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Physical activity, diet quality, and all-cause, cardiovascular disease and cancer mortality: A prospective study of 346,627 UK Biobank participants

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Abstract

Objectives: To examine independent and interactive associations of physical activity and diet with all-cause, cardiovascular disease (CVD) and physical activity, diet, and adiposity-related (PDAR) cancer mortality.

Methods: This population-based prospective cohort study (n=346,627) is based on the UK Biobank data with linkage to the National Health Service death records to 30 April 2020. A left-truncated Cox proportional hazards model was fitted to examine the associations between exposure (self-reported total moderate-to-vigorous intensity physical activity [MVPA], vigorous-intensity physical activity [VPA] and a diet quality index [score ranged 0 to 3]) and outcomes (all-cause, CVD and PDAR cancer mortality).

Results: During median of 11.2 years, 13,869 participants died from all causes, 2,650 from CVD, and 4,522 from PDAR cancers. Compared with Quartile 1 (Q1, 0-210 minutes/week), Q2-Q4 of MVPA were associated with lower risks of all-cause (HR ranged from 0.87 [95%CI: 0.83-0.91] to 0.91 [95%CI: 0.87-0.96]), CVD (HR ranged from 0.85 [95%CI: 0.76-0.95] to 0.90 [95%CI: 0.81-1.00]) and PDAR cancer mortality (HR ranged from 0.86 [95%CI: 0.79-0.93] to 0.94 [95%CI: 0.86-1.02]). Compared with no VPA, any VPA was associated with lower risk for all-cause and CVD mortality (HR ranged from 0.85 [95%CI: 0.80-0.89] to 0.89 [95%CI: 0.84-0.94] and from 0.75 [95%CI: 0.68-0.83] to 0.90 [95%CI: 0.81-1.02], respectively). Although not reaching statistical significance for all-cause and CVD mortality, being in the best dietary category (diet quality index=2-3) was associated with a reduction in PDAR cancer mortality (HR=0.85, 95%CI: 0.78-0.93). No additive or multiplicative interactions between physical activity categories and dietary quality was found. When comparing across physical activity and diet combinations, the lowest risk combinations consistently included the higher levels of physical activity and highest diet quality score.

Conclusions: Adhering to both quality diet and sufficient physical activity is important for reducing the risk of mortality from all causes, CVD and PDAR cancers during the follow-up period.

- **What is already known on this topic**

Both regular physical activity and a healthy diet play an important role in promoting health and longevity. A small number of overfeeding studies found that high-intensity exercise may counteract detrimental physiological responses to overfeeding. However, the long-term interactive effects between diet and physical activity remained less explored.

- **What this study adds**

No additive or multiplicative interaction between diet quality and physical activity categories was found. The lowest risk combinations consistently included the highest diet quality score and higher levels of physical activity. High levels of physical activity cannot counteract the detrimental effects of a poor diet on mortality risk.

- **How this study might affect research, practice or policy**

This study reinforces the importance of both physical activity and diet quality for reducing mortality risk. Public health messages and clinical advice should focus on simultaneous adherence to physical activity and dietary guidelines and debunk the myth that one could ‘outrun a bad diet’ or ‘out-diet an inactive lifestyle’.

Introduction

Regular physical activity and a healthy diet play a major role in the prevention of a range of chronic diseases, and are recommended by health authorities around the world.[1-5] Although both behaviours are critical components of a healthy lifestyle, their interlinked effects on energy balance and metabolic health have inspired popular beliefs, media headlines,[6] and scientific discussion[7,8] on whether one can 'outrun a bad diet' through high levels of physical activity.

The public's interest in this topic may be further fuelled by a small number of overfeeding studies, which provided tantalising evidence that high-intensity exercise may counteract inflammation and the deterioration of insulin sensitivity and the cardiometabolic profile associated with overfeeding, despite energy surplus.[9,10] However, these studies were designed to study the acute effects over a short period of time.

To date, a very small number of studies have explored the interaction between diet and physical activity in relation to long-term outcomes, such as mortality, and found no significant attenuation of risk associated with poor diet in those who were the most active.[11-13] These studies did not examine both additive and multiplicative interactions and were primarily focused on the overall volume/pattern of physical activity, without specifically examining the role vigorous-intensity physical activity (VPA) plays. Considering the promising evidence on the additional benefits of VPA independent of the overall volume of physical activity,[14,15] it is yet to be examined whether VPA offers particular risk reduction against a poor diet.

To address this research gap, we examine independent and joint associations of diet and physical activity with all-cause, cardiovascular disease (CVD) and cancer mortality using a large population-based sample of British adults from the UK Biobank Study. Considering the emerging evidence on the potential additional benefits associated with VPA,[14,15] independent of total activity volume, we further examine the role of VPA, in addition to moderate-to-vigorous intensity physical activity (MVPA). We hypothesise that physical activity and diet quality are independently associated with

lower mortality risk, and that high levels of physical activity, either in total MVPA or VPA, cannot offset detrimental effects of poor quality diet.

Methods

Sampling and procedures

The UK Biobank is a large population-based cohort study, which received ethical approval from the North-West Research Ethics Committee. Details about the cohort have been previously published.[16] Briefly, between April 2007 and December 2010, 502,632 participants (aged 40–69 years) were assessed at 22 assessment centres throughout the UK (5.5% response rate). During the baseline assessment visit, participants provided electronically signed consent, a self-completed touch-screen questionnaire, a brief computer-assisted interview, and had their physical measures and biological samples taken. In the current study, main exposures (i.e., diet and physical activity) and sociodemographic covariates were collected using the baseline touch-screen questionnaire and all-cause and cause-specific mortality data are based on linked death register data.

Measurement

Exposure variables: MVPA was measured using the short version of the International Physical Activity Questionnaire (IPAQ), which has established reliability and validity.[17] IPAQ asked separate questions regarding total minutes of walking, moderate physical activity (MPA) and VPA that lasted for at least 10 minutes at a time, in a typical week. First, we summed the total minutes of walking, MPA and VPA (weighted by two) as the total MVPA and analysed it as quartiles (0-210, 211-450, 451-920, 921-5040 min/week).[18] Second, considering that existing overfeeding studies that postulated 'outrunning a bad diet' focused on VPA,[9,10] and that VPA is found to convey potential additional benefits independent of the overall volume of MVPA,[14,15] we further used unweighted VPA minutes, instead of MVPA, as an exposure of interest. VPA was categorised as 0, 10-74 (1-9 minute-long bouts -not captured by the IPAQ questionnaire), 75-149, and 150+ minutes/week based on data distribution and congruent with recommended amount by physical activity guidelines.[2]

Diet quality was assessed at recruitment using a self-reported questionnaire regarding the frequency of consumption of common food items (https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/TouchscreenQuestionsMainFinal.pdf). We adopted the dietary index developed by Rutten-Jacobs et al.[19] based on adherence to selected dietary targets recommended by the American Heart Association.[20] Briefly, the index included the following categories of food items: 1) fruit and vegetable; 2) fish; and 3) red and processed meat. Meeting the target for each category (i.e., ≥ 4.5 cups/day of fruits and vegetables, ≥ 2 serves/week of fish, and ≤ 2 times/week intake of processed meat and ≤ 5 times/week of red meat intake) is dichotomised as yes (1) and no (0). An overall diet quality score is derived by summing the three categories of food items (0-3) and recoded into: 0 (lowest diet quality), 1 (medium diet quality) and 2-3 (high diet quality).

Outcome variables: Date of death was ascertained from death certificates held by the National Health Service (NHS). All participants from England, Scotland and Wales were censored on 30 April 2020. All-cause mortality was defined as a death record from any causes. CVD mortality was ascertained when the primary cause of death was CVD, defined by International Classification of Diseases (ICD)-10 I00-I99. Physical activity, diet, and adiposity-related cancer (PDAR cancer hereafter) mortality was determined when the primary cause of death was a type of cancer that is evidentially linked to physical inactivity, and/or diet and/or adiposity. Specifically, we selected the types of cancer for which there is strong/convincing evidence based on the 2018 US Physical Activity Guidelines Advisory Committee Scientific Report[21] and the World Cancer Research Fund Strong Evidence Matrix.[5] Cancer in the following sites was included for PDAR cancer mortality: bladder (C67), breast (postmenopausal; ascertained by C50 combined with self-related menopausal status), colorectal (C18-21), endometrium (C54.1), stomach (C16), kidney (C64), liver (C22), oesophagus (C15), and pancreas (C25). Based on the current sample, deaths from these PDAR cancers represented 59% of all cancer mortality.

Covariates: We used Directed Acyclic Graphs (DAG) developed in Dagitty[22] to identify confounders. DAG is a conceptual representation for mapping assumptions about a related set of variables involved in a causal research question.[22] Confounding paths and minimal sufficient adjustment variables were identified through the DAG (Supplementary Figures 2 and 3). We accordingly adjusted for age group

category (ages below 50, ages 50-59, and ages 60 and above, rationales for cut-off points in Supplementary Figure 4), sex (male vs female), educational attainment (categorised based on the British educational system as: University, A/AS levels or equivalent [11-12 years], O Levels/GCSEs/CSEs [7-10 years], NVQ/HND/HNC [vocational], or other), Townsend Index (quartiles, an indicator for area-level material deprivation,[23] measured immediately prior to participants joining the study), living arrangement (living with vs without partner), country of birth (UK vs non-UK), type of job (categorised into: manual and physically demanding, mainly walking or standing, sedentary, and not employed, based on self-reported frequencies of jobs involving mainly heavy manual and physical work, and walking or standing), smoking status (never, former, current), weekly alcohol consumption (0, 1-14 drinks, 14+ drinks), and physician diagnosis of hypertension and diabetes at baseline (yes vs no). It is unclear whether body mass index (BMI) is a confounder or a mediator, we therefore did not adjust for BMI in the model, but explored the effects of adjusting for BMI in a sensitivity analysis.

Statistical analysis:

The relationship between physical activity (MVPA or VPA), diet and mortality outcomes (all-cause, CVD, and PDAR cancer mortality) was examined using Cox proportional hazards model among non-pregnant, apparently healthy participants with complete data on exposure measures and covariates. To minimise the risk of 'reverse causation' (i.e., lifestyle change as a result of health conditions that increase risk of mortality), those with a baseline diagnosis of CVD, cancer, degenerative neurological disorder, late-stage renal disease, chronic obstructive pulmonary disease and emphysema (based on self-report and a range of administrative linkage data, such as hospital admissions and primary care data), and those who were underweight (BMI <18.5) or reported chronic widespread pain were excluded.[24] A left-truncated Cox proportional hazards model was fitted using age as the underlying time scale. This model is recommended where a wide range of ages is being assessed over a relatively long period, especially when investigating effects in older adults.[25] For all analyses, hazard ratios (HR) and 95% confidence interval (CI) were presented adjusted for all covariates described above. Analyses were further adjusted for MPA and walking time when VPA was modelled as the exposure variable. Models were assessed for any violation of the proportional hazards assumption by testing for

any significant correlation between Schoenfield residuals and time, and covariates were stratified if necessary until the assumption was met.

To explore the independent and joint associations of physical activity and diet quality, two sets of models were fitted. First, both diet and physical activity were included in the same model to assess the independent effects of an exposure variable when the other exposure and all covariates were adjusted for. Multiplicative interactions were tested by including a diet × physical activity interaction term to the adjusted model and using a Wald's test to assess the differences between the models with and without the interaction term. Additive interactions were tested by refitting all models using non-parametric Aalen additive regression models, allowing for an estimation of hazard difference on a linear scale, and we tested for interactions in these models. Where no evidence was found of multiplicative interactions between exposures of interest, the combined effects of diet and physical activity were estimated using linear combinations of hazard ratios with the theoretically highest-risk category (lowest physical activity: MVPA Quartile 1 or no VPA and worst diet quality: diet quality index=0) as the reference group. All analysis was performed in R (version 4.1.2).

We conducted several sensitivity analyses. First, considering the inconsistent evidence on occupational physical activity and mortality,[26,27] we conducted a sensitivity analysis excluding those whose job mainly involved manual and physically demanding work (8%), based on the assumption that for these participants, heavy occupational physical activity constituted most of their reported total MVPA. Second, to account for reverse causation caused by occult disease (i.e., people with low physical activity and poor diet were more likely to die within the first two years as a result of undiagnosed conditions), we reran the analysis by excluding the first two years of follow-up time. Third, as mentioned above, we explored models with BMI as an additional confounder. Fourth, considering the competing risk between CVD and cancer mortality, a Fine-Gray model of competing risks[28] was used accounting for the marginal probability of each 'sub-distribution' (e.g., those who died from CVD versus those dying from non-CVD related causes). Finally, we explored the associations of physical activity and diet with all cancer, in comparison with PDAR-cancer. The

reporting of the study follows the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist.

Results

The final analytical sample included 346,627 participants with complete data on physical activity, diet and all covariates, without diagnosed CVD, cancer, degenerative neurological disorder, late stage renal disease, chronic widespread pain, COPD and emphysema, or being underweight at baseline (Supplementary Figure 1). During a median of 11.2 (interquartile range [IQR]: 1.4) years and a total of 3,841,534 person years of follow-up, 13,869 participants died. Among those, 2,650 died from CVD, and 4,522 from PDAR cancers.

Baseline characteristics

Baseline characteristics of participants are described in Table 1. Overall, participants reported an average of 686 minutes/week (SD=679) (median = 672, IQR = 84) of weighted total MVPA (walking + MPA + VPA×2) with Quartile 1 reporting 0-210 minutes/week (mean=117; SD=60; median = 117, IQR=50), Quartile 2 reporting 211-450 minutes/week (mean=331; SD=69; median = 330, IQR=150), Quartile 3 reporting 451-920 minutes/week (mean=658; SD=134, median = 635, IQR=135), and Quartile 4 reporting 921-5,040 minutes/week (mean=1,644; SD=686; median = 1440, IQR=780). In terms of VPA, 40.8% reported doing no VPA at all, 26.5% less than 75 minutes/week, 15.4% reported 76-150 minutes/week, and 17.4% reported performing more than 150 minutes/week. Regarding diet quality, 22.1% of participants had a dietary index score of 0 (the poorest), 53.4% of participants had a dietary index score of 1, and 24.5% of participants had a dietary index score of 2-3 (the best). Overall, males, participants without university education, with manual jobs or jobs involving walking and standing, and those of normal weight reported higher levels of MVPA. Meanwhile, participants who were slightly older, female, university educated, not living with a partner, born overseas, not working, and those not currently smoking or drinking excessively, and of normal weight were more likely to report higher diet quality index (Table 1).

Physical activity and diet as individual risk factors

MVPA, VPA and diet quality index were significantly associated with all-cause, CVD and PDAR cancer mortality outcomes in unadjusted models (Table 2). The magnitude of associations was attenuated in the adjusted models. In adjusted models, higher levels of MVPA (Quartiles 2-4) were significantly associated with all three mortality outcomes with the strongest association observed in Q4 for all-cause (HR=0.87, 95%CI: 0.83-0.91) and PDAR cancer mortality (HR=0.86, 95%CI: 0.79-0.93) and in Q2 for CVD mortality (HR=0.85, 95%CI: 0.76-0.95). VPA was inversely associated with all-cause and CVD mortality but not significantly associated with PDAR cancer mortality. The association between VPA and CVD mortality appeared stronger than that between MVPA and CVD mortality. However, the associations between VPA and CVD mortality were not dose-dependent with the lowest risk observed for the two middle VPA categories (10-75 minutes/week: HR=0.75, 95%CI: 0.68-0.83; 76-150 minutes/week: HR=0.76, 95%CI: 0.67-0.86), not the highest category (Q4 HR=0.90, 95%CI: 0.81-1.02). The inverse associations of diet quality index with all-cause and CVD mortality were non-significant in most models, except that being in the best category of diet quality was associated with 15% lower risk in cancer mortality (HR=0.85, 95%CI: 0.78-0.93).

Physical activity and diet as interactive risk factors

We did not find evidence for statistically significant multiplicative or additive interactions in neither MVPA or VPA models for any outcome (Supplementary Tables 2-4). When exploring the linear combinations of joint effects between physical activity (MVPA and VPA) and diet quality index, we found that compared with the highest risk combination (MVPA Quartile 1 or no VPA and diet quality index =0), most other combinations had a significantly lower HR for all-cause, CVD and PDAR cancer mortality. For all-cause and PDAR cancer mortality, the incremental reductions of HR by both physical activity and diet quality index were clear, and the combinations with the lowest HR involved being in MVPA Quartiles 3 and 4 and a diet quality index of 2-3. For CVD mortality, the lowest HR was observed in Quartiles 2 and 3 and the highest diet quality index (Figure 1). The analysis of VPA and diet quality index combinations showed generally similar patterns (Figure 2). Overall, there is no evidence for high levels of physical activity, measured as MVPA or VPA, offsetting low diet quality

in any of the analyses; neither was there evidence for a higher diet quality index offsetting a lack of physical activity.

Sensitivity analysis

All sensitivity analyses, including restricting to participants without a physically demanding job (Supplementary Table 5, Supplementary Figures 5-7), those excluding the first two years of follow-up (Supplementary Table 6, Supplementary Figures 8-10), those additionally adjusted for BMI as a covariate (Supplementary Table 7, Supplementary Figures 11-13), and those accounting for the marginal probability of sub-distributions (Supplementary Figures 14-17) revealed no substantial changes in the associations identified from the main analyses, suggesting robustness of the findings. Finally, compared with the associations between exposures (MVPA, VPA and diet quality) and PDAR cancer, all exposures had a weaker association with all cancer (Supplementary Figure 18), perhaps because this outcome lacked specificity (including less relevant cancers to physical activity and diet), but the confidence interval was narrower, due to more statistical power.

Discussion

The current study examined independent and joint effects of physical activity and diet quality on long-term mortality outcomes. Findings from this study confirm the importance of both physical activity and quality diet in all-cause and cause-specific mortality, suggesting that one should adhere to both sufficient physical activity and quality diet to minimise mortality risk.

Both healthy diet and regular physical activity have long been considered critical protective lifestyle factors against chronic disease and premature mortality.[29] Because of their complementary and interactive effects on energy, lipid, glucose and metabolic homeostatic processes,[30] and their shared physiological mechanisms for chronic disease prevention,[31] it has been suggested that diet and physical activity be jointly considered in epidemiological studies.[29,30] However, more than two decades after such call for consideration,[29] epidemiological studies examining their interactive effects on health and mortality are still rare.[11-13,32-34]

Findings of this study

Our study found an inverse association between physical activity and mortality from any causes, CVD and cancer. Particularly, associations of MVPA with all-cause and PDAR cancer mortality showed a dose-response pattern, with 13%-14% lower hazards observed in the most active quartile compared with the least active one. Such magnitude of risk reduction is similar to that identified by previous analyses.[24,35,36]When we particularly examined the role of VPA, we found a larger magnitude of risk reduction in CVD mortality, particularly in the middle categories (10-150 minutes/week), while accounting for MPA and walking. Although the evidence on whether VPA and MPA protect against mortality risk to the same extent remains equivocal,[37] several large cohort studies have found that doing some VPA may offer additional benefits than doing none, holding constant the total volume of MVPA.[14,15,38] It has been argued that VPA may lead to more physiological adaptations[14] and elicit more insulin sensitizing and anti-inflammatory effects[39] than lower-intensity physical activity, which may explain why the stronger association with VPA are particularly pronounced for CVD mortality in our study.

Despite the association between diet and all-cause and CVD mortality not reaching statistical significance, we found that those in the best diet quality category had 15% lower risk of PDAR cancer mortality compared with those in the worst category. It is important to emphasise that diet quality remains an important aspect of non-communicable disease prevention. Diet consists of countless health influencing components, and different measures capture different aspects of dietary health.[40] For example, studies based on the UK Biobank data found dietary indicators to be differentially associated with CVD events, all-cause and cause-specific mortality,[40,41] suggesting that effects of diet on health could be specific to the dietary indicators. The current diet quality index is based on meeting the recommendations for fruit and vegetables, fish, and red and processed meat, all of which are important dietary components for chronic disease prevention.[42] These food groups were selected as markers for overall diet quality, because other important dietary components and/or nutrient groups, such as whole grains and dairy, were not measured during baseline assessment. Considering that

errors in reported dietary measures are likely to attenuate diet-disease associations towards the null,[43] one may expect the 'true' association between diet quality and mortality outcomes to be stronger.

Consistently across the three outcomes, nearly all risk combinations involving higher physical activity categories had significantly reduced mortality risk compared with the highest-risk reference groups. In fact, across outcomes, the lowest risk combinations almost always involved the highest diet quality index and the highest or second-highest physical activity categories.

Comparison with other studies

The current investigation was motivated by several animal and human studies with promising findings suggesting that exercise may counteract short-term adverse effects of overfeeding. For example, Gioscia-Ryan et al. randomised mice into normal vs Western diet (characterised as high fat, high sugar, low fibre) and the absence vs presence of aerobic exercise (running wheel); their study found that a Western diet exacerbates age-related endothelial dysfunction, aortic stiffening, vascular oxidative stress and aortic inflammation, but all these effects were attenuated or completely prevented by exercise.[44] A small number of experimental studies conducted in human participants generally found that high-intensity exercise protects against detrimental metabolic effects of overfeeding,[45] such as insulinemic responses,[9] cardiometabolic profiles,[10] and genes expression in adipose tissue,[9] despite energy surplus. While these studies focused on short-term outcomes, long-term cumulation of adverse physiological outcomes could lead to chronic disease and ill-health. A small number of epidemiological studies have examined the joint associations between physical activity and diet on mortality outcomes. Alvarez-Alvarez et al. examined the joint association between physical activity and Mediterranean diet score, in the Seguimiento Universidad de Navarra (SUN) cohort, and found the largest all-cause mortality risk reductions in the groups that adhered to both high physical activity and healthier dietary scores.[13] Two studies based on the National Health and Nutrition Examination Survey found that the participants with higher levels of physical activity and better quality diet had the lowest risk of all-cause mortality in both general adults[11] and pre-frail and frail older adults.[12] However, an analysis of a cohort of postmenopausal Black women in the US found that neither diet nor physical activity, independently or combined, was associated with site-specific obesity-related

cancers.[34] A study based on healthy middle-aged participants from the Melbourne Collaborative Cohort Study found a stronger association between physical activity and mortality than that between diet and mortality, and that the adherence to Mediterranean diet contributed to little gain in addition to physical activity.[32] These mixed findings imply that more research with more valid measures are needed to fully understand the long-term joint effects of diet and physical activity on health and longevity.

Strengths and limitations

This study is the first to our knowledge to examine the joint association of physical activity and diet quality with all-cause and cause-specific mortality. Comprehensive analysis was conducted in a large sample with more than 10 years of follow-up and both multiplicative and additive interactions were tested. Various sensitivity analyses led to similar results, suggesting robustness of the findings. However, findings should be interpreted in light of limitations. First, despite using validated measures,[17,19] both physical activity and diet quality measures are subject to measurement bias. Particularly, biases associated with the dietary instrument are likely to explain the non-significant associations between diet and all-cause and CVD mortality outcomes. UK Biobank did introduce accelerometer and 24-hour dietary recall, both considered more comprehensive and valid measures, during later follow-ups. However, because accelerometer and dietary recall were measured in different years and the sample with both measures is small, we therefore chose to use the large baseline sample with diet and physical activity measured simultaneously. Second, both physical activity and diet were measured at one time point only, therefore, could not capture long-term behavioural pattern. Furthermore, the lack of time-varying data could influence the relationships between exposures and covariates, and consequentially, lead to biases in model specification, such as collider stratification bias.[46] For example, BMI could be a 'cause' or 'effect' of physical activity, but because BMI was measured at the same time as physical activity, it is impossible to determine the temporal order to inform covariate selection. The same applies to intermediate health outcomes, such as hypertension. In this case, if BMI was adjusted for, the models could be subject to overadjustment, but if not adjusted for, they could be subject to confounding. We built DAGs with several unmeasured

time-varying variables to inform model specification. However, with the presence of unmeasured confounding and selection bias, we had to make various assumptions in model specification. An example of such assumptions is that hypertension and diabetes were 'pre-existing' conditions and BMI was an outcome of baseline exposures. Although we compared models with and without BMI as a covariate as a sensitivity analysis and found minimal difference in the exposure-outcome associations, the current model is still far from the 'ideal correct' model where all relevant variables were measured, at different time points, and the causal relationships among variables could be clearly mapped. It is important to interpret findings from the current models within the context of the possibility of residual confounding from both unmeasured confounders and measurement biases associated with existing covariates (e.g., socioeconomic status, alcohol consumption). Third, missing data (around 13% participants omitted in complete case analysis) could result in selection bias. Fourth, in analysing physical activity as a categorical variable, there is an assumption of equal risk within each category. Although this is a common practice, measurement error may have been introduced via this process. Fifth, hazard ratios assume a consistent exposure-outcome association over time. Although all final models satisfied the proportional hazards assumption, selection bias in these estimates is likely, due to the inherent time-varying nature of mortality risk.[47] Sixth, the competing risk between PDAR cancer and CVD should ideally be modelled using cause-specific models, which were not computationally feasible in the present study. Fine-Gray models treats those who died from competing events not of interest to the research question (e.g., non-CVD causes in the CVD mortality model and non-PDAR cancer in the PDAR cancer model) as still within the set at risk, which is difficult to interpret and may potentially lead to biases. Finally, the UK Biobank Study had a participation rate of less than 6%,[16] and the participants appeared much more active than average, posing concerns regarding the representativeness of the sample and the generalisability of the findings. A recent study comparing unweighted risk factor-outcome associations in the UK Biobank with those using poststratification to match a population representative sample found that the lack of population representativeness could distort risk factor-outcome associations, but the association of physical activity and a dietary indicator with all-cause and CVD mortality remained similar.[48] Future studies could improve the current evidence by combining accelerometer-based physical activity

measures with higher quality dietary measures, such as those derived from 24-hout dietary recall, and ideally, assessing behavioural patterns repeatedly across lifespan.

Implications

This study reinforces the importance of physical activity and diet quality. Simultaneous adherence to both health behaviours is endorsed by health professionals and disseminated through clinical and public health recommendations worldwide. However, sensationalised headlines[49] and misleading advertisement for exercise regimens to lure consumers into the idea of 'working out to eat whatever they want'[50] have fuelled the circulation of the myth about 'exercise outrunning a bad diet'. Our study provided important evidence for health professionals to debunk the myth and continue to recommend and advocate for both physical activity and healthy diet.

Conclusion

Findings from the UK Biobank study suggest that both physical activity and diet are important for reducing mortality risk, and participants with both higher levels of physical activity and high-quality diet and tended to have the lowest mortality risk. Furthermore, our data provide evidence that high levels of physical activity cannot counteract the detrimental effects of a poor diet on mortality risk.

Competing interests

There is no competing risk to report.

Author contribution

DD and LF conceptualised the research question. DD led the investigation and drafted the paper. JVB conducted data analysis, BN helped with literature searches, ME with data management, and NV with dietary measures. All authors provided critical feedback on the paper at various stages and approved the final version of the paper.

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Ethical approval information

The UK Biobank is a large population-based cohort study, which received ethical approval from the North-West Research Ethics Committee.

Data sharing statement

UK Biobank data could be obtained upon application from https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access

Patient involvement

Not applicable

References

1. World Health Organization. Guidelines on physical activity and sedentary behaviour. In. Geneva: World Health Organization; 2020.
2. US Department of Health and Human Services. *Physical Activity Guidelines for Americans, 2nd edition.* Washington, DC2018.
3. Department of Health and Social Care. *UK Chief Medical Officers' Physical Activity Guidelines.* Department of Health and Social Care;2019.
4. Australian Government Department of Health and Ageing. *Eat for health: Australian Dietary Guidelines.* Canberra City, ACT: National Health and Medical Research Council 2013.
5. World Cancer Research Fund/American Institute for Cancer Research. Continuous update project: Diet, nutrition, physicla activity and the prevention of cancer. Summary of strong evidence https://www.wcrf.org/sites/default/files/CUP-Strong-Evidence-Matrix.pdf. Published 2019. Accessed 14 August 2019.
6. Steen J. Huffpost Web site. https://www.huffingtonpost.com.au/2017/10/19/why-cant-you-out-exercise-a-bad-diet_a_23246817/?guccounter=1. Published 2017 Accessed.
7. Malhotra A, Noakes T, Phinney S. It is time to bust the myth of physical inactivity and obesity: you cannot outrun a bad diet. *Br J Sports Med.* 2015;49(15):967-968.
8. Phillips SM, Joyner MJ. Out-running 'bad' diets: beyond weight loss there is clear evidence of the benefits of physical activity. *Br J Sports Med.* 2019;53(14):854.
9. Walhin JP, Richardson JD, Betts JA, Thompson D. Exercise counteracts the effects of short-term overfeeding and reduced physical activity independent of energy imbalance in healthy young men. *J Physiol.* 2013;591(24):6231-6243.

10. Duval C, Rouillier MA, Rabasa-Lhoret R, Karelis AD. High Intensity Exercise: Can It Protect You from A Fast Food Diet? *Nutrients.* 2017;9(9).

11. Edwards MK, Shivappa N, Mann JR, Hebert JR, Wirth MD, Loprinzi PD. The association between physical activity and dietary inflammatory index on mortality risk in U.S. adults. *Phys Sportsmed.* 2018;46(2):249-254.

12. Brown JC, Harhay MO, Harhay MN. Physical Activity, Diet Quality, and Mortality among Community-Dwelling Prefrail and Frail Older Adults. *J Nutr Gerontol Geriatr.* 2016;35(4):253-266.

13. Alvarez-Alvarez I, Zazpe I, Pérez de Rojas J, et al. Mediterranean diet, physical activity and their combined effect on all-cause mortality: The Seguimiento Universidad de Navarra (SUN) cohort. *Prev Med.* 2018;106:45-52.

14. Gebel K, Ding D, Chey T, Stamatakis E, Brown WJ, Bauman AE. Effect of Moderate to Vigorous Physical Activity on All-Cause Mortality in Middle-aged and Older Australians. *JAMA Intern Med.* 2015;175(6):970-977.

15. Shiroma EJ, Sesso HD, Moorthy MV, Buring JE, Lee IM. Do moderate-intensity and vigorous-intensity physical activities reduce mortality rates to the same extent? *Journal of the American Heart Association.* 2014;3(5):e000802.

16. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLoS Med.* 2015;12(3):e1001779.

17. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc.* 2003;35(8):1381-1395.

18. International Physical Activity Questionnaire. Guidelines for Data Processing and Analysis of International Physical Activity Questionnaire (IPAQ).

http://www.ipaq.ki.se/dloads/IPAQ%20LS%20Scoring%20Protocols_Nov05.pdf. Published 2005. Accessed.

19. Rutten-Jacobs LC, Larsson SC, Malik R, et al. Genetic risk, incident stroke, and the benefits of adhering to a healthy lifestyle: cohort study of 306 473 UK Biobank participants. *BMJ.* 2018;363:k4168.

20. Benjamin Emelia J, Blaha Michael J, Chiuve Stephanie E, et al. Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association. *Circulation.* 2017;135(10):e146-e603.

21. 2018 Physical Activity Guidelines Advisory Committee. *2018 Physical Activity Guidelines Advisory Committee Scientific Report.* Washington, DC: U.S. Department of Health and Human Services;2018.

22. Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *Int J Epidemiol.* 2016;45(6):1887-1894.

23. Townsend P PP, Beattie A. . *Health and deprivation: Inequality and the North.* Bristol: Croom Helm 1988.

24. Sanchez-Lastra MA, Ding D, Dalene K-E, Ekelund U, Tarp J. Physical Activity and Mortality Across Levels of Adiposity: A Prospective Cohort Study From the UK Biobank. *Mayo Clin Proc.* 2021;96(1):105-119.

25. Lamarca R, Alonso J, Gómez G, Muñoz A. Left-truncated data with age as time scale: an alternative for survival analysis in the elderly population. *J Gerontol A Biol Sci Med Sci.* 1998;53(5):M337-343.

26. Coenen P, Huysmans MA, Holtermann A, et al. Do highly physically active workers die early? A systematic review with meta-analysis of data from 193 696 participants. *Br J Sports Med.* 2018;52(20):1320-1326.

27. Holtermann A, Krause N, van der Beek AJ, Straker L. The physical activity paradox: six reasons why occupational physical activity (OPA) does not confer the cardiovascular health benefits that leisure time physical activity does. *Br J Sports Med.* 2018;52(3):149.

28. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med.* 2017;36(27):4391-4400.

29. Blair SN, Horton E, Leon AS, et al. Physical activity, nutrition, and chronic disease. *Med Sci Sports Exerc.* 1996;28(3).

30. Baranowski T. Why combine diet and physical activity in the same international research society? *Int J Behav Nutr Phys Act.* 2004;1(1):2.

31. Vuori IM. Health benefits of physical activity with special reference to interaction with diet. *Public Health Nutr.* 2001;4(2B):517-528.

32. Williamson EJ, Polak J, Simpson JA, et al. Sustained adherence to a Mediterranean diet and physical activity on all-cause mortality in the Melbourne Collaborative Cohort Study: application of the g-formula. *BMC Public Health.* 2019;19(1):1733.

33. Lee J, Walker ME, Bourdillon MT, et al. Conjoint Associations of Adherence to Physical Activity and Dietary Guidelines With Cardiometabolic Health: The Framingham Heart Study. *Journal of the American Heart Association.* 2021;10(7):e019800.

34. Chebet JJ, Thomson CA, Kohler LN, et al. Association of Diet Quality and Physical Activity on Obesity-Related Cancer Risk and Mortality in Black Women: Results from the Women's Health Initiative. *Cancer Epidemiol Biomarkers Prev.* 2020;29(3):591-598.

35. Matthews CE, Moore SC, Arem H, et al. Amount and Intensity of Leisure-Time Physical Activity and Lower Cancer Risk. *J Clin Oncol.* 2020;38(7):686-697.

36. Celis-Morales CA, Lyall DM, Anderson J, et al. The association between physical activity and risk of mortality is modulated by grip strength and cardiorespiratory fitness: evidence from 498 135 UK-Biobank participants. *Eur Heart J.* 2017;38(2):116-122.

37. Rey Lopez JP, Sabag A, Martinez Juan M, Rezende LFM, Pastor-Valero M. Do vigorous-intensity and moderate-intensity physical activities reduce mortality to the same extent? A systematic review and meta-analysis. *BMJ Open Sport & Exercise Medicine.* 2020;6(1):e000775.

38. Rey Lopez JP, Gebel K, Chia D, Stamatakis E. Associations of vigorous physical activity with all-cause, cardiovascular and cancer mortality among 64 913 adults. *BMJ Open Sport & Exercise Medicine.* 2019;5(1):e000596.

39. Balducci S, Zanuso S, Nicolucci A, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. *Nutr Metab Cardiovasc Dis.* 2010;20(8):608-617.

40. Livingstone KM, Abbott G, Bowe SJ, Ward J, Milte C, McNaughton SA. Diet quality indices, genetic risk and risk of cardiovascular disease and mortality: a longitudinal analysis of 77 004 UK Biobank participants. *BMJ open.* 2021;11(4):e045362.

41. Kebbe M, Gao M, Perez-Cornago A, Jebb SA, Piernas C. Adherence to international dietary recommendations in association with all-cause mortality and fatal and non-fatal cardiovascular disease risk: a prospective analysis of UK Biobank participants. *BMC Medicine.* 2021;19(1):134.

42. U.S. Department of Agriculture and U.S. Department of Health and Human Services. *Dietary Guidelines for Americans, 2020-2025.* 2020.

43. Paeratakul S, Popkin BM, Kohlmeier L, Hertz-Picciotto I, Guo X, Edwards LJ. Measurement error in dietary data: implications for the epidemiologic study of the diet-disease relationship. *Eur J Clin Nutr.* 1998;52(10):722-727.

44. Gioscia-Ryan RA, Clayton ZS, Zigler MC, et al. Lifelong voluntary aerobic exercise prevents age- and Western diet- induced vascular dysfunction, mitochondrial oxidative stress and inflammation in mice. *J Physiol.* 2021;599(3):911-925.

45. Bray GA, Bouchard C. The biology of human overfeeding: A systematic review. *Obes Rev.* 2020;21(9):e13040.

46. Cole SR, Platt RW, Schisterman EF, et al. Illustrating bias due to conditioning on a collider. *Int J Epidemiol.* 2010;39(2):417-420.

47. Hernán MA. The hazards of hazard ratios. *Epidemiology (Cambridge, Mass).* 2010;21(1):13-15.

48. Stamatakis E, Owen KB, Shepherd L, Drayton B, Hamer M, Bauman AE. Is Cohort Representativeness Passé? Poststratified Associations of Lifestyle Risk Factors with Mortality in the UK Biobank. *Epidemiology (Cambridge, Mass).* 2021;32(2):179-188.

49. Miller K. How to eat whatever you want without gaining weight. https://www.self.com/story/how-to-eat-whatever-you-want-without-gaining-weight. Published 2016. Accessed.

50. Do you workout so you can eat whatever you want? https://www.popsugar.com/fitness/Eat-Whatever-You-Want-Work-Out-8959986. Published 2010. Accessed.

Table 1. Descriptive statistics of the study sample (n=346,627, 2007-2010)

	Overall	Moderate-to-vigorous physical activity quartiles[1]				Diet quality index[2]		
		Q 1 n= 86,461	Q2 n= 85,109	Q3 n= 89,421	Q4 n= 85,636	0 (poorest) n= 76,519	1 n= 185,190	2-3 (best) n= 84,918
Age: median (IQR) years	57 (13)	56 (13)	56 (13)	57 (13)	57 (14)	55 (14)	56(13)	58 (13)
Female: n (column %)	186,439 (54)	48,148 (56)	47,297 (56)	48,136 (54)	42,858 (50)	26,588 (35)	106,350 (57)	53,501 (63)
Education								
University	125,416 (36)	32,073 (37)	34,512 (41)	34,840 (39)	23,991 (28)	25,575 (33)	67,856 (37)	31,985 (38)
A levels (11-12 years)	41,574 (12)	10,826 (13)	10,729 (13)	10,691 (12)	9,328 (11)	9,290 (12)	22,393 (12)	9,891 (12)
O levels/GCSEs/CSEs (7-10 years)	93,713 (27)	23,074 (27)	21,408 (25)	23,292 (26)	25,939 (30)	22,178 (29)	49,887 (27)	21,648 (25)
Vocational	21,954 (6)	4,943 (6)	4,658 (5)	5,374 (6)	6,979 (8)	5,555 (7)	11,310 (6)	5,089 (6)
Other	63,970 (18)	15,545 (18)	13,802 (16)	15,224 (17)	19,399 (23)	13,921 (18)	33,744 (18)	16,305 (19)
Townsend Deprivation Index quartile								
Q1 (least derived)	91,206 (26)	23,248 (27)	22,706 (27)	23,967 (27)	21,285 (25)	19,787 (26)	49,352 (27)	22,067 (26)
Q2	89,441 (26)	22,303 (26)	21,974 (26)	23,271 (26)	21,893 (26)	19,598 (26)	48,101 (26)	21,742 (26)
Q3	87,446 (25)	21,329 (25)	21,511 (25)	22,583 (25)	22,023 (26)	19,231 (25)	46,894 (25)	21,321 (25)
Q4 (most deprived)	78,534 (23)	19,581 (23)	18,918 (22)	19,600 (22)	20,435 (24)	17,903 (23)	40,843 (22)	19,788 (23)
Living with partner	257,329 (74)	64,305 (74)	63,384 (74)	66,737 (75)	62,903 (73)	58,888 (77)	138,513 (75)	59,928 (71)
Born outside of UK	29,806 (9)	8,023 (9)	7,518 (9)	7,609 (9)	6,656 (8)	4,908 (6)	16,217 (9)	8,681 (10)
Types of occupation								
Not working	128,110 (37)	29,159 (34)	30,662 (36)	34,845 (39)	33,444 (39)	25,863 (34)	67,718 (37)	34,529 (41)
Sedentary	126,677 (37)	41,737 (48)	37,015 (43)	32,884 (37)	15,041 (18)	27,863 (36)	69,388 (37)	29,426 (35)
Mainly walking or standing	65,593 (19)	13,256 (15)	14,523 (17)	16,937 (19)	20,877 (24)	15,087 (20)	35,123 (19)	15,383 (18)
Manual and physically demanding	26,247 (8)	2,309 (3)	2,909 (3)	4,755 (5)	16,274 (19)	7,706 (10)	12,961 (7)	5,580 (7)
Smoking status								
Never	197,959 (57)	49,821 (58)	49,619 (58)	51,315 (57)	47,204 (55)	41,741 (55)	107,317 (58)	48,901 (58)

Previous	115,745 (33)	27,763 (32)	28,008 (33)	30,468 (34)	29,506 (34)	25,187 (33)	60,898 (33)	29,660 (35)
Current	32,923 (9)	8,877 (10)	7,482 (9)	7,638 (9)	8,926 (10)	9,591 (13)	16,975 (9)	6,357 (7)
Alcohol consumption								
0 unit per week	76,239 (22)	21,303 (25)	17,991 (21)	17,978 (20)	18,967 (22)	14,249 (19)	41,473 (22)	20,517 (24)
1-14 units per week	204,794 (59)	49,823 (58)	51,500 (61)	54,102 (61)	49,369 (58)	43,128 (56)	111,104 (60)	50,562 (60)
>14 units per week	65,594 (19)	15,335 (18)	15,618 (18)	17,341 (19)	17,300 (20)	19,142 (25)	32,613 (18)	13,839 (16)
Body mass index (kg/m^2)								
18.5-24.9	120,001 (35)	25,173 (29)	29,573 (35)	33,352 (37)	31,903 (37)	21,981 (29)	66,502 (36)	31,518 (37)
25-29.9	149,059 (43)	36,346 (42)	36,679 (43)	38,708 (43)	37,326 (44)	34,628 (45)	78,881 (43)	35,550 (42)
>30	76,323 (22)	24,559 (29)	18,541 (22)	17,074 (19)	16,149 (19)	19,626 (26)	39,171 (21)	17,526 (21)
Diagnosed with hypertension	83,300 (24)	22,863 (26)	20,506 (24)	20,475 (23)	19,456 (23)	18,841 (25)	42,974 (23)	21,485 (25)
Diagnosed with diabetes	14,058 (4)	4,528 (5)	3,336 (4)	3,300 (4)	2,894 (3)	3,504 (5)	6,977 (4)	3,577 (4)

[1]Physical activity minutes/wk calculated as walking + moderate-intensity + vigorous-intensity physical activity ×2 using the International Physical Activity Questionnaire. Quartiles: Q1: 0-210 min/wk; Q2: 211-450 min/wk; Q3: 451-920 min/wk; Q4: 921-5040 min/wk.

[2]Validated diet quality index, developed based on the American Heart Association Guidelines regarding 1) fruit and vegetable; 2) red and processed meat; and 3) fish intake. An overall score ranged from 0 to 3 and recoded into: 0 (poorest), 1 (medium diet quality) and 2-3 (best).

Table 2. Associations of moderate-to-vigorous physical activity (MVPA), vigorous-intensity physical activity (VPA) and diet with all-cause, cardiovascular disease and cancer mortality (n=346,627)

	n[1]	Person - years	Deaths (n)	Unadjusted incidence density rate[2]	Unadjusted hazard ratio	Adjusted hazard ratio[3]
All-cause mortality						
MVPA quartile						
Q1 (0-210 min/wk)	86,461	959,282.3	3,710	3.87	Ref	Ref
Q2 (211-450 min/wk)	85,109	944,274.3	3,259	3.45	0.88 (0.84 - 0.92)	0.91 (0.87 - 0.96)
Q3 (451-920 min/wk)	89,421	990,950.9	3,393	3.42	0.85 (0.81 - 0.89)	0.88 (0.84 - 0.92)
Q4 (921-5040 min/wk)	85,636	947,028.5	3,507	3.70	0.88 (0.84 - 0.93)	0.87 (0.83 - 0.91)
VPA categories (min/week)						
0	141,428	1,564,835.6	6,806	4.35	Ref	Ref
10-75	91,789	1,018,271.1	3,235	3.18	0.80 (0.76 - 0.83)	0.87 (0.84 - 0.91)
76-150	53,231	591,393.6	1,707	2.89	0.77 (0.73 - 0.81)	0.85 (0.80 - 0.89)
>150	60,179	667,035.7	2,121	3.18	0.85 (0.81 - 0.89)	0.89 (0.84 - 0.94)
Diet quality index score[4]						
0 (poorest)	76,519	845,242.3	3,376	3.99	Ref	Ref
1	185,190	2,053,778.5	7,100	3.46	0.82 (0.79 - 0.85)	0.97 (0.93 - 1.01)
2-3 (best)	84,918	942,515.1	3,393	3.60	0.77 (0.73 - 0.81)	0.95 (0.91 - 1.00)
Cardiovascular disease mortality						
MVPA quartile						
Q1 (0-210 min/wk)	86,461	959,282.3	724	0.75	Ref	Ref
Q2 (211-450 min/wk)	85,109	944,274.3	581	0.62	0.80 (0.72 - 0.89)	0.85 (0.76 - 0.95)
Q3 (451-920 min/wk)	89,421	990,950.9	637	0.64	0.82 (0.73 - 0.91)	0.86 (0.77 - 0.96)
Q4 (921-5040 min/wk)	85,636	947,028.5	708	0.75	0.91 (0.82 - 1.01)	0.90 (0.81 - 1.00)
VPA categories (min/week)						
0	141,428	1,564,835.6	1,368	0.87	Ref	Ref
10-75	91,789	1,018,271.1	544	0.53	0.67 (0.60 - 0.74)	0.75 (0.68 - 0.83)
76-150	53,231	591,393.6	300	0.51	0.68 (0.60 - 0.77)	0.76 (0.67 - 0.86)
>150	60,179	667,035.7	438	0.66	0.87 (0.78 - 0.97)	0.90 (0.81 - 1.02)
Diet quality index score						
0 (poorest)	76,519	845,242.3	720	0.85	Ref	Ref
1	185,190	2,053,778.5	1,313	0.64	0.71 (0.65 - 0.78)	0.92 (0.84 - 1.01)
2-3 (best)	84,918	942,515.1	617	0.65	0.65 (0.59 - 0.73)	0.89 (0.80 - 1.00)
Physical activity, diet and adiposity related cancer mortality[5]						
MVPA quartile						
Q1 (0-210 min/wk)	86,461	959,282.3	1,215	1.27	Ref	Ref
Q2 (211-450 min/wk)	85,109	944,274.3	1,086	1.15	0.90 (0.83 - 0.97)	0.94 (0.86 - 1.02)
Q3 (451-920 min/wk)	89,421	990,950.9	1,115	1.13	0.86 (0.79 - 0.93)	0.90 (0.83 - 0.97)
Q4 (921-5040 min/wk)	85,636	947,028.5	1,106	1.17	0.86 (0.79 - 0.93)	0.86 (0.79 - 0.93)
VPA categories (min/week)						
0	141,428	1,564,835.6	2,161	1.38	Ref	Ref
10-75	91,789	1,018,271.1	1,105	1.09	0.85 (0.79 - 0.91)	0.94 (0.87 - 1.01)
76-150	53,231	591,393.6	587.0	0.99	0.83 (0.76 - 0.91)	0.93 (0.84 - 1.02)

>150	60,179	667,035.7	669.0	1.00	0.84 (0.77 - 0.92)	0.91 (0.83 - 1.00)
Diet quality index score						
0 (poorest)	76,519	845,242.3	1,099	1.30	Ref	Ref
1	185,190	2,053,778.5	2,392	1.16	0.85 (0.79 - 0.91)	0.96 (0.89 - 1.03)
2-3 (best)	84,918	942,515.1	1,031	1.09	0.72 (0.66 - 0.79)	0.85 (0.78 - 0.93)

[1]Analysis was restricted to participants with complete data on physical activity, diet and all covariates, and who were, at baseline, not underweight and without diagnosed cardiovascular disease, cancer, degenerative neurological disorder, late stage renal disease, chronic widespread pain, COPD and emphysema, or being underweight.

[2]Death per 1000 person-years.

[3]All models adjusted for age, sex, educational attainment, marital status, country of birth, type of occupation, neighbourhood deprivation, smoking status, alcohol intake, hypertension, diabetes, and diet quality index (when treating MVPA or VPA as the main exposure) and MVPA (when treating diet as the main exposure). Models for VPA further adjusted for moderate-intensity physical activity and walking.

[4]Validated diet quality index, developed based on the American Heart Association Guidelines regarding 1) fruit and vegetable; 2) red and processed meat; and 3) fish intake. An overall score ranged from 0 to 3 and recoded into: 0 (poorest diet quality), 1 (medium diet quality) and 2-3 (best diet quality).

[5]Including cancers for which there is strong evidence for diet, physical activity or adiposity being risk factors, including cancer in the bladder, breast (postmenopausal), colorectum, endometrium, stomach, kidney, liver, oesophagus, pancreas.

Figure 1. Combinations of moderate-to-vigorous physical activity (MVPA) quartiles and diet quality index and all-cause, cardiovascular disease and physical activity, diet, and adiposity-related cancer mortality outcomes (n=346,627)

Quartiles: Q1: 0-210 min/wk; Q2: 211-450 min/wk; Q3: 451-920 min/wk; Q4: 921-5040 min/wk

An overall score ranged from 0 to 3 and recoded into: 0 (poorest), 1 (medium diet quality) and 2-3 (best).

All models adjusted for age, sex, educational attainment, marital status, country of birth, type of occupation, neighbourhood deprivation, smoking status, alcohol intake, hypertension, diabetes and diabetes.

Figure 2. Combinations of vigorous-intensity physical activity (VPA) and diet quality index and all-cause, cardiovascular disease and physical activity, diet, and adiposity-related cancer mortality outcomes (n=346,627)

An overall diet quality score ranged from 0 to 3 and recoded into: 0 (poorest), 1 (medium diet quality) and 2-3 (best).

All models adjusted for age, sex, educational attainment, marital status, country of birth, type of occupation, neighbourhood deprivation, smoking status, alcohol intake, hypertension, diabetes, moderate-intensity physical activity and walking.