardial infarction (8,388), heart failure (200), angina (11,504), peripheral vascular disease (761); sum is greater than 480,940 as participants may have more than one CVD]; METs=metabolic equivalent of task; Sedentary behaviour= total number of self-reported hours spent watching television, using the computer, or driving; IQR=interquartile range; SD=standard deviation; Inactive <500 METs-minutes/week; Active ≥500 METs- minutes/week.

Table 2 All-cause mortality by baseline disease status

	Disease status at baseline							
	None	**Diabetes**	**CVD**	**Depression**	**Diabetes + CVD**	**Diabetes + Depression**	**CVD + Depression**	**Diabetes + CVD + Depression**
Total (480,940 participants)								
No. participants (%)	414,055 (86.1)	15,213 (3.2)	21,403 (4.5)	23,835 (5.0)	3,508 (0.7)	1,011 (0.2)	1,619 (0.3)	296 (0.1)
No. deaths (%)	7,969 (1.9)	709 (4.7)	1,213 (5.7)	518 (2.2)	390 (11.1)	51 (5.0)	117 (7.2)	39 (13.2)
Mortality rate (95% CI) , 1000 py	2.76 (2.70, 2.82)	6.78 (6.30, 7.30)	8.17 (7.73, 8.64)	3.11 (2.85, 3.39)	16.36 (14.82, 18.07)	7.29 (5.54, 9.60)	10.40 (8.68, 12.67)	19.43 (14.20, 26.60)
Hazard ratio for all-cause mortality (95% CI)								
Model 1	Reference	1.89 (1.75, 2.05)	1.90 (1.79, 2.02)	1.29 (1.18, 1.41)	3.67 (3.31, 4.07)	2.55 (1.93, 3.35)	3.00 (2.47, 3.56)	5.56 (4.06, 7.62)
Model 2	Reference	1.69 (1.56, 1.82)	1.60 (1.51, 1.70)	1.22 (1.12, 1.33)	2.89 (2.61, 3.20)	2.02 (1.53, 2.67)	2.32 (1.93, 2.79)	3.83 (2.79, 5.25)
Model 3	Reference	1.58 (1.46, 1.71)	1.51 (1.42, 1.61)	1.13 (1.04, 1.24)	2.63 (2.37, 2.92)	1.76 (1.34, 2.33)	2.02 (1.68, 2.42)	3.33 (2.43, 4.57)
Years of life lost at the age of 45 years (95% CI)								
Model 1	Reference	4.99 (4.31, 5.68)	5.03 (4.47, 5.58)	1.92 (1.23, 2.61)	10.54 (9.46, 11.62)	7.47 (5.09, 9.85)	8.76 (7.10, 10.42)	13.97 (11.09, 16.84)
Model 2	Reference	3.83 (3.20, 4.45)	3.43 (2.93, 3.92)	1.40 (0.75, 2.05)	8.13 (7.17, 9.08)	5.26 (3.05, 7.47)	6.36 (4.84, 7.87)	10.41 (7.73, 13.09)
Model 3	Reference	3.25 (2.65, 3.86)	2.92 (2.45, 3.40)	0.86 (0.24, 1.48)	7.18 (6.27, 8.10)	4.09 (2.00, 6.21)	5.11 (3.66, 6.56)	9.06 (6.47, 11.65)
Years of life lost at the age of 65 years (95% CI)								
Model 1	Reference	4.41 (3.81, 5.01)	4.44 (3.95, 4.93)	1.71 (1.09, 2.32)	9.06 (8.15, 9.97)	6.53 (4.51, 8.54)	7.61 (6.21, 9.00)	11.73 (9.50, 13.95)
Model 2	Reference	3.36 (2.82, 3.91)	3.01 (2.58, 3.45)	1.24 (0.66, 1.81)	6.99 (6.19, 7.80)	4.59 (2.71, 6.48)	5.52 (4.23, 6.80)	8.84 (6.69, 10.98)
Model 3	Reference	2.86 (2.33, 3.38)	2.57 (2.15, 2.98)	0.76 (0.21, 1.31)	6.19 (5.42, 6.97)	3.58 (1.76, 5.40)	4.45 (3.22, 5.69)	7.73 (5.63, 9.83)

CVD=cardiovascular disease [stroke (4,725), myocardial infarction (8,388), heart failure (200), angina (11,504), peripheral vascular disease (761); sum is greater than 480,940 as participants may have more than one CVD];

CI=confidence interval; py=person years.

% No. participants = total no. of participants in each group / total no. participants.

% No. deaths= total no. of deaths in each group / total no. participants in each group.

Model 1: unadjusted.

Model 2: adjusted for cancer + sociodemographic factors [sex (male, female), ethnicity (white, non-white), socioeconomic status (most or least deprived), and employment status (working, retired, other)].

Model 3: Model 2 + lifestyle factors [body mass index, smoking status (never, previous, current), alcohol intake (less than or more than 14 units/wk), meet fruit and vegetable intake (yes, no), and sedentary behaviour].

Figure 1 Years of life lost by baseline disease status
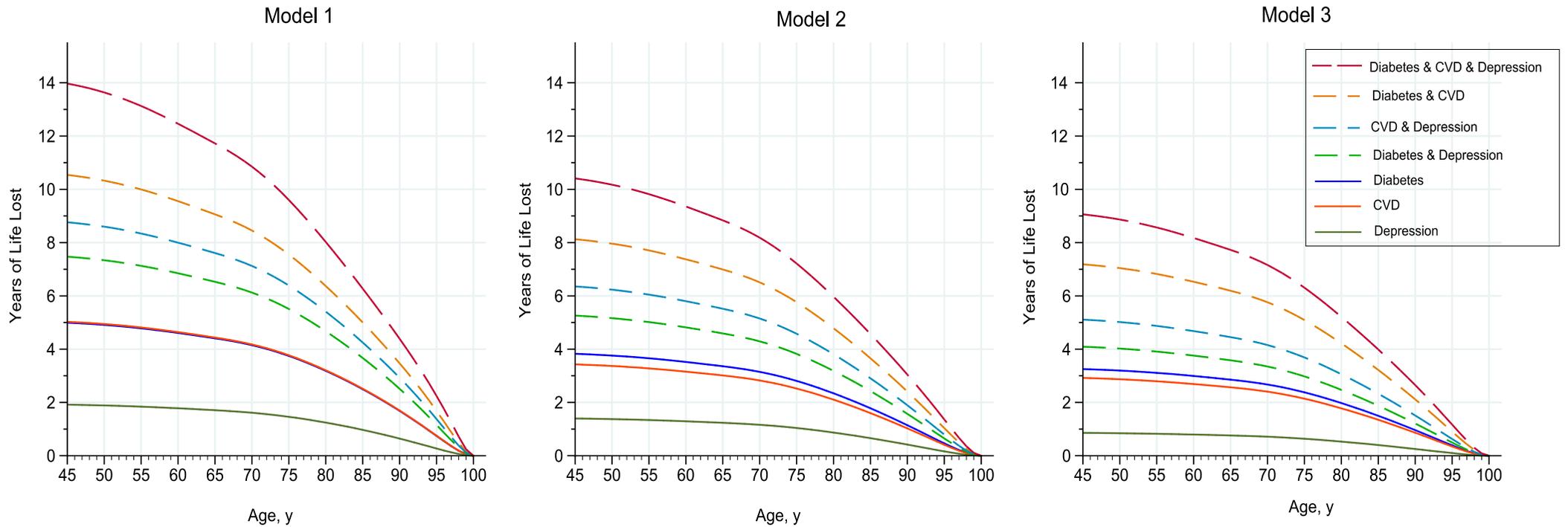
CVD=cardiovascular disease [stroke, myocardial infarction, heart failure, angina, peripheral vascular disease]; y=years.

Years of life lost were estimated as the difference in residual life expectancy between participants with the specific disease(s) and participants with no disease at baseline.

Model 1: unadjusted.

Model 2: adjusted for cancer + sociodemographic factors [sex (male, female), ethnicity (white, non-white), socioeconomic status (most or least deprived), and employment status (working, retired, other)].

Model 3: Model 2 + lifestyle factors [body mass index, smoking status (never, previous, current), alcohol intake (less than or more than 14 units/wk), meet fruit and vegetable intake (yes, no), and sedentary behaviour].

Table 3 All-cause mortality by baseline disease status and leisure-time physical activity group, active vs inactive

	Disease status at baseline							
	None	**Diabetes**	**CVD**	**Depression**	**Diabetes + CVD**	**Diabetes + Depression**	**CVD + Depression**	**Diabetes + CVD + Depression**
Inactive (210,142 participants)								
No. participants (%)	192,431 (46.5)	8,870 (58.3)	11,086 (51.8)	13,331 (55.9)	2,221 (63.3)	695 (68.7)	1,093 (67.5)	218 (73.7)
No. deaths (%)	4,182 (2.2)	460 (5.2)	726 (6.6)	314 (2.4)	268 (12.1)	36 (5.2)	89 (8.1)	32 (14.7)
Mortality rate (95% CI) , 1000 py	3.11 (3.02, 3.21)	7.56 (6.90, 8.29)	9.47 (8.80, 10.18)	3.37 (3.02, 3.77)	17.81 (15.80, 20.07)	7.50 (5.41, 10.39)	11.75 (9.55, 14.47)	21.78 (15.40, 30.80)
Active (270,798 participants)								
No. participants (%)	221,624 (53.5)	6,343 (41.7)	10,317 (48.2)	10,504 (44.1)	1,287 (36.7)	316 (31.3)	526 (32.5)	78 (26.4)
No. deaths (%)	3,787 (1.7)	249 (3.9)	487 (4.7)	204 (1.9)	122 (9.5)	15 (4.8)	28 (5.3)	7 (9.0)
Mortality rate (95% CI) , 1000 py	2.45 (2.37, 2.53)	5.69 (5.02, 6.44)	6.79 (6.21, 7.42)	2.77 (2.42, 3.18)	13.89 (11.63, 16.58)	6.85 (4.13, 11.36)	7.62 (5.26, 11.03)	13.01 (6.20, 27.29)
Hazard ratio for all-cause mortality (95% CI), active vs inactive								
Model 1	0.75 (0.72, 0.79)	0.72 (0.62, 0.84)	0.67 (0.60, 0.76)	0.80 (0.67, 0.95)	0.73 (0.59, 0.90)	0.80 (0.44, 1.46)	0.61 (0.40, 0.93)	0.54 (0.24, 1.22)
Model 2	0.74 (0.70, 0.77)	0.70 (0.60, 0.82)	0.67 (0.60, 0.75)	0.83 (0.69, 0.99)	0.74 (0.60, 0.92)	0.67 (0.36, 1.26)	0.62 (0.40, 0.96)	0.52 (0.23, 1.21)
Model 3	0.79 (0.75, 0.83)	0.76 (0.64, 0.89)	0.73 (0.64, 0.82)	0.89 (0.74, 1.07)	0.78 (0.63, 0.98)	0.70 (0.37, 1.33)	0.72 (0.47, 1.12)	0.45 (0.19, 1.09)
Years of life gained at age 45 years (95% CI), active vs inactive								
Model 1	2.03 (1.70, 2.36)	2.95 (1.53, 4.38)	3.43 (2.35, 4.50)	1.74 (0.39, 3.10)	3.42 (0.92, 5.91)	2.15 (-3.59, 7.90)	4.75 (0.38, 9.12)	6.30 (-3.25, 15.84)
Model 2	2.08 (1.77, 2.40)	2.96 (1.61, 4.30)	2.98 (2.06, 3.89)	1.33 (0.09, 2.58)	2.72 (0.53, 4.91)	3.12 (-1.91, 8.16)	3.90 (-1.03, 8.82)	5.54 (-2.16, 13.24)
Model 3	1.58 (1.27, 1.89)	2.34 (0.93, 3.54)	2.28 (1.40, 3.16)	0.80 (-0.46, 2.05)	2.15 (0.05, 4.26)	3.07 (-2.46, 8.59)	2.34 (-1.24, 5.91)	6.81 (-1.50, 15.13)
Years of life gained at age 65 years (95% CI), active vs inactive								
Model 1	1.84 (1.54, 2.14)	2.42 (1.24, 3.59)	2.93 (2.01, 3.85)	1.52 (0.34, 2.70)	2.65 (0.70, 4.61)	1.75 (-2.97, 6.47)	3.90 (0.26, 7.54)	5.04 (-2.82, 12.90)
Model 2	1.86 (1.58, 2.14)	2.42 (1.30, 3.53)	2.55 (1.77, 3.33)	1.16 (0.07, 2.25)	2.22 (0.41, 4.03)	2.39 (-1.67, 6.44)	3.38 (-1.02, 7.78)	4.39 (-1.80, 10.58)
Model 3	1.41 (1.13, 1.68)	1.85 (0.76, 2.93)	1.97 (1.21, 2.73)	0.70 (-0.41, 1.80)	1.78 (0.03, 3.52)	2.36 (-1.98, 6.70)	2.06 (-1.11, 5.24)	5.26 (-1.13, 11.64)

CVD=cardiovascular disease [stroke (4,725), myocardial infarction (8,388), heart failure (200), angina (11,504), peripheral vascular disease (761); sum is greater than 480,940 as participants may have more than one CVD];

Inactive <500 METs-minutes/week; Active ≥500 METs-minutes/week; CI=confidence interval; py=person years.

% No. participants = total no. of participants in each group / total no. participants.

% No. deaths= total no. of deaths in each group / total no. participants in each group.

Model 1: unadjusted.

Model 2: adjusted for cancer + sociodemographic factors [sex (male, female), ethnicity (white, non-white), socioeconomic status (most or least deprived), and employment status (working, retired, other)].

Model 3: Model 2 + lifestyle factors [body mass index, smoking status (never, previous, current), alcohol intake (less than or more than 14 units/wk), meet fruit and vegetable intake (yes, no), and sedentary behaviour].

Figure 2 Years of life gained by baseline disease status and leisure-time physical activity group, active vs inactive (reference)
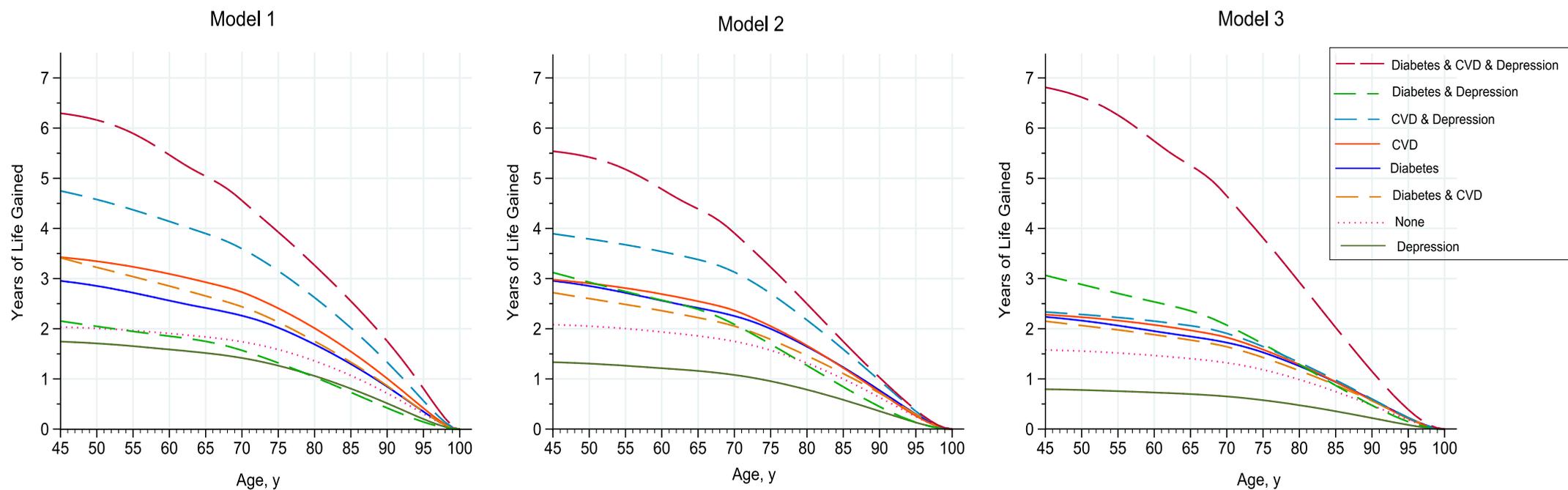
CVD=cardiovascular disease [stroke, myocardial infarction, heart failure, angina, peripheral vascular disease]; Inactive <500 METs-minutes/week; Active ≥500 METs-minutes/week; y=years.

Years of life gained were calculated as the difference in residual life expectancy between active and inactive participants.

Model 1: unadjusted.

Model 2: adjusted for cancer + sociodemographic factors [sex (male, female), ethnicity (white, non-white), socioeconomic status (most or least deprived), and employment status (working, retired, other)].

Model 3: Model 2 + lifestyle factors [body mass index, smoking status (never, previous, current), alcohol intake (less than or more than 14 units/wk), meet fruit and vegetable intake (yes, no), and sedentary behaviour].