An opportunity for prevention: associations between the Life's Essential 8 score and cardiovascular incidence using prospective data from UK Biobank

Abstract

Aim – To investigate the association between the Life's Essential 8 (LE8) score and the incidence of four cardiovascular outcomes (ischemic heart disease, myocardial infarction, stroke, and heart failure [HF]) – separately and as a composite outcome of major adverse cardiovascular events (MACE) – in UK Biobank.

Methods – 250,825 participants were included in this prospective study. Smoking, non-HDL cholesterol, blood pressure, body mass index, HbA1c, physical activity, diet, and sleep were used to create a modified version of the LE8 score. Associations between the score (both as a continuous score and as quartiles) and outcomes were investigated using adjusted Cox proportional hazard models. The potential impact fractions of two scenarios were also calculated.

Results – Over a median follow-up of 10.4 years, there were 25,068 MACE. Compared to individuals in the highest quartile of the score (healthiest), those in the lowest quartile (least healthy) had 2.07 (95% CI: 1.99; 2.16) higher risk for MACE. The highest relative risk gradient of the individual outcomes was observed for HF ($HR_{lowest\ quartile}$: 2.67 [95% CI: 2.42; 2.94]). The magnitude of association was stronger in participants below 50 years, women, and ethnic minorities. A targeted intervention that increased, by 10-points, the score among individuals in the lowest quartile could have prevented 9.2% of MACE.

Conclusion – Individuals with a lower LE8 score experienced more MACE, driven especially by incident HF. Our scenarios suggested that relevant interventions targeted towards those in the lowest quartile may have a greater impact than interventions producing small equal changes across all quartiles.

Keywords: Cardiovascular diseases; lifestyle; incidence; mortality; prospective studies

Introduction

Along with cancer, cardiovascular disease (CVD) remains one of the leading causes of death around the globe.[1,2] The World Health Organisation has estimated that around 17.9 million people die each year due to CVD, primarily due to heart attacks and strokes (85% of the causes).[1] In the UK, around a quarter of all deaths are attributable to heart or circulatory diseases.[3] Moreover, the healthcare costs linked to heart and circulatory diseases are estimated at £9 billion per year according to the British Heart Foundation (BHF) report from January 2022.[3] Therefore, reducing the burden of CVD continues to be critical from a public health point of view.

Healthier lifestyles such as stopping smoking, increasing physical activity and having a balanced diet (e.g., eating more fruit and vegetables and reducing salt intake) have been broadly acknowledged as critical factors in reducing the burden of CVD.[4] In this line, the American Heart Association (AHA) proposed, in 2010, the 'Life's Simple 7' (LS7) score,[4] which defined seven health metrics that need to be encouraged in the population to achieve better cardiovascular health. In July 2022, the AHA published an updated algorithm that addressed the limitations of the LS7 score and incorporated sleep as an additional health metric. The new score was called 'Life's Essential 8' (LE8)[5].

There have been extensive longitudinal investigations of the associations between the LS7 and different cardiovascular outcomes in American cohorts[6-15] and some European countries[16,17], including the UK.[18,19] In contrast, no studies have yet explored the longitudinal associations between the new LE8 score and cardiovascular outcomes in the UK. Therefore, this study aimed to investigate the association between the LE8 score and the incidence of four cardiovascular outcomes (ischemic heart disease [IHD], myocardial infarction [MI], stroke, and heart failure [HF]) – separately and as a composite outcome of major adverse cardiovascular events (MACE) – in UK Biobank: one of the largest population cohorts worldwide.

Methods

UK Biobank recruited over 500,000 participants (5.5% response rate) from the general population between 2006 and 2010.[20] Participants (aged 37 to 73 years) attended one of 22 assessment centres across Wales, Scotland and England[21,22] where they completed a touch-screen questionnaire, had physical measurements taken, and provided biological samples, as described in detail elsewhere.[21,22] Outcomes were ascertained via record linkage to hospital

admissions and death certificates.

Ethics information

UK Biobank was approved by the North West Multi-Centre Research Ethics Committee (Ref: 11/NW/0382).[20] This work was conducted under the UK Biobank application number 7155. More information about the UK Biobank protocol can be found online (http://www.ukbiobank.ac.uk)

Life's Essential 8 score

A modified version of the original AHA LE8 score was developed for this study (Supplementary Table 1). In brief, the original version included the following health metrics: smoking, non-HDL cholesterol, blood pressure, body mass index [BMI], HbA1c, physical activity, a healthy diet based on the DASH diet, and sleep. BMI, physical activity, sleep, blood pressure, non-HDL cholesterol, Hb1Ac, and smoking classifications were treated as per the original version (Supplementary Table 1). However, diet was adapted using the available data from the UK Biobank study. For diet, instead of using the DASH-style eating pattern as proposed by the AHA, we used a previous diet score adapted for the UK Biobank data and published it elsewhere.[23]

Each health metric was scored from 0 to 100, with a lower score indicating the least healthy while a higher score indicating the healthiest, as suggested by Lloyd-Jones et al.[24] The complete information for each parameter is available in Supplementary Table 1.

The mean LE8 score for each individual was derived by summing the eight health metrics and dividing them by 8. The score was treated as both a continuous score as well as quartiles (quarters) of distribution in the analyses.

Outcomes

The primary outcome of the study included four cardiovascular outcomes (IHD, MI, stroke, and HF) – separately and as a composite outcome of MACE. The outcomes were ascertained from linked hospitalisation and death records using the relevant International Classification of Diseases 10 revision (ICD10) codes: MACE (ICD10: I20-I25, I60-I64, I50, I70-I74), IHD (ICD10: I20-I25), MI, (ICD10: I21-I23), stroke (ICD10: I60, I61, I63 or I64) and HF (ICD 10: I50.0, I50.1, I50.9). The date of death was obtained from death certificates held by the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). Dates and causes of hospital admission were identified

via record linkage to Health Episode Statistics (HES) (England and Wales) and the Scottish Morbidity Records (SMR01) (Scotland). Details of the linkage procedure can be found at http://content.digital.nhs.uk/services. Hospital admissions data were available until September 2021 in England, July 2021 in Scotland and February 2018 in Wales. Therefore, incident event models were censored on these dates or the date of death if this occurred earlier. Mortality data were available until the end of October 2021. Therefore, mortality follow-up was censored on this date. Only the first event was taken for all analyses.

Covariates

Age at baseline was derived from dates of birth and baseline assessment. Sex was self-reported. Deprivation (area-based socioeconomic status) was derived from the postcode of residence, using the Townsend score.[25] Ethnicity was self-reported and categorised into white, Asian (South Asian and Chinese) and others. Frequency of alcohol intake was self-reported at baseline and categorised as: daily/almost daily, 3-4 times a week, once/twice a week, 1-3 times a month, special occasions only, or never. The average time spent driving, using a computer, and watching television were summed to derive the total time spent on sedentary behaviours. Prevalent morbidity was ascertained during a nurse-led interview at baseline and participants classified as having no prevalent morbidity or ≥1 prevalent morbidity based on 43 long-term conditions (including depression) selected initially for a large epidemiological study in Scotland and subsequently adapted for UK Biobank.[26,27]

Statistical analyses

Descriptive baseline characteristics by quartiles of the LE8 score are presented as means with standard deviations (SD) for quantitative variables and as frequencies and percentages for categorical variables.

Nonlinear associations between the continuous LE8 score and outcomes (both MACE and individual cardiovascular outcomes) were investigated using restricted cubic splines (with 3 knots placed at the 25th, 50th and 75th percentiles of distribution) fitted into Cox proportional hazard models. From the fitted model, we obtained adjusted hazard ratios (HR) across the entire range of LE8 scores using the cohort median (74 points) as the reference point (HR =1.00).

For interpretability, we also fit LE8 scores as a categorical variable, having divided the score into quartiles. Associations between quartiles of the LE8 score and the outcomes mentioned

above were investigated using Cox-proportional hazard models, with the time of follow-up used as the timeline variable. Individuals in the highest quartile were used as the referent category. The results are reported as HR and their 95% confidence intervals (95% CI).

Participants with missing data for the LE8 score (n=227,792), CVD at baseline (n=9932) or missing data for one or more covariates (n=3235), were excluded from all analyses. In addition, analyses were performed using a 2-year landmark analysis, excluding participants who experienced events within the first two years of follow-up (n=10,601). All analyses were adjusted for age, sex, deprivation, ethnicity, prevalent (non-CVD) morbidity, sedentary time, and alcohol intake.

The population attributable fraction (PAF) was estimated to calculate the proportion of incident MACE events due to LE8 score, assuming causality.[28] This PAF was estimated based on the adjusted HR derived from the nonlinear associations. The potential impact fractions (PIF) of two scenarios were calculated to evaluate which counterfactual scenarios may have a more substantial public health impact, under the assumption that the effect of the intervention on the LE8 score was constant across the range of LE8 values.[29] The first scenario represented a general intervention approach which would increase the score across the whole population by 2.5 points. The second scenario represented a targeted intervention which would reduce the number of people with low LE8 scores, by increasing by 10-points the scores of those individuals in the lowest quartile (score <66.25). The two scenarios correspond to the same population level improvement (2.5-points improvement in the whole population vs. 10-points in one-quarter of the population).

To investigate whether the associations between LE8 score quartiles and outcomes (MACE and individual cardiovascular outcomes) differed by population groups, the analyses were stratified by age (< 50 years, 50 to 59 years, and ≥ 60 years), sex (men and women), deprivation (Townsend score ≤ and > the median), ethnicity (white, Asian, and other), prevalent morbidity (0 vs ≥1), and alcohol intake (never/special occasions and regular drinking). An interaction term among the subgroups, the quartiles of the LE8 score, and the outcomes was fitted into the model to test for interaction.

Finally, the Spearman rank correlation between the new LE8 score and the previous LS7 score was calculated.

Stata 17 statistical software (StataCorp LP) and R 4.0.5 were used to perform all analyses. A p-value lower than 0.05 was considered statistically significant. This study follows the STROBE reporting guidelines for cohort studies.[30]

Results

After excluding participants with missing data and pre-existing CVD, 250,852 participants were eligible for inclusion (Supplementary Figure 1). Over a median follow-up of 10.4 years (interquartile range 9.6 to 11.1 years), 25,068 (10%) individuals had a MACE. Of these, 15,337 (6.1%) were due to IHD, 4,547 (1.8%) to MI, 5,635 (2.2%) to stroke and 5,360 (2.1%) to HF.

General characteristics of participants by quartiles of LE8 score are available in Table 1. Overall, participants in the highest quartile were younger, less deprived, and more likely to be women than those in the lowest quartile. Instead, those in the lowest quartile were more likely to have ≥1 prevalent chronic condition, to drink alcohol daily or almost daily, and self-reported more time spent in sedentary activities (Table 1). Additionally, a comparison between the included participants and those excluded due to missingness is available in Supplementary Table 2. In brief, excluded participants were similar in relation to many characteristics, but had more prevalent conditions (62.4% vs 68.6%) and a higher proportion reported never drinking alcohol (7.0% vs 9.2%) (Supplementary Table 2).

Associations of quartiles of LE8 score with MACE and individual cardiovascular outcomes are shown in Table 2. Overall, there was a dose-repose association between the LE8 and the health outcomes investigated. Compared to those in the highest quartile (healthiest), those in the lowest (least healthy) had 2.07 times (95% CI: 1.99 to 2.16) higher risk of MACE. Of the individual outcomes, the strongest association was observed for HF among individuals in the lowest quartile (HR: 2.67 [95% CI: 2.42 to 2.94]), while the weakest association was observed for stroke (HR: 1.60 [95% CI: 1.47 to 1.74]).

Associations of continuous LE8 score with MACE are shown in Figure 1. Overall, the observed risk was primarily linear (nonlinear p= 0.047). A higher LE8 score was associated with lower risk of incident MACE. For instance, using 74 (median) as the referent score, individuals with a score of 40 or 60 had 2.71- (95% CI: 2.57 to 2.87) and 1.48-times (95% CI: 1.46 to 1.51) higher risk of incident MACE while individuals with a score of 80 were associated with a 16% (95%CI: 0.83 to 0.86) lower risk of MACE (Figure 1). The

associations of the continuous score with the individual cardiovascular outcomes are presented in Supplementary Figure 2.

Based on PAF analyses, all the factors contributing to overall LE8 scores could have accounted for 50.9% (95% CI: 50.8 to 51.0) of incident MACE. A general intervention that increased the score by 2.5 points across the whole population would have prevented 6.6% (95% CI: 6.52 to 6.76) of incident MACE. In contrast, a targeted intervention that increased, by 10 points, the score among individuals in the lowest quartile (score ≤66.25 points) would have prevented 9.2% of MACE (Supplementary Figure 3).

Sub-group analyses identified significant associations between LE8 score quartiles and the outcomes across all sub-groups (Supplementary Tables 3 to 7). While similar associations were observed across all studied sub-groups, the magnitude of associations was stronger in participants younger than 50 years, female, and more deprived (Supplementary Table 3). Asian participants also had a higher risk of IHD, MI, stroke and HF incidence than white participants (Supplementary Tables 4 to 7). Other associations between the different outcomes can be found in Supplementary Tables 4 to 7.

Finally, the Spearman correlation between the new LE8 score and the previous LS7 score was 0.72 (p-value: <0.001) and is shown in Supplementary Figure 4.

Discussion

Using data from the UK Biobank study, we observed that individuals with a lower LE8 score had a higher adjusted risk of MACE and individual cardiovascular outcomes. This risk was higher in individuals in the lowest quartile of the score, with the strongest association observed for incident HF. Moreover, the linear associations implied that participants with the highest risk would be those who benefit the most from an intervention.

Assuming full causality – and that an intervention is equally efficacious at improving LE8 across the range of LE8 values as well as that individuals in whom LE8 is reduced immediately take on the risk based on the unmodified LE8 score (e.g., ex-smokers immediately have the same risk as never smokers) – our PIF scenarios suggested that an intervention targeted towards those in the lowest quartile may have a greater impact than an intervention producing small equal changes in lifestyle across all quartiles. This targeted intervention would only require the LE8 score to increase by 10-points, which can be achieved by sleeping 1 hour more per day or increasing physical activity from 120 to ≥240

MET/min/week (Supplementary Table 1). In other words, small changes could produce greater benefits for the most at-risk people, who may also have more resistance to making significant changes. In addition, within the cohort studied, modifiable lifestyle, measured by LE8 scores, accounted for a significant burden of CVD (half of incident CVD cases). In 2022, the BHF reported that the total inpatient cost for treating CVD in the NHS was £6.5 billion annually, making up approximately half of the total healthcare expenditure.[31] Therefore, a targeted intervention that reduces incident CVD by 9.2% can potentially save the NHS £0.5 billion.

The sub-analyses showed that the magnitude of associations was greater in some subgroups suggesting that interventions could be focused on these people. Importantly, young patients (< 50 years) in the lowest LE8 quartiles were disproportionately affected, meaning that primary prevention should also commence early in life. With an ageing global population and a longer life expectancy, we expect that the disease-free years of life gained from preventing incident events will likely increase.[32] Consequently, even if prevention and promotion should be encouraged throughout the lifetime, special attention and focus are required in earlier stages since this is when habits are formed. Recent data also demonstrate that CVD is a leading cause of death among women.[33] Possible reasons could be their atypical symptoms, which may delay diagnosis and treatment.[34] Therefore, our observation underlining the importance of the LE8 score among women is particularly important. Physicians can calculate the baseline score and start appropriate preventive measures well ahead of time. On the other hand, prior studies from the UK report increased cardiovascular disease among Asians and ethnic minorities people.[35-37] This strengthens the rationale for promoting healthier lifestyle patterns as simple measures to prevent CVD in ethnic minority groups.

Our study is likely the first to investigate the prospective association between the LE8 score and cardiovascular outcomes in the UK. Other two studies have reported information using the LE8 score, but they did not investigate the prospective association with cardiovascular outcomes.[5,24] While the earlier AHA LS7 score has been widely studied in the US,[6-15] in the UK, only two prior studies investigated its association with CVD outcomes.[18,19] Perrot et al. identified that compared to individuals in the bottom quartile of a modified LS7 score, those in the highest quartile had a significantly lower risk of calcific aortic valve stenosis (HR: 0.45. [95% CI: 0.31 to 0.65]).[18] Likewise, using data on 7,274 men from the British Regional Heart Study, Ahmed et al. showed a non-significant 5% lower stroke risk for each unit increase in the score.[19] Recent studies highlighted the importance of sleep in the occurrence

of CVD.[38] Therefore, adding sleep as the 8th metric and changing the scale from categorical to continuous seems to have improved the discriminatory capacity of the revised score.

Strengths and limitations

The use of UK Biobank enabled us to study the AHA LE8 score in a single, large, and well-characterised general population cohort of middle-aged and older adults and adjust for a large range of potential confounding factors. Furthermore, we were able to assess whether the associations were linear or not and whether they were consistent across subgroups, addressing the limitations of most previous studies. However, this study is not without limitations. Firstly, diet and alcohol intake were self-reported at baseline. Therefore, we might have had some recall and misclassification bias in these variables, and the consumption might have changed during follow-up. We tried to limit potential reverse causation by using a 2-year landmark analysis. Secondly, we used a modified version of diet, different from the original AHA LE8 score, since not all the diet information was available in the UK Biobank study. However, we used a similar or proxy variable to mitigate these differences. Thirdly, mean LE8 score assumes equal weighting for each health metric which is counter-intuitive given that different risk factors have differential weightings for different outcomes. Fourthly, UK Biobank is not representative of the UK population regarding characteristics, lifestyle, and prevalent diseases. Therefore, whilst risk estimates can be generalised [39], summary statistics such as prevalence and incidence cannot be generalised to the UK population.[40] Finally, the observational nature of our study does not allow us to infer causality from the results. In particular, PAF and PIF calculations assume causality and can overestimate. Also, they cannot automatically be generalised to another population where the prevalence of risk factors may differ. Therefore, an intervention study including both clinical- and cost-effectiveness analysis is needed to compare the different approaches to intervention suggested in this study.

In conclusion, over a 10-year follow-up, individuals with a lower LE8 score were more likely to develop MACE. This was especially true in participants below 50 years, women, and ethnic minorities. Moreover, our PIF analyses highlighted that a targeted intervention – that would increase just 10-points in the overall LE8 score – would have the greatest benefit among the most at-risk people than a general intervention producing small equal changes across all quartiles. Our study, therefore, reinforces the relevance of promoting healthier

lifestyle patterns as simple measures in preventing MACE, one of the leading causes of death worldwide.

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Conflict of interest

N.S declares consulting fees and/or speaker honoraria from Abbott Laboratories, Afimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi; and grant support paid to his university from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics. None of these disclosures are directly related to the study, nor its conception, analyses or interpretation. The other authors declare none conflict of interest.

Authors' Contributions

F.P-R and S.D contributed to the conception and design of the study. F.K.H advised on all statistical aspects. F.P-R performed the literature search, the analyses and interpreted the data with support from S.D., F.K.H, N.D and J.P.P. All authors critically reviewed this and previous drafts. All authors approved the final draft for submission. F.P-R and S.D contributed equally to this work and are joint first authors. N.D and J.P.P contributed equally to this work and are joint senior authors. J.P.P is the guarantor.

Data Availability

All UK Biobank information is available online on the webpage www.ukbiobank. Data access are available through applications.

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Table 1. General cohort characteristics at baseline of participants included by quartiles of the LE8 score

	Total	1st quartile (Least healthy)	2nd quartile	3rd quartile	4th quartile (Healthiest)
n, (%)	250,852	61.228 (24.4)	61,354 (24.5)	63,563 (25.3)	64,707 (25.8)
Baseline age (years), mean (SD)	55.9 (8.1)	57.4 (7.7)	56.9 (8.0)	55.8 (8.1)	53.8 (8.1)
Sex, n (%)					
Women	136,481 (54.4)	24,813 (40.5)	30,050 (49.0)	36,129 (56.8)	45,489 (70.3)
Men	114,371 (45.6)	36,415 (59.5)	31,304 (51.0)	27,434 (43.2)	19,218 (29.7)
Deprivation index, mean (SD)	-1.49 (2.96)	-0.96 (3.19)	-1.50 (3.0)	-1.70 (3.0)	-1.78 (2.8)
Ethnicity, n (%)					
White	239,133 (95.3)	57,914 (94.6)	58,431 (95.2)	60,716 (95.5)	62,072 (95.9)
Others	11,719 (4.7)	3,314 (5.4)	2,923 (4.8)	2,847 (4.5)	2,635 (4.1)
Morbidity count, n (%)					
0	94,235 (37.6)	14,953 (24.4)	20,940 (34.1)	26,213 (41.2)	32,219 (49.8)
≥1	156,527 (62.4)	46,275 (75.6)	40,414 (65.9)	37,350 (58.8)	32,488 (50.2)
Alcohol frequency intake, n (%)					
Daily or almost daily	52,919 (21.1)	15,265 (24.9)	14,091 (23.0)	12,999 (20.4)	10,564 (16.3)
3-4 times a week	61,187 (24.4)	13,149 (21.5)	15,205 (24.8)	16,246 (25.6)	16,587 (25.7)
Once or twice a week	65,527 (26.1)	14,555 (23.8)	15,436 (25.2)	16,974 (26.7)	18,562 (28.7)
1-3 times a month	27,501 (11.0)	6,426 (10.5)	6,400 (10.4)	6,967 (11.0)	7,708 (11.9)
Special occasions only	26,162 (10.4)	7,167 (11.7)	6,118 (10.0)	6,143 (9.7)	6,734 (10.4)
Never	17,556 (7.0)	4,666 (7.6)	4,104 (6.6)	4,234 (6.6)	4,552 (7.0)
Sedentary time (h/day), mean (SD)	5.0 (2.2)	5.7 (2.5)	5.2 (2.2)	4.8 (2.1)	4.4 (1.9)

n: number; SD: standard deviation, h/day: hours per day.

Table 2. Associations between quartiles of the Life's Essential 8 score and incidence of five cardiovascular outcomes.

	Total n	Events	Quartile 4 (healthiest)	Quartile 3		Quartile 2		Quartile 1 (least healthy)		Trend	
			HR (95% CI)	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
CVD incidence											
Main model	250,852	25,068	1.00 (Ref.)	1.20 (1.15; 1.26)	<0.001	1.47 (1.41; 1.53)	<0.001	2.07 (1.99; 2.16)	<0.001	1.28 (1.27; 1.30)	<0.001
IHD incidence											
Main model	250,852	15,337	1.00 (Ref.)	1.30 (1.23; 1.38)	<0.001	1.63 (1.54; 1.72)	<0.001	2.27 (2.15; 2.40)	<0.001	1.32 (1-30; 1.34)	<0.001
MI incidence											
Main model	250,852	4,547	1.00 (Ref.)	1.37 (1.23; 1.53)	<0.001	1.77 (1.60; 1.97)	<0.001	2.38 (2.15; 2.63)	<0.001	1.33 (1.29; 1.37)	<0.001
Stroke incidence											
Main model	250,852	5,635	1.00 (Ref.)	1.13 (1.04; 1.24)	0.005	1.28 (1.18; 1.40)	<0.001	1.60 (1.47; 1.74)	<0.001	1.17 (1.14; 1.20)	<0.001
HF incidence											
Main model	250,852	5,360	1.00 (Ref.)	1.27 (1.14; 1.41)	<0.001	1.67 (1.51; 1.84)	<0.001	2.67 (2.42; 2.94)	<0.001	1.41 (1.37; 1.45)	<0.001

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by the LE8 quartiles. Participants in the highest quartile were used as the reference group. All analyses were performed using a 2-year landmark analysis, excluding participants who experienced events within the first two years of follow-up. Analyses were adjusted by age, sex, deprivation, ethnicity (white vs others), morbidity count (yes/no), alcohol intake and total sedentary time.

Figure 1. Nonlinear association between the continuous Life's Essential 8 score and MACE incidence.

All analyses were performed using a 2-year landmark analysis, excluding participants who experienced events within the first two years of follow-up. Analyses were adjusted by age, sex, deprivation, ethnicity (white vs others), morbidity count (yes/no), alcohol intake and total sedentary time.