Walking pace improves all-cause and cardiovascular mortality risk prediction:

A UK Biobank prognostic study

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Abstract

Aims: To quantify and rank the prognostic relevance of dietary, physical activity and physical function factors in predicting all-cause and cardiovascular mortality in comparison to the established risk factors included in the European Society of Cardiology Systematic COronary Risk Evaluation (SCORE).

Methods: We examined the predictive discrimination of lifestyle measures using C-index and R^2 in sex-stratified analyses adjusted for: model 1, age; model 2, SCORE variables (age, smoking status, systolic blood pressure, total and HDL cholesterol).

Results: The sample comprised 298,829 adults (median age, 57 years; 53.5% women) from the UK Biobank free from cancer and cardiovascular disease at baseline. Over a median follow-up of 6.9 years, there were 2174 and 3522 all–cause and 286 and 796 cardiovascular deaths in women and men, respectively. When added to model 1, self-reported walking pace improved C-index in women and men by 0.013 (99% CI: 0.007, 0.020) and 0.022 (0.017, 0.028) respectively for all-cause mortality; and by 0.023 (0.005, 0.042) and 0.034 (0.020, 0.048) respectively for cardiovascular mortality. When added to model 2, corresponding values for women and men were: 0.008 (0.003, 0.012) and 0.013 (0.009, 0.017) for all-cause mortality; and 0.012 (-0.001, 0.025) and 0.024 (0.013, 0.035) for cardiovascular mortality. Other lifestyle factors did not consistently improve discrimination across models and outcomes. The pattern of results for R^2 mirrored those for C-index.

Conclusion: A simple self-reported measure of walking pace was the only lifestyle variable found to improve risk prediction for all-cause and cardiovascular mortality when added to established risk factors.

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Keywords: Walking pace; Mortality; Cardiovascular risk; Prognosis

Introduction

Cardiovascular disease (CVD) is a global epidemic representing a major public health issue. [1] Modifiable lifestyle behaviours, such as smoking, physical inactivity, and unhealthy diets are established risk factors for cardiovascular mortality.[2–5] Epidemiological evidence further suggests that self-reported or easily collected measures of physical function, such as walking pace and handgrip strength, are also strongly associated with mortality and CVD.[6–8] However, while the literature reporting associations among diet, physical activity and physical function with health outcomes is extensive, there has been less attempt to quantify whether these factors improve the prediction of mortality outcomes in a large contemporary cohort, with analysis largely restricted to single lifestyle factors and all-cause mortality.[9,10]

In recent years, a focused approach on prognostic research has been suggested whereby the identification of an association between risk factors and outcomes represents only the initial research step (i.e., aetiological association).[11] Proof of association does not necessarily translate into a better prediction ability, even in the case of very strong, independent, and causal associations. Such a relevant distinction relies on the substantial difference between aetiological and prognostic research as the prediction of an outcome is not equivalent to explaining its cause.[11]

Investigating the prognostic importance of dietary and lifestyle factors also has potential for public health relevance. Current established risk scores for cardiovascular or all-cause mortality largely relay on non-modifiable (age, sex) or biological (e.g. blood pressure, cholesterol) risk factors.[12–15] For example, the European Society of Cardiology Systematic Coronary Risk Evaluation (SCORE) risk score, which was developed to estimate the probability of cardiovascular mortality, is based on age, smoking status, systolic blood pressure, total and HDL cholesterol.[15] SCORE is one of the most widely investigated and validated risk models developed on a European population.[16–19] The discordance between health promotion campaigns, which are based on modifiable lifestyle behaviours (i.e. encouragement of physical activity), and risk prediction is therefore evident. Consequently,

behaviour change does not necessarily affect current risk prediction, whilst risk prediction does not reinforce the importance of healthy lifestyle behaviours. This limitation has been recognised in the development of prediction tools for some chronic diseases: for example, the established Finnish Diabetes Risk Score included questions related to diet and physical activity for educational purposes and not because those particular questions were found to be prognostically relevant.[20] Research is therefore needed across a broad range of lifestyle factors to identify those with the greatest potential for improving risk prediction for disease outcomes, including cardiovascular disease.

In view of these limitations and of current standards for defining clinical usefulness of risk factors in risk prediction,[21] we aimed to systematically quantify and rank the potential usefulness of simple, easily collected dietary, physical activity and physical function variables as prognostic markers for all-cause and cardiovascular mortality in comparison with, and when added to, the SCORE risk factors in the contemporary UK Biobank population. This will provide novel evidence whether lifestyle variables that could easily be collected within routine care settings add to the prognostic information that is already contained within established risk factors.

Methods

UK Biobank

This analysis used data from 502 621 volunteers within UK Biobank, aged between 38 and 73 at recruitment (UK Biobank Application Number 3140). UK Biobank is an ongoing prospective cohort study with data collected in 22 centres throughout England, Wales, and Scotland between March 2006 and July 2010. Data field (DF) identification numbers are reported below for each variable included in this analysis and can be used to search for detailed information about measurement procedures within the UK Biobank data showcase.[22] Ethical approval for the UK Biobank study was obtained from the North West Centre for Research Ethics Committee (MREC, 11/NW/0382). In Scotland, UK Biobank has approval from the Community Health Index Advisory Group (CHIAG).

Diet variables

A touchscreen food frequency questionnaire captured information on diet. We used several diet variables: oily fish (DF 1329), non-oily fish (1339), poultry (1359), cheese (1408), beef (1369), lamb/mutton (1379), and pork (1389) intake, fresh fruit (1309), dried fruit (1319), bread (1438) and cereal (1458). Processed meat (1349) was defined through a single variable assessing any intake of bacon, ham, sausages, meat pies, kebabs, burgers, and nuggets. For each of the above variables, participants were asked about their frequency of consumption through selecting one of the following: never, less than once a week, once a week, 2–4 times a week, 5–6 times a week, once or more daily. For the above variables, frequency categories were converted to a continuous weekly score, as follows: a value of 0 was allocated to “never”, 0.5 for “less than once a week”, 1 for “once a week”, 3 for “2–4 times a week, 5.5 for “5–6 times a week” and 7 for “once or more daily”. Salad/raw vegetables (1299) and cooked vegetables (1289) variables were also reported as tablespoons/day. In addition, we used the following categorical diet variables: milk type (1418), which was converted to animal milk (full-cream, semi-skimmed, skimmed), plant milk

(soya), never/rarely have milk, and other (other type of milk); spread type (1428), which was converted to animal based spread (butter/spreadable butter), plant based spread (flora pro-active/Benecol), never/rarely use spread, and other (other type of spread/margarine).

Alcohol intake was also calculated using data on: beer (1588), alcopop (5364), wine (1568 and 1578), fortified wine (1608), and spirits (1598) consumption in an average week. Each drink was converted into equivalent standard units using the guidelines from the Office for National Statistics to convert volumes to units, where 1 unit contains 10 ml of ethyl alcohol. Total weekly units of alcohol were calculated by adding the units of beer, wine, and spirits. Excess alcohol consumption was defined as the consumption of more than 14 units of alcohol a week based on the current National Health Service guidelines.[23]

A healthy eating score was also calculated using current guidelines on healthy eating.[24] Participants were given a score of 1 or 0 based on their engagement with the current healthy eating guidelines: red meat, ≤3 portions per week = 1 and >3 portions per week = 0; processed meat, ≤1 portion per week = 1 and >1 portion per week = 0; fruit and vegetable consumption, ≥5 per day = 1 and <5 per day = 0; oily fish, ≥1 per week = 1 and <1 per week = 0; non-oily fish, ≥2 per week = 1 and <2 per week = 0; alcohol intake, never drink/≤14 units per week = 1 and >14 units/week = 0. Higher scores therefore indicated healthier eating.

Measures of physical activity and physical function

Measures of physical activity included: number of days/week walked 10 or more minutes (864); number of days/week of moderate-intensity physical activity undertaken for 10 or more minutes (884); and number of days/week of vigorous-intensity physical activity undertaken for 10 or more minutes (904). The UK Biobank self-reported touchscreen questionnaire was used to capture usual walking pace (924) at baseline; participants were also asked to answer the following question: “How would you describe your usual walking

pace? (a) Slow; (b) Steady/average; and (c) Brisk". Objectively measured handgrip strength was also assessed as described elsewhere.[6]

Other variables

Data were also captured for other variables including age (21003; years); systolic blood pressure (BP) (4080; mmHg); smoking status (20116; current, previous, never, prefer not to answer); total cholesterol (30690; mmol/L) and HDL cholesterol (30760; mmol/L). Total cholesterol and HDL cholesterol serum samples were measured using Beckman Coulter AU5800 analytical platform by enzymatic and enzyme immuno-inhibition, respectively.

Outcomes

The study outcomes were all-cause and cardiovascular mortality. Date and cause of death were obtained from the NHS Information Centre, for participants from England and Wales, and from the NHS Central Register, for participants from Scotland. Cause of death was classified using DF 40001 and the International Classification of Diseases (ICD) code assigned to the underlying (primary) cause of death. We defined cardiovascular mortality using ICD–10 codes I00–I79.

Cohort definition

From the initial sample of 502,621 participants, we excluded people with prevalent cancer [number of self–reported cancers (DF 134); n= 41,706] or prevalent CVD [defined as peripheral vascular disease, angina, heart attack/myocardial infarction, heart failure/pulmonary oedema, stroke, and transient ischaemic attack (DF 20002); n=28,078]. From the remaining sample, subjects with information available for all covariates (n=298,829) were included (**Figure 1**). Patients were followed-up between study entry until

date of death or censoring dates (31 January 2016 for England and Wales; 30 November 2015 for Scotland).

Statistical analysis

This paper used the concordance index (Harrell's C-index) to quantify model predictive discrimination ability. The C-index has been frequently used as a metric for evaluating the performance of prognostic models: in survival analysis, C-index is the probability of concordance between the predicted and observed survival, with values ranging from 0.5 (no discrimination) to 1.0 (perfect discrimination).[25] The added prognostic value of each investigated factor was quantified as the difference (Δ) in C-index compared to the base model. To address the key aims of the paper, two prognostic models were used. In Model 1, the dietary, physical activity and physical function factors used in this study were added individually to a sex stratified base model that was adjusted for age. In order to assess the comparative relevance of the resulting C-index statistics, each factor from the SCORE model (smoking status, systolic blood pressure, total and HDL cholesterol) was also added individually to the age adjusted model to allow for a comparison between investigated and established risk factors. In Model 2, dietary, physical activity and physical function factors were added individually to a sex-stratified base model containing all the SCORE risk factors to assess whether each investigated factor provided added prognostic discrimination when added on top of well-established risk factors. We complemented C-index metric with adjusted R^2 estimation (i.e., the explained variation of the survival outcome) in models with and without each investigated factor.[26] Finally, in order to highlight differences between prognostic outcomes and those typically reported for observational research, we also report the sex-specific association of each variable with all-cause and cardiovascular mortality using Cox proportional hazard models with time to event measured from study entry (baseline) to death in model 1 (age only) and model 2 (SCORE risk factors: age, smoking status, systolic blood pressure, total and HDL cholesterol).

All analyses were conducted using Stata MP 14.1 (Stata Corporation, College Station, TX, USA). Statistical significance was set at a conservative level of $p<0.01$ to account for multiple testing and results reported with 99% confidence interval (CI).

Results

Tables S1 and **S2** show the characteristics of the 298,829 participants included in this study. The median age of participants was 57 (interquartile range (IQR), 49-62) years and 159,832 (53.5%) were women. There were 2174 (0.72%) and 3522 (1.17%) all–cause and 286 (0.10%) and 796 (0.27%) CVD deaths in women and men, respectively, during a median (IQR) of 6.92 (6.25-7.56) years of follow-up (2 061 373 person-years).

For all-cause mortality, when added to model 1 (age), smoking status and walking pace provided the greatest risk discrimination in both women and men (**Figure S3** and **Table 1**; **Table S3**). When adding diet, physical activity and physical function factors to model 2 (SCORE risk factors), in women the C-index for all-cause mortality was only improved by walking pace, while in men it was improved by walking pace, handgrip strength, cereal intake, healthy eating score, and processed meat intake (**Figure S3** and **Table 1**; **Table S4**).

For cardiovascular mortality, when added to model 1 smoking status provided the greatest discrimination in women, whilst walking pace did in men (**Figure S3** and **Table 1**; **Table S3**). In model 2, none of the lifestyle factors improved the C-index for cardiovascular mortality in women; conversely, in men it was improved by walking pace, handgrip strength, and cereal intake (**Figure S3** and **Table 1**; **Table S4**).

The pattern of results for R^2 mirrored those of the C-index, for both all-cause and cardiovascular mortality (**Figure S4**). Model 2 R^2 for all-cause mortality was 0.294 and 0.323 in women and men, respectively; these values increased to 0.326 and 0.374, respectively, upon the inclusion of walking pace; corresponding estimates for CVD mortality were 0.460 and 0.319 for model 2 and 0.515 and 0.405 upon the inclusion of walking pace (**Figure S4**).

More frequent associations were observed when quantified by hazard ratios compared to the prognostic factors identified with the C-index. In age-adjusted models, all-cause mortality hazard ratios were significant for 9 and 13 dietary factors, and for 5 and 3 physical activity and physical function factors, in women and men, respectively; corresponding values for

CVD mortality were 2 and 7 (dietary factors) and 1 and 3 (physical activity and function factors) (**Figure S5**). For the SCORE risk factors, total cholesterol and HDL cholesterol were negatively associated with all-cause mortality in women and men, while systolic blood pressure was positively associated with all-cause mortality in men. HDL cholesterol was negatively associated with cardiovascular mortality in women and systolic blood pressure was positively associated with cardiovascular mortality in men. All-cause and CVD mortality hazard ratios estimates for each lifestyle when adjusted for the SCORE variables are displayed in **Figure S6**.

Discussion

The aim of this study was to investigate the prognostic relevance of simple measures of diet, physical activity and physical function in comparison with, and when added to, established risk factors used to predict cardiovascular mortality. Several factors were highlighted as improving prediction, the most notable of which was walking pace, which improved predictive discrimination for of all-cause and cardiovascular mortality to a similar extent as smoking status in age-adjusted models, particularly for men. Importantly, walking pace also improved predictive discrimination for both all-cause mortality (women and men) and cardiovascular mortality (men) when added to a base model containing the conventional SCORE[12] risk factors age, smoking status, systolic blood pressure, total and HDL cholesterol, which are also widely used in other established risk prediction models, including PCE (Pooled Cohort Equations)[15], FRS (Framingham Risk Score)[14] and RRS (Reynolds Risk Score).[13] Handgrip strength was also found to improve discrimination for both all-cause mortality and cardiovascular mortality in men, but to a lesser extent compared to walking pace. These results highlight that a simple measure of self-reported walking pace may be an important prognostic marker of all-cause and cardiovascular disease mortality when added to established risk factors commonly used in risk prediction tools.

There is wealth of literature investigating the association between lifestyle factors and mortality outcomes, with diet and physical activity thought to directly influence the risk of all-cause and cardiovascular mortality, including previous work conducted by our group.[2–4,27–30] However, few studies have systematically investigated diet and physical activity in relation to mortality prediction, with previous research restricted to assessing the predictive discrimination of lifestyle scores incorporating a limited number of factors.[9,10] As far as we are aware, this is the first study to systematically compare the predictive discrimination of multiple dietary, physical activity and physical function measures with the aim of highlighting those with the greatest predictive potential.

The finding that walking pace provides a similar magnitude of improvement in predictive discrimination as smoking for all-cause and cardiovascular mortality outcomes and that it adds predictive information when added to established risk factors highlights it as a simple, non-invasive measure with potential to improve the performance of established risk prediction tools. These findings adds novel prognostic information to previous, more aetiological research which demonstrated a strong association between walking pace and health outcomes. For example, slow walkers have been shown to have between 2 to 4 times higher risk of all-cause and cardiovascular mortality compared to fast walkers, as evidenced by hazard ratio values in the present and previous UK Biobank publications.[6,31] Recent research has also found that fast walkers have a longer life expectancy across all categories of normal weight and obesity status.[32] Self-reported walking pace has also been shown to be more strongly associated with mortality outcomes than measures of physical activity volume,[31,33] which further corresponds to the findings of this study where the frequency of walking or other physical activity did not improve prediction of all-cause or cardiovascular mortality. Walking pace is widely used measure of functional status and physical frailty and self-reported walking pace has been shown to be strongly associated with cardiorespiratory fitness,[6,34] which is considered a clinical vital sign.[35] A slow self-reported walking pace is therefore likely to identify people with low physiological reserve and an impaired ability to resist physical and/or psychological stressors. Our findings suggest that the consistent evidence of an association between walking pace and health outcomes translates also into improved risk prediction.

Out of all the dietary variables considered, when added to established risk factors none improved risk discrimination in women whilst only cereal intake improved discrimination for both all-cause and cardiovascular mortality in men, despite multiple dietary factors displaying an association with mortality outcomes when assessed through hazard ratios in both men and women (i.e. red and processed meat). The discrepancy in findings between association (measured using Hazard Ratio) and prediction (measured using the C-index) for dietary factors further highlights that establishing an association does not necessarily translate into

improved prediction. The importance of cereal intake in the association with, and prediction of, mortality outcomes observed in this study may be related to fibre intake. A recent systematic review and meta-analysis of prospective cohort studies suggests that cereal fibre intake is inversely associated with all-cause and cardiovascular mortality.[36] Our study adds to this evidence by further suggesting that cereal intake could improve risk prediction in men.

There are some strengths and limitations that deserve to be mentioned. Strengths include the large contemporary sample of participants, the follow-up duration allowing a large number of events, and the availability of multiple risk factors, including cholesterol, blood pressure and smoking. Nevertheless, there are a number limitations. There were more deaths in men than women, with a higher proportion dying of cardiovascular disease; therefore, the lower number of lifestyle factors found to improve prediction in women compared to men may be related to a lower number of events.[25] Diet was assessed using a food frequency questionnaire, therefore the measure of dietary variables included in this analysis may have some degree of measurement error whilst limiting the ability to capture energy intake and macronutrient content. However, the food frequency questionnaire used in UK Biobank has been shown to have reasonable reliability for the dietary variables used in this study.[37] Physical activity, physical function and dietary intake were self-reported, thus residual confounding due to limited measurement precision also remains a possibility. The limitations around confounding and causality in observational research are, however, less relevant for prognostic research, where the aim is to investigate whether factors aid risk prediction, as opposed to interest in identifying factors that can be used for health promotion (aetiological research). UK Biobank is not representative of the general population; this may limit the generalizability of these findings to other populations.[38]

In conclusion, this study suggests than amongst several easily measured dietary, physical activity and physical function measures, self-reported walking pace has the potential to significantly improve the prediction of all-cause and cardiovascular mortality beyond

established risk factors. Future studies in other populations are needed to validate the role of walking pace on top of established risk assessment tools.

Supplementary material

Supplementary material is available with this manuscript.

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Conflicts of interest:

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Figure Legends:

Figure 1: Participant flowchart

Table 1: C-index significant variables for all-cause and cardiovascular mortality (models 1 and 2)

Outcome	Model	Sex	Variable	C-index (99% CI)	C-index difference
All-cause mortality	Model 1	Women	Smoking status	0.695 (0.680, 0.709)	0.020 (0.013, 0.028)
			Usual walking pace	0.687 (0.673, 0.702)	0.013 (0.007, 0.020)
			Oily fish intake (portions per week)	0.675 (0.660, 0.690)	0.001 (0.000, 0.001)
		Men	Smoking status	0.706 (0.695, 0.717)	0.025 (0.019, 0.031)
			Usual walking pace	0.704 (0.692, 0.715)	0.022 (0.017, 0.028)
			Hand grip strength	0.689 (0.678, 0.700)	0.008 (0.004, 0.012)
			Cereal intake (bowls per week)	0.687 (0.676, 0.698)	0.006 (0.003, 0.009)
			Processed meat intake (portions per week)	0.685 (0.673, 0.696)	0.003 (0.001, 0.006)
			Healthy eating score	0.684 (0.673, 0.696)	0.003 (0.001, 0.006)
			Total cholesterol	0.684 (0.673, 0.695)	0.003 (0.000, 0.005)
			Fresh fruit intake (pieces per day)	0.683 (0.672, 0.695)	0.002 (0.000, 0.004)
			Dried fruit intake (pieces per day)	0.683 (0.672, 0.695)	0.002 (0.000, 0.004)
			Beef intake (servings per week)	0.683 (0.672, 0.695)	0.002 (0.000, 0.004)
			Milk type	0.683 (0.672, 0.694)	0.002 (0.000, 0.003)
			Spread type	0.683 (0.671, 0.694)	0.002 (0.000, 0.003)
	Model 2	Women	Usual walking pace	0.705 (0.690, 0.720)	0.008 (0.003, 0.012)
		Men	Usual walking pace	0.722 (0.711, 0.733)	0.013 (0.009, 0.017)
			Hand grip strength	0.716 (0.705, 0.727)	0.007 (0.004, 0.010)
			Cereal intake (bowls per day)	0.711 (0.700, 0.722)	0.002 (0.000, 0.004)
			Healthy eating score	0.711 (0.700, 0.722)	0.002 (0.000, 0.003)
			Processed meat intake (portions per week)	0.711 (0.700, 0.722)	0.002 (0.000, 0.003)
Cardiovascular mortality	Model 1	Women	Smoking status	0.745 (0.707, 0.783)	0.030 (0.009, 0.052)
			Usual walking pace	0.738 (0.699, 0.778)	0.023 (0.005, 0.042)
		Men	Usual walking pace	0.709 (0.685, 0.733)	0.034 (0.019, 0.048)
			Smoking status	0.698 (0.674, 0.722)	0.022 (0.010, 0.035)
			Cereal intake (bowls per day)	0.684 (0.660, 0.707)	0.008 (0.001, 0.015)
			Healthy eating score	0.682 (0.658, 0.707)	0.007 (0.000, 0.014)
	Model 2	Women	-	-	-
		Men	Usual walking pace	0.727 (0.704, 0.751)	0.024 (0.012, 0.035)
			Hand grip strength	0.712 (0.688, 0.736)	0.008 (0.001, 0.016)
			Cereal intake (bowls per day)	0.708 (0.685, 0.731)	0.004 (0.000, 0.008)

*Shown are variables with significant ($p<0.01$) change in C-index compared to base models (all C-index values are reported in Table S2 and S3). Within each model and sex, variables are sorted by descending order of C-index difference.

All-cause mortality: †Reference C-index (99% CI) for base model 1 (age adjusted):
Women: 0.674 (0.663, 0.685); Men: 0.681 (0.673, 0.690)

All-cause mortality: ‡Reference C-index (99% CI) for base model 2 (SCORE variables):
Women: 0.697 (0.686, 0.709); Men: 0.709 (0.701, 0.718)

Cardiovascular mortality: †Reference C-index (99% CI) for base model 1 (age adjusted):
Women: 0.715 (0.685, 0.744); Men: 0.676 (0.657, 0.694)

Cardiovascular mortality: ‡Reference C-index (99% CI) for base model 2 (SCORE variables):
Women: 0.756 (0.729, 0.783); Men: 0.704 (0.686, 0.722)

-indicates non-significant