Public Health in Practice 2 (2021) 100065

Contents lists available at ScienceDirect

Public Health in Practice

journal homepage: www.journals.elsevier.com/public-health-in-practice

Original Research

Associations of weight changes with all-cause, cancer and cardiovascular mortality: A prospective cohort study

Jufen Zhang *, Karen Hayden, Ruth Jackson, Rudolph Schutte **

Medical School, Faculty of Health, Education, Medicine and Social Care, Anglia Ruskin University, Chelmsford, UK

ARTICLE INFO

Keywords:
Weight change
All-cause mortality
Cancer death
CV death
UK Biobank

ABSTRACT

Objectives: Previous studies suggest that changes in body weight can lead to an increased risk of mortality in the general population, although the results are controversial. The current study sought to investigate this association further using data from the UK Biobank.

Study design: This is a large prospective population-based cohort study. Data were derived from the UK Biobank, with the initial assessments commencing between 2006 and 2010.

Methods: Proportional hazard models were used to assess the association between self-reported weight change and risk of all-cause, cancer and cardiovascular mortality. The effect of gender was also investigated.

Results: Of 433,829 participants with data for self-reported weight change, the mean age was 56 (standard deviation [SD]: 8.1) years and 55% were female. In total, 55% of participants reported no weight change, 28% gained weight, 15% lost weight, 2% did not know and 0.1% preferred not to give an answer. The median follow-up was 7.1 (interquartile range [IQR]: 6.4–7.8) years. Compared with participants with no weight change, those with weight loss had an increased risk of all-cause mortality (adjusted hazard ratio [HR] 1.25, 95% confident interval [CI] 1.18–1.32), cancer death (HR 1.17, 95% CI 1.08–1.27) and cardiovascular death (HR 1.26, 95% CI 1.12–1.43). Similarly, participants reporting weight gain also had an increased risk of all-cause mortality (HR 1.08, 95% CI 1.02–1.13), cancer death (HR 1.14, 95% CI 1.07–1.22) and cardiovascular death (HR 1.27, 95% CI 1.14–1.42). Participants who had a response 'do not know' or 'prefer not to answer' showed an increased risk of all-cause and cardiovascular mortality, particularly in men.

Conclusions: The results of this study highlight the importance of maintaining a stable weight in middle-aged adults. Further studies are needed to understand the pathophysiology of weight change and its effects on mortality.

1. Introduction

Cardiovascular (CV) disease and cancer are leading causes of death globally [1]. One of the contributing factors is change in body weight. Studies have shown that weight change, in particular, weight loss, was associated with an increased risk of all-cause mortality in patients with CV disease [2–5]. In patients with heart failure, mild-to-moderate obesity is associated with a lower mortality, the so-called obesity paradox [6–8]. In cancer patients, a growing number of studies [9–11] have described increased mortality in those who experience weight gain [12,13].

There is lack of consensus in existing studies regarding the effect of weight change on mortality in the general population [14,15]. Some studies suggest that weight loss is associated with increased mortality [14–16], and Myers et al. [17] found that weight gain in healthy men was related to lower mortality compared with men whose weight remained stable. The association between weight gain and risk of adverse health outcomes is unclear. Clarifying and understanding these associations is important so that more specific advice on weight monitoring can be provided. It is important to understand the association of weight changes and the effects this has on all-cause mortality, cancer death and CV death.

Using data from the UK Biobank, this study aimed to evaluate the associations between self-reported weight change and all-cause

* Corresponding author. Medical School, Faculty of Health, Education, Medicine and Social Care, Anglia Ruskin University, Bishop Hall Lane, Chelmsford, CM1 1SQ, UK.

** Corresponding author. Allied Health, Faculty of Health, Education, Medicine and Social Care, Anglia Ruskin University, Bishop Hall Lane, Chelmsford, CM1 1SQ, UK.

E-mail addresses: Jufen.Zhang@anglia.ac.uk, Jufen.Zhang@aru.ac.uk (J. Zhang), Rudolph.Schutte@aru.ac.uk (R. Schutte).

https://doi.org/10.1016/j.puhip.2020.100065
Received 23 March 2020; Received in revised form 20 October 2020; Accepted 4 December 2020
Available online 11 December 2020

mortality, cancer death and CV death. In addition, an investigated on how gender impacts the adverse health outcomes was conducted.

2. Methods

2.1. Study population

The data used in this study were from the UK Biobank [18,19], a large general population-based prospective cohort study. The UK Biobank is an open-access resource containing information from 22 assessment centres across the UK, taken between 2006 and 2010 for adults aged between 40 and 69 years at the point of recruitment. The data include detailed information on participant demographics, social, lifestyle, physical activity, medical history, hospital records and mortality data. In this study, participants with CV disease, such as angina, myocardial infarction and stroke, were excluded. Participants with cancer (malignant neoplasms) were also excluded. All participants provided electronic informed consent. In this study, all participants who self-reported weight change were included.

This study was based on the UK Biobank resource. Details of patients and public involvement in the UK Biobank are available online [18].

2.2. Weight change

Data on self-reported weight change was used in this study and was assessed at baseline as weight change one year prior to the baseline. A response of the weight change could be 'no change', 'gained weight', 'lost weight', 'do not know' or 'prefer not to answer'.

2.3. Endpoints

The main study endpoints were all-cause mortality, cancer death and CV death. The cause of death was defined according to the 10th edition of the International Classification of Diseases (ICD-10), cancer death (C00–C97) and CV death (I00–I99). The study period for participants was the date of their attendance at the recruitment centre (until the 1st March 2016) or the date of death. The date of the outcomes was taken from hospital admissions data.

2.4. Statistical analyses

Baseline characteristics of the participants were described by categories of weight change. Continuous variables were expressed as mean with standard deviation (SD) or median with interquartile range (IQR) depending on the distribution of the data, and categorical variables were recorded as frequency and percentage. Univariate and multivariable Cox proportional hazard regression models were used to assess association between changes in body weight and the time of all-cause mortality, cancer death and CV death, and the results were presented as hazard ratio (HR) with the 95% confidence intervals (CIs). The reference group was 'no change'. The proportional hazards assumption was checked based on Schoenfeld residuals [20,21].

The multivariable models were developed by firstly adjusting for age and sex, and then additionally adjusting for ethnicity, body mass index (BMI), an interaction between age and BMI, smoking status, alcohol consumption status, systolic blood pressure, diabetes and overall health. The confounders used in the analysis were based on the literature [14]. Variables with a large number of missing values, such as physical activity, were not included. Median imputation was used to assign the missing values for the continuous variables with missing values $< 3\%$, as they were not normally distributed. Subgroup analysis was carried out using the multivariable models by gender (male and female). Statistical analyses were conducted using STATA version 14.2. The level of significance was set at alpha $= 0.05$ with two tails.

3. Results

3.1. Baseline characteristics

Of 502,542 participants in the dataset, 67,824 were excluded due to severe CV events (such as angina, heart attack or stroke) or cancer, resulting in a study population of 434,718 individuals.

In this analysis, 433,829 participants who self-reported weight change were included. The mean age was 56 (SD: 8.1) years and 55% of the participants were female. In total, 88% of participants were from a White ethnic background, including British, Irish and any other White ethnic background (Table 1). More than half of participants reported no weight change (55%), 28% gained weight, 15% lost weight, 2% did not know their weight change and 0.1% preferred not to give an answer. Compared with other weight change groups, participants with a stable weight had lower BMI values and were less likely to have diabetes. Individuals in the stable weight group also had a higher rate of overall excellent health (83%), spent more time doing physical activity (79%) and were more likely to be current alcohol consumers (93%), but were less likely to be current smokers (10%). Among those who gained weight, a higher proportion were women (64%). The average dietary iron intake was slightly lower in participants who gained weight (mean [SD]: 13.3 [4.5] mg) compared to those who lost weight (mean [SD]: 13.5 [4.5] mg). It is recognised that participants who did not know their weight change were more likely to be current smokers (15.4%). In addition, participants who preferred not to provide information on their weight change were also more likely to be those who did not disclose their smoking status, alcohol consumption status or overall health rating.

3.2. Association between weight change and all-cause, cancer and CV mortality

Of 433,829 participants who self-reported weight change during a median follow-up period of 7.1 (IQR: 6.4–7.8) years, 9214 had died, of whom 5058 (55%) died due to cancer and 1895 (21%) died because of CV disease. Compared to the no weight change group, both weight loss and gain were associated with an increased risk of all-cause mortality (fully adjusted HR 1.25 [95% CI 1.18–1.32] for weight loss and HR 1.08 [95% CI 1.02–1.13] for weight gain) (see Table 2).

Weight loss showed an increased risk of cancer death and CV death (fully adjusted HR 1.17 [95% CI 1.08–1.27] for cancer death and HR 1.26 [95% CI 1.12–1.43] for CV death) and weight gain was also associated with cancer and CV mortality (HR adjusted for age and sex 1.14 [95% CI 1.07–1.22] for cancer death and HR 1.27 [95% CI 1.14–1.42] for CV death).

Participants who did not know their weight change or preferred not to provide information on their weight change had an increased risk of all-cause mortality and CV death (Table 2).

Fig. 1 shows Kaplan-Meier curves of all-cause mortality by the weight change groups and the percentages of each type of weight change. It shows that participants who had a response of 'prefer not to answer' or 'do not know' had a higher risk of all-cause mortality, although their percentages were relevantly lower.

In men, 5595 deaths were recorded (2812 [50%] deaths from cancer and 1353 [24%] from CV disease). Weight loss was a significant risk factor for all-cause mortality and CV death. Weight gain was also shown to be associated with all-cause mortality. Giving a response of 'do not know' or 'prefer not to answer' with regard to their weight change was more likely to have a risk of all-cause mortality and CV death. The wider confidence intervals of HR for 'prefer not to answer' responders reflect the uncertainty of the results (Fig. 2). In women, 3619 deaths were recorded (2246 [62%] deaths from cancer and 542 [15%] from CV disease). Weight loss was associated with an increased risk of all-cause mortality, cancer death and cardiovascular death (Fig. 2).

Table 1
Baseline characteristics by weight change groups (n = 433,829).

Characteristic	N	Lost weight (n = 64,426)	Gained weight (n = 120,900)	No change (n = 240,267)	Do not know (n = 7848)	Prefer not to answer (n = 388)
Age (years) [mean (SD)]	433,829	55.0 (8.1)	55.0 (8.0)	56.5 (8.1)	55.0 (8.3)	54.0 (8.9)
<60 years [n (%)]	260,255	40,154 (62.3)	78,356 (64.8)	136,447 (56.8)	5045 (64.3)	253 (65.2)
≥60 years [n (%)]	173,574	24,272 (37.7)	42,544 (35.2)	103,820 (43.2)	2803 (35.7)	135 (34.8)
Female [n (%)]	237,798	36,353 (56.4)	77,227 (63.9)	119,950 (49.9)	4074 (51.9)	191 (49.2)
Ethnicity-White [n (%)]	381,630	56,314 (87.4)	105,361 (87.2)	213,643 (88.9)	6213 (79.2)	99 (25.5)
Hip circumference (cm) [mean (SD)]	432,274	103.8 (9.8)	106.3 (9.4)	101.6 (8.4)	103.8 (9.9)	104.4 (10.8)
Waist circumference (cm) [mean (SD)]	432,319	90.5 (13.6)	92.9 (13.4)	88.2 (12.9)	91.5 (13.7)	94.8 (13.4)
Waist-to-hip ratio [mean (SD)]	432,244	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Waist-to-height ratio [mean (SD)]	431,914	0.5 (0.1)	0.6 (0.1)	0.5 (0.1)	0.5 (0.1)	0.6 (0.1)
Body mass index (kg/m^2) [mean (SD)]	433,829	27.8 (5.0)	29.0 (4.8)	26.4 (4.4)	27.7 (5.1)	28.4 (5.0)
Weight (kg) [mean (SD)]	433,829	78.9 (16.6)	81.2 (16.1)	75.8 (15.2)	78.6 (16.5)	78 (16.8)
Dietary iron (mg) [mean (SD)]	185,177	13.5 (4.5)	13.3 (4.5)	13.9 (4.4)	13.2 (4.6)	11.3 (6.9)
Smoking status [n (%)]						
Never	242,519	34,721 (53.9)	65,644 (54.3)	137,471 (57.2)	4514 (57.5)	169 (43.6)
Previous	144,289	22,142 (34.4)	42,188 (34.9)	77,891 (32.4)	2030 (25.9)	38 (9.8)
Current	45,349	7304 (11.3)	12,622 (10.4)	24,171 (10.1)	1206 (15.4)	46 (11.9)
Prefer not to answer	1672	259 (0.4)	446 (0.4)	734 (0.3)	98 (1.3)	135 (34.8)
Alcohol consumption status [n (%)]						
Never	19,138	3073 (4.8)	5650 (4.7)	9519 (4.0)	795 (10.1)	101 (26.0)
Previous	14,594	2854 (4.4)	4392 (3.6)	6927 (2.9)	410 (5.2)	11 (2.8)
Current	399,580	58,414 (90.7)	110,750 (91.6)	223,687 (93.1)	6596 (84.1)	133 (34.3)
Prefer not to answer	517	85 (0.1)	108 (0.1)	134 (0.1)	47 (0.6)	143 (36.9)
Systolic blood pressure (mmHg) [mean (SD)]	404,397	137.9 (19.2)	139.6 (19.5)	139.9 (19.8)	140.8 (20.2)	140.1 (19.3)
Diabetes [n (%)]	19,476	5382 (8.4)	4780 (4.0)	8943 (3.7)	348 (4.4)	23 (5.9)
Activity (Duration of moderate activity)	320,966	66.3 (76.0)	62.1 (74.2)	67.6 (79.0)	65.7 (81.6)	68.5 (81.2)
Overall health rating [n (%)]						
Excellent	349,815	50,535 (78.4)	93,600 (77.4)	199,676 (83.1)	5936 (75.6)	68 (17.5)
Good	56,282	8,813 (13.7)	17,623 (14.6)	28,730 (12.0)	1101 (14.0)	15 (3.9)
Fair	26,214	4895 (7.6)	9,313 (7.7)	11,379 (4.7)	610 (7.8)	17 (4.4)
Prefer not to answer	1518	183 (0.3)	364 (0.3)	482 (0.2)	201 (2.6)	288 (74.2)

Table 2
Hazard ratio (95% confidence interval) for all-cause mortality, cancer death and cardiovascular (CV) death.

Mortality type and model[a]	Weight change (n = 433,829)				
	Lost weight (n = 64,426)	**Gained weight** (n = 120,900)	**No change** (n = 240,267)	**Do not know** (n = 7848)	**Prefer not to answer** (n = 388)
All-cause mortality					
[n (%)]	1612 (2.5)	2381 (2.0)	4988 (2.1)	216 (2.8)	17 (4.4)
Model 1	1.22 (1.15–1.29)***	0.95 (0.90–0.99)*	Reference	1.33 (1.16–1.52)***	2.40 (1.49–3.86)***
Model 2	1.38 (1.31–1.46)***	1.17 (1.12–1.23)***	Reference	1.53 (1.33–1.75)***	2.80 (1.74–4.50)***
Model 3	1.25 (1.18–1.32)***	1.08 (1.02–1.13)**	Reference	1.37 (1.19–1.57)***	2.54 (1.57–4.10)***
Cancer deaths					
[n (%)]	817 (1.3)	1329 (1.1)	2805 (1.2)	102 (1.3)	5 (1.3)
Model 1	1.10 (1.02–1.19)*	0.94 (0.88–1.00)	Reference	1.12 (0.92–1.37)	1.26 (0.52–3.03)
Model 2	1.24 (1.15–1.34)***	1.14 (1.07–1.22)**	Reference	1.28 (1.05–1.56)*	1.48 (0.62–3.56)
Model 3	1.17 (1.08–1.27)***	1.07 (1.00–1.15)	Reference	1.20 (0.98–1.46)	1.57 (0.65–3.79)
CV deaths					
[n (%)]	343 (0.5)	481 (0.4)	1015 (0.4)	50 (0.6)	6 (1.6)
Model 1	1.30 (1.15–1.47)***	0.96 (0.86–1.06)	Reference	1.53 (1.15–2.03)***	4.11 (1.84–9.17)***
Model 2	1.52 (1.35–1.72)***	1.27 (1.14–1.42)***	Reference	1.78 (1.34–2.37)**	4.74 (2.12–10.58)**
Model 3	1.26 (1.12–1.43)***	1.05 (0.93–1.17)	Reference	1.46 (1.10–1.94)**	3.49 (1.54–7.92)**

Significant of HRs: ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

[a] Model 1: unadjusted; Model 2: Model 1 + adjusted for age and sex; Model 3: Model 2 + further adjusted for ethnicity, body mass index (BMI), the interaction between age and BMI, systolic blood pressure, diabetes, smoking status, alcohol consumption status and overall health.

4. Discussion

In this study, the associations between self-reported weight change and risk of all-cause mortality, cancer death and CV death were examined using data from 433,829 participants in the UK Biobank database. The findings suggest that weight loss led to an increased risk of all-cause mortality by 25%, cancer death by 17% and CV death by 26%. In addition, participants who were unaware of their weight change were found to have an increased risk of all-cause mortality and CV death, this was particularly evident in men. Participants who preferred not to give an answer about their weight change may have a higher risk of all-cause mortality and CV death.

This study showed that weight loss was associated with an increased risk of all-cause mortality, which is in accordance a recent report by Angela et al. [14] that included 12,580 participants from the general population. The results of the current study are also consistent with

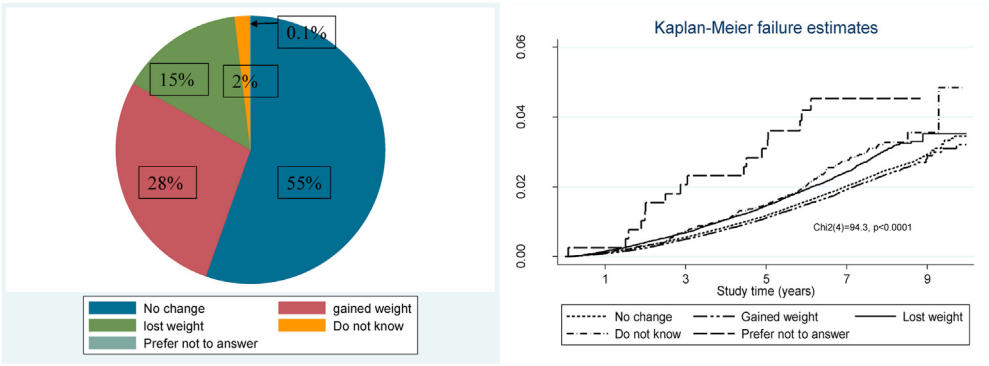

Fig. 1. Kaplan-Meier curves for all-cause mortality by the weight change groups (Right) and the percentages of each category of the groups (Left).

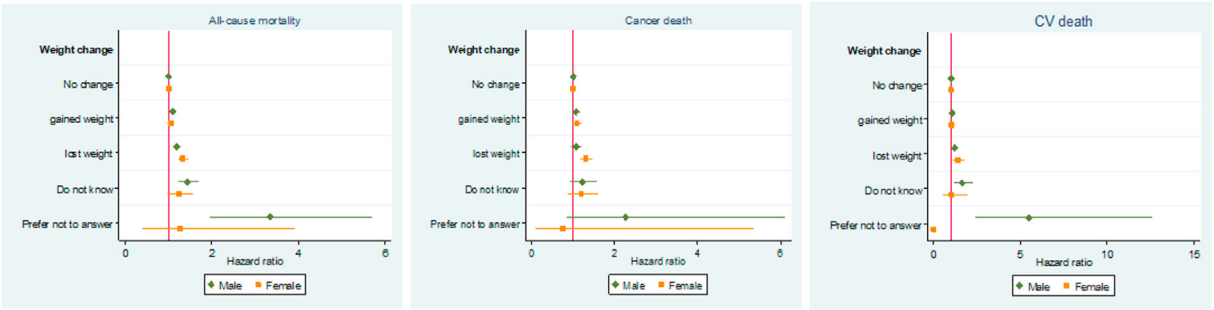

Fig. 2. Hazard ratio (HR) with 95% confidence interval (CI) for all-cause mortality (left), cancer death (middle) and CV death (right) for the self-reported weight change adjusted for age, ethnicity, body mass index, the interaction between age and body mass index, systolic blood pressure, diabetes, smoking status, alcohol status and overall health by male and female.

several other studies [15,22–24] that found an increased risk of CV mortality in people who lost weight. In addition, the current findings support the previously described increase in risk of cancer death in women with weight loss [25–27]. In men, weight loss increased all-cause mortality and CV death, which is consistent with studies conducted in Japanese men [27,28] and a nationwide longitudinal study in Korea [29]. A study of 6441 European middle-aged men [16] also showed a significant relationship between all-cause mortality and weight loss (HR 1.3 [95% CI 1.2–1.5]). One study reported that individuals who lost at least 10% of their body weight in the previous year were likely to be diagnosed with some ill-related condition [29].

This study found that weight gain was associated with an increased risk of all-cause mortality. Being overweight or obese may be linked to an overall increased risk of cancer. According to Sung et al., excess body weight accounted for nearly 4% of all cancer (544,300 cases) [30]. The present study revealed that for women there is an association between weight gain and cancer death. Similar results have been reported in the Norwegian Women and Cancer study, where they showed that large weight gain increased the risk of overall obesity-related cancer [31]. For men, no association was found between weight gain and CV death. One of the explanations for this may be due to the fact that weight gain might be protective in patients with CV disease. Additional fat might provide an energy reserve to help patients with CV disease cope with the metabolic costs of illness, protecting muscle and bone from the catabolic effects of the worsening CV disease. Further study is needed to determine whether this association is causal. In addition, the current study did not find an association between weight change and cancer death in men. Studies found that obesity affects iron absorption [32].

The present results also confirm findings from previous studies reporting that both moderate-to-large weight gain and loss were associated with all-cause and CV mortality [33,34]. One study was carried out in the Singapore Chinese population [33] and similar results were found in a Korean population [35]. Several studies have shown that there was an obesity-paradox association between BMI and all-cause mortality [36,37]. In addition, there was a non-linear association between weight change and all-cause mortality [14,35]. The HRs in the current study (1.08 for weight gain, 1.0 for no weight change and 1.25 for weight loss) for all-cause mortality showed a similar pattern.

This study found that the participants who 'prefer not to answer' the question regarding weight change had a higher risk of all-cause mortality and CV death, particularly for men. This may suggest that middle-aged men are less likely to take care of their weight compared with women, which may also indicate that they are more likely to be overweight/obese, which is a risk factor of adverse outcomes. However, the results might be inconclusive due to the wide 95% CIs. Further studies are needed to confirm the results presented here as this is the first study to evaluate the association.

In this study, there were some confounding variables, such as age, smoking status and alcohol consumption status. Without including the adjustment in the model, the association of weight gain with the risk of cancer death and CV death could not be established, compared with no weight change. Smoking as a confounding variable was also found in the Cancer in Norfolk (EPIC-Norfolk) cohort study [14]. The present results show that current alcohol status was beneficial, especially in women in contrast to never drinkers. There are other potential confounding variables, such as physical activity and overall health status [38].

To the best of the authors' knowledge, this is the largest dataset of self-reported weight change used to study the association between weight change and all-cause mortality, cancer death and CV death. The main strength of the study is that the associations between weight change and outcome were evaluated based on a large middle-aged population. In addition, the models were adjusted for a number of lifestyle variables, such as smoking status and alcohol consumption status.

There are a number of limitations to this study. First, self-reported weight change was used, which could cause measurement error (the definition of weight change could differ between participants). However,

the large number of participants with self-reported weight change, and the fact that significant associations between self-reported weight change and all-cause mortality, death from cancer and CV death were found, indicates that the power of the study is satisfied. Second, changes in body weight only were studied, and there was no investigation of other relative measures, such as height, hip circumference, waist circumference, waist-to-hip ratio, and waist-to-height ratio. Nevertheless, the models were adjusted for BMI in the analysis.

In conclusion, self-reported weight change was associated with an increased risk of all-cause mortality, cancer death and CV death. Weight loss appeared to have a slightly higher risk than weight gain. Recognising weight change as a risk factor in mortality is important, particularly among middle-aged men. Further studies are required to understand the full extent of the mechanism of weight change and mortality outcome.

Ethical approval

This study was conducted based on the UK Biobank resource. Ethical approval was not necessary. Details of patients and public involvement in the UK Biobank are available online (http://www.ukbiobank.ac.uk/about-biobank-uk/and https://www.ukbiobank.ac.uk/wp-content/uploads/2011/07/Summary-EGF-consultation.pdf?phpMyAdmin = trmKQlYdjjnQIgJ%2CfAzikMhEnx6).

Funding

None.

Declaration of competing interestCOI

None declared.

Acknowledgements

This research has been conducted using UK Biobank resource under application number 23183.

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