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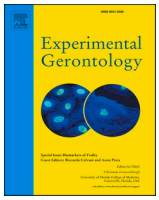

Oxidative balance score as a useful predictive marker for new-onset type 2 diabetes mellitus in Korean adults aged 60 years or older: The Korean Genome and Epidemiologic Study–Health Examination (KoGES-HEXA) cohort

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ABSTRACT

Background: The oxidative balance score (OBS) is a comprehensive pro- and anti-oxidative marker for assessing the risk of various metabolic diseases and cancers. However, it is not well established whether OBS is related to type 2 diabetes mellitus (T2DM), particularly in elderly populations. Therefore, our objective was to investigate the longitudinal effect of OBS on T2DM in a large cohort of Korean adults aged 60 years and older.

Methods: We assessed the data for 3516 participants aged 60 years and older without diabetes mellitus from the Health Examinees cohort of the Korean Genome and Epidemiology Study. We classified the participants into three groups according to OBS tertiles. We prospectively assessed hazard ratios (HRs) with 95 % confidence intervals (CIs) for new-onset T2DM using multivariable Cox proportional-hazard regression models during the mean 3.5 years following the baseline survey.

Results: A total of 109 participants (3.1 %) developed T2DM during a mean follow-up of 3.5 years. The incidence rates per 1000 person-years were 11.73 for the lowest OBS tertile (T1), 8.19 for the second tertile (T2), and 6.23 for the highest tertile (T3). Adjusting for all confounding factors, compared with the referent T1, the HR (95 % CI) of new-onset T2DM was not significant in T2 (0.71 [0.47–1.07]) but was significant in T3 at (0.47 [0.30–0.75]) (p for trend = 0.002).

Conclusions: The study suggests that a OBS could serve as a valuable predictive marker for new-onset T2DM in older adults. Our study suggests that maintaining an appropriate body weight through healthy lifestyle modification has the potential to lower T2DM incidence in elderly. This implies that the OBS may be a useful tool for assessing the incidence of T2DM even in older individuals.

1. Introduction

Diabetes mellitus (DM) is a chronic disease resulting from insufficient production of insulin in the pancreas or inefficient utilization of produced insulin within the body (Sun et al., 2022). As reported by Sun et al. (2022), in the 21st century, diabetes is on the rise

Abbreviations: ANOVA, Analysis of variance; ATE, Alpha-tocopherol equivalents; BMI, Body mass index; BP, Blood pressure; CIs, Confidence intervals; CKD, Chronic kidney disease; eGFR, Estimated glomerular filtration rate; FFQ, Food frequency questionnaire; FPG, Fasting plasma glucose; HbA1c, Glycated hemoglobin; HDL-C, High-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin resistance; HRs, Hazard ratios; IRB, Institutional Review Board; KoGES-HEXA, Korean Genome and Epidemiologic Survey–Health Examinees; NAFLD, Non-alcoholic fatty liver disease; OBS, Oxidative balance score; OGTT, Oral glucose tolerance test; PG, Plasma glucose; ROS, Reactive oxygen species; T1, First tertile; T2, Second tertile; T2DM, Type 2 diabetes mellitus; T3, Third tertile; WC, Waist circumference.

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worldwide (Sun et al., 2022). According to the International Diabetes Federation, the prevalence of diabetes in adults aged 20–79 has more than tripled since the first report was published in 2000 (Sun et al., 2022). In 2000, the global population with diabetes was approximately 151 million (4.6 %), while in 2021, it has increased to 536.6 million (10.5 %) (Sun et al., 2022). Of these, the rise of type 2 diabetes mellitus (T2DM), which accounts for about 90 % of all diabetes cases (Khan et al., 2020), is placing a huge burden on healthcare systems around the world. According to a 2019 report published by NHS digital, approximately 50 % of all adults diagnosed with diabetes are 65 years of age or older (NHS Digital, 2018). Three in 10 (30.1 %) adults aged 65 or older in South Korea are diabetic, and those aged 60 or older account for more than half (56.3 %) of the total diabetic population (27.7 % aged 60–69 and 28.6 % aged 70 or older) (Lee et al. 2022).

Many factors contribute to the development of T2DM, but one of the most important is aging (NHS Digital, 2018). According to a recent report by Bellary et al., aging is strongly associated with both increased insulin resistance and decreased insulin secretory function, both of which are important mechanisms of T2DM (Bellary et al., 2021). For older adults, the complexity of managing T2DM is compounded by the presence of comorbidities, an increased propensity for hypoglycemia, individualized care needs, and a lack of resilience that can lead to an increased risk of frailty compared to younger populations (Bellary et al., 2021; Lee et al., 2022b; Sinclair et al., 2015). Given the limited number and type of glucose-lowering medications available for older adults with T2DM, lifestyle modifications should be prioritized to prevent the development of T2DM (Bellary et al., 2021).

Oxidative stress is defined as an imbalance between the production of reactive oxygen species (ROS) and antioxidant defense from endogenous and exogenous sources (Sies, 2015). The oxidative balance score (OBS) is a comprehensive index that includes dietary and lifestyle factors. Higher OBSs indicate lifestyles in which antioxidants predominate over oxidants. At present, there is substantial evidence that higher OBSs have a negative correlation with the occurrence of various metabolic diseases, including new-onset hypertension (Lee et al., 2022a), non-alcoholic fatty liver disease (NAFLD) (Sohouli et al., 2023), chronic kidney disease (CKD) (Son et al., 2023), and T2DM (Golmohammadi et al., 2019; Kwon et al., 2023; Wu et al., 2023) in the general population. However, to our best knowledge, no strong evidence of an inverse epidemiologic relationship between OBS as an integrated marker of lifestyle control and T2DM risk has been published in prospective cohorts of older adults. Therefore, we investigated the effect of OBSs on the development of T2DM in adults aged 60 years or older in a large prospective community-based Korean cohort followed for a mean of 3.5 years.

2. Materials and methods

2.1. Study design and population

The Korean Genome and Epidemiologic Survey–Health Examinees (KoGES-HEXA) is a nationwide government-funded prospective cohort study that was designed to find genetic and environmental factors in common complex diseases in Koreans. The cohort consists of community residents aged ≥40 years at the baseline visit who were recruited from the National Health Examinee Registry. The baseline survey was conducted between 2004 and 2013 at 38 health examination centers and hospitals in eight regions of Korea, with the follow-up from 2012 to 2016. For follow-up, participants were periodically mailed and telephoned to complete surveys. The anonymized data of 173,195 participants aged ≥40 years were combined with the death certificate database of the National Statistical Office. The KoGES-HEXA dataset consists of anthropometric and clinical measurements, lifestyle information (ie. diet, smoking, drinking, and physical activity), and food frequency questionnaire (FFQ) responses. The study details have been published elsewhere (Kim et al., 2017).

This study investigated the OBS in patients aged ≥60 years. Fig. 1 presents a flow chart describing the study sample selection. Participants who were younger than 60 years ($n = 130,379$) or lost to follow-up ($n = 76,699$) were excluded, followed by those with incomplete data at baseline ($n = 34,874$) or with pre-existing diabetes ($n = 350$). After applying these exclusion criteria, 3516 participants with disease history and mortality records were included.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Korean Health and Genomic Study at the Korea National Institute of Health. The KoGES-HEXA study protocol was reviewed and approved by the Institutional Review Board (IRB) of the Korea Centers for Disease Control and Prevention, and all study participants provided written informed consent. Approval for this research was granted by the IRB of Yongin Severance Hospital (IRB number: 9–2023-0045).

2.2. Data collection and covariates

During the exam period, each participant completed a comprehensive questionnaire that captured information about their lifestyle and medical history and underwent a comprehensive medical check-up performed by well-trained medical staff according to standard procedures. Participants were classified by smoking status as never smokers, former smokers, or current smokers. Bodyweight and height were measured while the participants were wearing light indoor clothing and no shoes to an accuracy of 0.1 kg and 0.1 cm, respectively. Waist circumference (WC) was measured after normal expiration, midway between the lower rib margin and the iliac crest, parallel to the horizontal plane, to within 0.1 cm. Body mass index (BMI) was calculated by dividing a participant's weight by the square of their height (kg/m^2). Systolic and diastolic blood pressure (BP) were measured using a standard mercury sphygmomanometer (Baumanometer, W.A. Baum Co. Inc., Copiague, NY, USA) after a 10-minute resting period in the seated position. Mean arterial pressure was calculated as (systolic BP + [2 × diastolic BP])/3. Participants were classified by a never smoker was defined as a participant who had never smoked or had smoked fewer than 100 cigarettes in their lifetime. A former smoker was defined as a participant who had quit smoking but had smoked >100 cigarettes during their lifetime. Current smokers were defined as a participant who had smoked 100 cigarettes in their lifetime and answered "currently smoking" in the questionnaire. Participants were classified by drinking status as never drinkers, light and moderate drinkers (0–209 g/week in men, 0–139 g/week in women), or heavy drinkers (≥210 g/week in men, ≥140 g/week in women) based on their self-reported frequency of alcohol consumption (Choi et al., 2020). Regular drinkers were defined as participants who drank alcohol at least once per month. Regular exercise was defined as answering 'yes' to the question 'Do you regularly engage in physical activity that makes you sweat?'

Hypertension was defined as systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg, and/or current use of hypertensive medication. CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 $mL/min/1.73\ m^2$. The eGFR was calculated using the CKD Epidemiology Collaboration equation. Dyslipidemia was defined as meeting one or more of the following definitions: hyper–low-density lipoprotein (LDL) cholesterolemia, defined as serum LDL cholesterol ≥160 mg/dL and/or current use of a lipid-lowering drug; hypo–high-density lipoprotein (HDL) cholesterolemia, defined as serum HDL cholesterol <40 mg/dL; and/or hypertriglyceridemia, defined as serum triglycerides ≥200 mg/dL.

A 103-item FFQ facilitated by well-trained dietitians was used to estimate dietary intake. The validity and reproducibility of the FFQ were previously demonstrated for the KoGES. We calculated each participant's daily intake of total energy (kcal/day), dietary fiber (g/day), carotene (μg/day), riboflavin (mg/day), niacin (mg/day), vitamin B6 (mg/day), total folate (mcg/day), vitamin C (mg/day), vitamin E (alpha-tocopherol equivalents [ATE]) (mg/day), calcium (mg/day), zinc (mg/

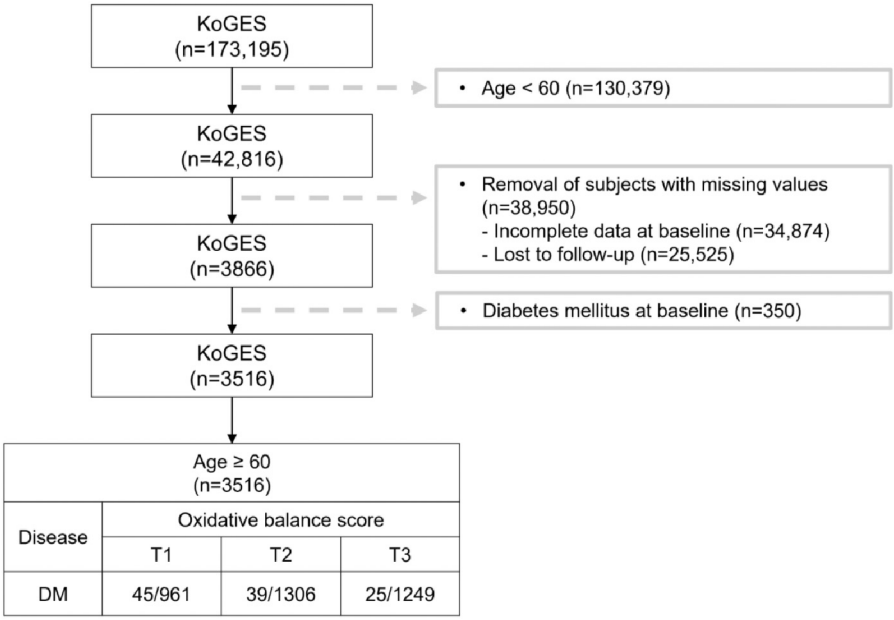

Fig. 1. Flowchart for the selection of study participants.

day), total fat (g/day), and iron (mg/day) using the Computer Aided Nutritional Analysis program (CAN-pro version 5.0, The Korean Nutrition Society, Korea).

Blood samples were obtained from subjects via an antecubital vein after a 12-hour overnight fast. Concentrations of total cholesterol, HDL cholesterol, triglycerides, fasting plasma glucose (FPG), aspartate aminotransferase, and alanine aminotransferase were measured enzymatically using a Chemistry Analyzer (Hitachi 7600, Tokyo, Japan until August 2002, and ADVIA 1650, Siemens, Tarrytown, NY, from September 2002). Further details of the study design and procedures have been described previously (Kim et al., 2017).

2.3. OBS assessment

The OBS was calculated as the sum of eleven antioxidant factors and five pro-oxidant factors chosen based on previous studies (Cho et al., 2018; Hernández-Ruiz et al., 2019; Kong et al., 2015; Valenzuela et al., 2018). Table 1 shows the dietary and lifestyle OBS components and whether each has pro- or anti-oxidant properties. Participants were categorized into sex-specific tertile groups based on their OBS. Higher scores were given for higher amounts of antioxidant factors (first tertile [T1] scored 0, second tertile [T2] scored 1, and third tertile [T3] scored 2) and lower amounts of pro-oxidant factors (T1 scored 2, T2 scored 1, and T3 scored 0).

The antioxidant factors include physical activity and intake of dietary fiber, carotene, riboflavin, niacin, vitamin B6, total folate, vitamin C, vitamin E (ATE), calcium, and zinc. Two points were given to very active (mainly engaged in standing work or engaging in active leisure activities such as exercise) patients, one to those who were active (mainly sedentary but does standing work, commuting, shopping, housework, regular light exercise), and zero to those who were inactive (limited physical activity, such as hospitalized) or had low physical activity (spending most of their time in sedentary, sedentary activities, such as general office workers who do not actively exercise regularly during their free time). The dietary fiber, carotene, riboflavin, niacin, vitamin B6, total folate, vitamin C, vitamin E (ATE), calcium, and zinc intake components were assigned 0–2 points according to the sex-specific tertile values of each variable corresponding to high (2 point), intermediate (1 point), and low intake (0 point).

The pro-oxidant factors include total fat and iron intake, drinking status, smoking status, and obesity status (determined using BMI). The total fat and iron intake components were assigned 0–2 points according to the sex-specific tertile values of each variable corresponding to low (2 points), intermediate (1 point), and high intake (0 points). For smoking status, the scores for never smokers, former smokers, and current smokers were 2, 1, and 0, respectively. For drinking status, the scores for non-drinkers, light and moderate drinkers (0–29 g/day for men, 0–19 g/day for women), and heavy drinkers ($\leq$ 30 g/day for men, $\leq$20 g/day for women) were 2, 1 and 0, respectively. For obesity status, the scores for the low BMI group ($\leq$23.23 kg/m^2 for men, $\leq$22.26 kg/m^2 for women), moderate BMI group (23.23–25.47 kg/m^2 for men, 22.26–24.67 kg/m^2 for women), and high BMI group (>25.47 kg/m^2 for men, >24.67 kg/m^2 for women) were 2, 1, and 0, respectively. The sums of the OBSs ranged from 0 to 32 points.

2.4. Study outcomes

Disease information in the KoGES-HEXA cohort is linked to national data sources (Korea National Statistical Office) through data linkage based on the personalized identification key code system. New-onset T2DM was defined as the diagnostic criteria of the American Diabetes Association and Korean Diabetes Association: Current use of glucose-lowering medications and/or insulin; 8-h FPG $\geq$ 7.0 mmol/L (126 mg/dL); HbA1c $\geq$ 6.5 %; and/or random plasma glucose (PG) $\geq$ 11.1 mmol/L (200 mg/dL) (ElSayed et al., 2023a; Lee et al. 2022).

2.5. Statistical analysis

Participants were categorized into three groups based on their baseline OBS: T1, OBS $\leq$ 14; T2, OBS 15–21; and T3, OBS $\geq$ 22. The data are presented as means with standard deviations or percentages. The baseline characteristics of the study population were compared using Pearson's chi-squared test for categorical variables and an analysis of variance (ANOVA) model for continuous variables, according to the OBS tertiles. Distribution normality was evaluated using the Kolmogorov-Smirnov test. Homogeneity of variance was evaluated using the Levene's test. In post-hoc analysis, subgroups of OBS tertiles (T1, T2, and T3) of each variable were pairwise matched and compared using Bonferroni's method.

The study utilized reverse Kaplan–Meier curves to evaluate the

Table 1
Components of the oxidative balance score.

OBS components	Property	Men			Women		
		T1	T2	T3	T1	T2	T3
Dietary OBS components							
Dietary fiber (g/day)	A	≤6.18	>6.18 ≤8.45	>8.45	≤5.79	>5.79 ≤8.25	>8.25
Carotene (μg/day)	A	≤2732.60	>2732.6 ≤5155.51	>5155.51	≤2969.60	>2969.6 ≤5215.53	>5215.53
Riboflavin (mg/day)	A	≤0.85	>0.85 ≤1.15	>1.15	≤0.81	>0.81 ≤1.14	>1.14
Niacin (mg/day)	A	≤12.37	>12.37 ≤16.86	>16.86	≤11.2	>11.2 ≤15.08	>15.08
Vitamin B_6 (mg/day)	A	≤1.32	>1.32 ≤1.76	>1.76	≤1.23	>1.23 ≤1.63	>1.63
Total folate (mcg/day)	A	≤285.54	>285.54 ≤397.07	>397.07	≤265.02	>265.02 ≤376.62	>376.62
Vitamin C (mg/day)	A	≤74.94	>74.94 ≤114.66	>114.66	≤76	>76 ≤119.28	>119.28
Vitamin E (ATE) (mg/day)	A	≤7.14	>7.14 ≤10.02	>10.02	≤6.96	>6.96 ≤9.71	>9.71
Calcium (mg/day)	A	≤385.54	>385.54 ≤552.95	>552.95	≤367.85	>367.85 ≤528.62	>528.62
Zinc (mg/day)	A	≤6.41	>6.41 ≤8.11	>8.11	≤5.93	>5.93 ≤7.62	>7.62
Total fat (g/day)	P	≤22.8	>22.8 ≤34.69	>34.69	≤20.73	>20.73 ≤31.79	>31.79
Iron (mg/day)	P	≤11.47	>11.47 ≤15.72	>15.72	≤10.98	>10.98 ≤15.14	>15.14
Lifestyle OBS components							
Physical activity [a]	A	Inactive or low activity	Active	Very active	Inactive or low activity	Active	Very active
Alcohol (g/day) [b]	P	None	>0 <30	≥30	None	>0 <20	≥20
Body mass index (kg/m^2)	P	≤23.05	>23.05 ≤25.19	>25.19	≤22.69	>22.69 ≤24.96	>24.96
Smoking status[c]	P	Never smoker	Former smoker	Current smoker	Never smoker	Former smoker	Current smoker
Tertile Scores for Property 'A'		T1: 0	T2: 1	T3: 2	T1: 0	T2: 1	T3: 2
Tertile Scores for Property 'P'		T1: 2	T2: 1	T3: 0	T1: 2	T2: 1	T3: 0

Notes: Low, intermediate, and high categories correspond to sex-specific tertile values among participants in the KoGES at the baseline survey.
Abbreviations: OBS, oxidative balance score; A, antioxidant; P, pro-oxidant; ATE, alpha-tocopherol equivalents; KoGES, Korean Genome and Epidemiology Study.
[a] Inactive, limited physical activity, such as hospitalized; Low active, spending most of their time in sedentary, sedentary activities, such as general office workers who do not actively exercise regularly during their free time; Active, mainly sedentary but does standing work, commuting, shopping, housework, regular light exercise; Very active, mainly engaged in standing work or engaging in active leisure activities such as exercise.
[b] Never smoker, participants who had never smoked or had smoked <100 cigarettes in their lifetime; Former smoker, participants who had quit smoking and had smoked ≥100 cigarettes in their lifetime; Current smoker, participants who had smoked >100 cigarettes in their lifetime and answered "currently smoking".
[c] Never drinker, participants who answered "None" in the questionnaire; Light and moderate drinker, 0–209 g/week in men, 0–139 g/week in women; Heavy drinker, ≥210 g/week in men, ≥140 g/week in women.

cumulative incidence of T2DM. The log-rank test was employed to determine if there were any differences in the distribution of cumulative T2DM incidence among the groups. In the multivariable analysis, hazard ratios (HRs) and 95 % confidence intervals (CIs) for T2DM incidence were calculated using the Cox proportional hazards regression model, after setting the lowest tertile of OBS values as a reference group and adjusting for potential confounding variables. The following variables were identified as potential confounding factors: age, sex, BMI, WC, systolic BP, diastolic BP, FPG, total cholesterol, HDL cholesterol, triglycerides, smoking status, alcohol intake, regular exercise, hypertension, dyslipidemia, CKD, total energy intake, and follow up duration. All of these procedures were performed after ensuring that there was no multicollinearity between the all confounding variables and OBS. The statistical analyses were conducted using SAS version 9.2 software (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided, and p values < 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics of the study population

Table 2 shows the baseline characteristics of the study population according to the OBS tertiles. The study included 1388 men and 2127 women. For BMI, WC, triglyceride, smoking status (current smokers), alcohol intake (current drinkers), dyslipidemia, and CKD, the T1 group had higher levels or rates compared to the T3 group, whereas for HDL cholesterol and regular exercise, the T1 group had lower levels or rates compared to the T3 group. No significant differences were found between the tertile groups in the levels or proportions of systolic BP, diastolic BP, FPG, total cholesterol, and hypertension.

3.2. Longitudinal association of OBS and T2DM incidence

Table 3 presents the results of the univariable analyses conducted to determine the effect of each OBS component on T2DM incidence using subgroup analysis. In the univariable analysis, the OBS component most strongly associated with incident T2DM was BMI. The HRs (95 % CIs) of new-onset T2DM decreased significantly with decreasing BMI in both

Table 2
Baseline characteristics of the study population by oxidative balance score tertiles.

	Total	Group 1	Group 2	Group 3	*p* value			
	(*n* = 3515)	T1 [2, 14] (*n* = 1209)	T2 (14, 21] (*n* = 1174)	T3 (21,31] (*n* = 1132)	T1 vs T2	T2 vs T3	T1 vs T3	Overall
Sex (men)	1388 (39.5)	530 (43.8)	473 (40.3)	385 (34.0)	0.029	<0.001	<0.001	<0.001
Age (years)	63.9 ± 2.9	63.9 ± 3.0	63.9 ± 3.0	63.8 ± 2.8	1.000	0.959	0.629	0.418
BMI (kg/m^2)	24.0 ± 2.8	24.4 ± 2.8	24.0 ± 2.8	23.6 ± 2.6	<0.001	0.001	<0.001	<0.001
Waist circumference (cm)	82.1 ± 8.2	83.3 ± 8.1	82.1 ± 8.3	80.7 ± 8.0	<0.001	<0.001	<0.001	<0.001
Systolic BP (mm Hg)	125.9 ± 14.4	125.8 ± 14.3	126.3 ± 14.6	125.7 ± 14.3	1.000	0.969	1.000	0.546
Diastolic BP (mm Hg)	76.1 ± 8.9	76.0 ± 8.9	76.3 ± 9.0	76.0 ± 8.8	1.000	1.000	1.000	0.768
FPG (mg/dL)	95.8 ± 14.2	96.3 ± 15.0	95.7 ± 13.5	95.4 ± 14.0	1.000	1.000	0.435	0.332
Total cholesterol (mg/dL)	199.4 ± 36.8	199.1 ± 37.5	199.2 ± 36.2	199.8 ± 36.7	1.000	1.000	1.000	0.891
HDL cholesterol (mg/dL)	53.7 ± 13.0	52.8 ± 13.1	53.7 ± 13.0	54.5 ± 12.9	0.295	0.482	0.007	0.009
Triglycerides (mg/dL)	125.7 ± 72.1	131.4 ± 72.3	127.7 ± 80.3	117.6 ± 61.3	0.636	0.002	<0.001	<0.001
Smoking status, n (%)[a]					<0.001	0.003	<0.001	<0.001
Never smoker	2454 (69.8)	774 (64.0)	825 (70.3)	855 (75.5)				
Former smoker	812 (23.1)	309 (25.6)	275 (23.4)	228 (20.1)				
Current smoker	249 (7.1)	126 (10.4)	74 (6.3)	49 (4.3)				
Alcohol intake, n (%)[b]					0.244	0.013	0.002	0.024
Never drinker	2092 (59.5)	690 (57.1)	684 (58.3)	718 (63.4)				
Former drinker	174 (5.0)	66 (5.5)	57 (4.9)	51 (4.5)				
Current drinker	1249 (35.5)	453 (37.5)	433 (36.9)	363 (32.1)				
Regular exercise (Yes)[c]	2090 (59.5)	637 (52.7)	704 (60.0)	749 (66.2)	<0.001	<0.001	<0.001	<0.001
Hypertension, n (%)	1178 (33.5)	416 (34.4)	401 (34.2)	361 (31.9)	0.310	0.089	0.071	0.370
Dyslipidemia, n (%)	1147 (32.6)	435 (36.0)	370 (31.5)	342 (30.2)	0.008	0.176	0.001	0.007
CKD, n (%)	61 (1.7)	22 (1.8)	28 (2.4)	11 (1.0)	0.137	0.005	0.039	0.033

Notes: Data are expressed as the mean (standard deviation), median (interquartile range), or number (percentage).
p values were calculated with the use of analysis of variance or chi-square test.
Abbreviations: BMI, Body mass index; BP, blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein.
Hypertension, systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, or current use of hypertensive medication; CKD, eGFR <60 mL/min/1.73 m^2; Dyslipidemia, satisfying any of the following criteria: (1) serum LDL cholesterol ≥160 mg/dL or current use of lipid-lowering medication; (2) serum HDL cholesterol <40 mg/dL; (3) serum triglycerides ≥200 mg/dL.
[a] Never smokers, participants who had never smoked or had smoked <100 cigarettes in their lifetime; Former smokers, participants who had quit smoking and had smoked ≥100 cigarettes in their lifetime; Current smokers, participants who had smoked >100 cigarettes in their lifetime and answered, "currently smoking."
[b] Never drinkers, participants who answered "None" in the questionnaire; Light and moderate drinkers, 0–209 g/week in men, 0–139 g/week in women; Heavy drinkers, ≥210 g/week in men, ≥140 g/week in women.
[c] Regularly performing an exercise that causes sweating.

the T2 (0.56 [0.36–0.87], $p = 0.010$) and T1 groups (0.48 [0.30–0.78], $p = 0.003$), with a dose-dependent trend. The HRs (95 % CIs) of new-onset T2DM were significantly reduced in the T3 group compared with the T1 group for dietary fiber ($p = 0.002$), niacin ($p = 0.041$), vitamin B6 ($p = 0.048$), total folate ($p = 0.016$), vitamin C ($p = 0.033$), calcium ($p = 0.040$), and zinc ($p = 0.015$) but did not show a dose-dependent trend in the multivariable analysis. No significant results were found for the remaining components, including carotene, riboflavin, vitamin E (ATE), total fat, iron, physical activity, alcohol consumption, and smoking.

Table 4 presents the correlation between OBS and T2DM incidence among individuals aged 60 years or older. Over the median 3.5-year follow-up period, 109 (3.1 %) participants developed new-onset T2DM. The incidence rates per 1000 person-years were 11.73 for the T1 group, 8.19 for T2, and 6.23 for T3. After adjusting for all confounding factors, compared with the referent T1, the HR (95 % CI) of new-onset T2DM in T2 (0.71 [0.47–1.07], $p = 0.101$) was not significant; however, that in T3 (0.47 [0.30–0.75], $p = 0.001$) was significant (p for trend = 0.002).

Fig. 2 presents the cumulative new-onset T2DM according to the OBS tertiles as Kaplan–Meier curves. The group T3 exhibited the lowest cumulative incidence of T2DM, which was statistically significant (log-rank test, $p = 0.004$). The T2 and T1 groups followed in that order.

4. Discussion

In this study of a large community-based prospective cohort of Korean adults over a mean of 3.5 years, we found that the incidence of T2DM in adults aged 60 years or older decreased with increasing OBSs, even after adjusting for potential confounders. The group T3 exhibited a 54 % lower risk of new-onset T2DM incidence compared to T1 group. This result is similar with previous prospective cohort studies that have investigated the relationship between OBS and T2DM incidence in the general population. Our study suggests that prevention of overweight is the most important of the OBS components to prevent the development of T2DM and should be accompanied by a combination of lifestyle modifications, including exercise and dietary interventions to prevent obesity.

A few previous studies have attempted to shed light on the relationship between OBS and T2DM. In a cross-sectional study of patients with T2DM in Iran, higher OBSs were associated with significantly lower mean glycated hemoglobin and fasting glucose in the lowest tertile compared with the highest tertile (Golmohammadi et al., 2019). Another cross-sectional study using National Health and Nutrition Examination Survey data also found significantly lower odds ratios in the highest OBS quartile compared with the lowest OBS quartile (Wu et al., 2023). In a study using the KoGES prospective cohort, Kwon et al. showed that higher OBS tertiles were associated with a lower incidence of T2DM after adjusting for confounders in the general population (Kwon et al., 2023). However, no prospective cohort study has confirmed the correlation between OBS and T2DM incidence in an older population.

According to a recent report by Bellary et al., T2DM in older adults is caused by an imbalance between increased insulin resistance and decreased insulin secretory function due to a combination of potential contributing factors from aging and obesity (Bellary et al., 2021). Obesity-related factors and hyperglycemia accelerate biological aging, and conversely, the aging of various organs and tissues accelerates ectopic adipogenesis and central obesity, perpetuating a vicious cycle (Li

Table 3
Hazard ratios and 95 % confidence intervals from univariable and multivariable analyses of the incidence of type 2 diabetes mellitus according to components of the oxidative balance score.

	Univariable		Multivariable*	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Dietary OBS components				
Dietary fiber (ref. T1)				
T2	0.74 (0.49–1.14)	0.175	0.82 (0.49–1.38)	0.461
T3	0.46 (0.28–0.76)	0.002	0.51 (0.25–1.03)	0.062
Carotene (ref. T1)				
T2	0.65 (0.40–1.06)	0.084	0.86 (0.51–1.45)	0.562
T3	1.03 (0.67–1.60)	0.885	1.89 (1.07–3.35)	0.029
Riboflavin (ref. T1)				
T2	0.75 (0.48–1.17)	0.205	0.92 (0.52–1.62)	0.760
T3	0.69 (0.43–1.09)	0.107	0.89 (0.42–1.86)	0.751
Niacin (ref. T1)				
T2	0.62 (0.39–0.98)	0.042	0.68 (0.39–1.19)	0.172
T3	0.63 (0.40–0.98)	0.041	0.72 (0.35–1.47)	0.370
Vitamin B6 (ref. T1)				
T2	1.04 (0.68–1.61)	0.846	1.58 (0.92–2.72)	0.096
T3	0.61 (0.37–1.00)	0.048	1.09 (0.51–2.31)	0.830
Total folate (ref. T1)				
T2	0.80 (0.52–1.23)	0.307	0.95 (0.56–1.60)	0.852
T3	0.55 (0.34–0.89)	0.016	0.77 (0.39–1.52)	0.451
Vitamin C (ref. T1)				
T2	0.74 (0.47–1.14)	0.174	0.84 (0.50–1.39)	0.490
T3	0.60 (0.38–0.96)	0.033	0.73 (0.39–1.40)	0.349
Vitamin E (ATE) (ref. T1)				
T2	1.00 (0.64–1.56)	0.986	1.24 (0.73–2.09)	0.431
T3	0.76 (0.47–1.22)	0.256	1.14 (0.59–2.18)	0.700
Calcium (ref. T1)				
T2	0.74 (0.48–1.16)	0.188	0.88 (0.53–1.46)	0.617
T3	0.61 (0.38–0.98)	0.040	0.88 (0.46–1.67)	0.687
Zinc (ref. T1)				
T2	0.50 (0.31–0.80)	0.004	0.55 (0.31–0.97)	0.039
T3	0.58 (0.37–0.90)	0.015	0.70 (0.36–1.39)	0.313
Total fat (ref. T3)				
T2	0.78 (0.49–1.26)	0.313	0.58 (0.34–0.99)	0.046
T1	1.05 (0.67–1.63)	0.841	0.56 (0.30–1.06)	0.077
Iron (ref. T3)				
T2	1.12 (0.69–1.83)	0.642	0.90 (0.50–1.61)	0.715
T1	1.52 (0.96–2.41)	0.073	0.83 (0.40–1.69)	0.601
Lifestyle OBS components				
Physical activity (ref. inactive or low activity)[a]				
Active	1.43 (0.80–2.57)	0.224	1.54 (0.86–2.77)	0.149
Very active	0.94 (0.36–2.47)	0.894	1.10 (0.41–2.94)	0.848
Drinking (ref. Men: ≥30 g/day, Women: ≥20 g/day)				
Men: 0–30 g/day, Women: 0–20 g/day	0.68 (0.31–1.51)	0.347	0.72 (0.32–1.61)	0.423
None	0.91 (0.44–1.89)	0.807	1.08 (0.49–2.37)	0.849
Body mass index (ref. T3)				
T2	0.56 (0.36–0.87)	0.010	0.56 (0.36–0.88)	0.013
T1	0.48 (0.30–0.78)	0.003	0.50 (0.31–0.81)	0.005
Smoking (ref. Current smoker)[b]				
Former smoker	1.01 (0.48–2.13)	0.978	0.97 (0.45–2.08)	0.933
Never smoker	0.79 (0.39–1.58)	0.504	0.70 (0.29–1.69)	0.429

Notes: *Adjusted for age and sex.
Abbreviations: OBS, oxidative balance score; ATE, alpha-tocopherol equivalents; FPG, fasting plasma glucose.
[a] Inactive, limited physical activity, such as while hospitalized; Low physical activity, spending most of their time sedentary or doing sedentary activities, such as general office workers who do not regularly exercise during their free time; Active, mainly sedentary but does standing work, commuting, shopping, housework, regular light exercise; Very active, mainly engaged in standing work or engaging in active leisure activities, such as exercise.
[b] Never smokers, participants who had never smoked or had smoked <100 cigarettes in their lifetime; Former smokers, participants who had quit smoking and had smoked ≥100 cigarettes in their lifetime; Current smokers, participants who had smoked >100 cigarettes in their lifetime and answered, "currently smoking."

et al., 2019). Aging can also promote T2DM by indirectly increasing insulin resistance through several comorbidities that are prevalent in older adults, including vascular disease, chronic stress, and poor mental health (Bellary et al., 2021).

Another challenge is that the management of T2DM in older adults is more complex than in younger adults. The older adult population has greater individual differences in physical and cognitive abilities, more comorbidities, a higher likelihood of hypoglycemia, and a greater risk of frailty due to a lack of resilience (Bellary et al., 2021). Furthermore, the options for hypoglycemic agents available to older adults are limited. Therefore, it is crucial to prioritize lifestyle modifications to prevent the development of T2DM in this population (Bellary et al., 2021). For example, a balanced, healthy diet is recommended for the prevention and control of T2DM in all age groups, especially by reducing intake of saturated fats, simple sugars, and salt and adjusting portion sizes and total daily caloric intake according to body weight (ElSayed et al., 2023b). Furthermore, studies have demonstrated the benefits of combining resistance exercise and diet interventions in pre-frail and frail older adults (Rodriguez-Mañas et al., 2019).

Since 2002, the OBS has been widely used to clinically and comprehensively understand the impact of lifestyle factors related to oxidative and antioxidant stress on the development and progression of various chronic diseases (Van Hoydonck et al., 2002). It is a composite measure of dietary and lifestyle factors, including all of the T2DM management points mentioned above, and higher scores indicate that antioxidant factors predominate over oxidative factors. In this study, we included the factors in the KoGES dataset that have been most-studied in previous research on the relationship between OBS and chronic diseases, such as vitamin C, vitamin E, β-carotene, total iron, alcohol consumption, and smoking status (Hernández-Ruiz et al., 2019; Wu et al., 2023). This study limited OBS components to exogenous exposures, such as dietary and non-dietary lifestyle factors. However, past studies have demonstrated that the OBS with diet and lifestyle factors was associated with biomarkers of oxidative stress, such as C-reactive protein (Kong

Table 4
Hazard ratios and 95 % confidence intervals for incident type 2 diabetes mellitus by oxidative balance score.

		Group 1	Group 2	Group 3	
		T1 [2, 14] (n = 1209)	T2 (14, 21] (n = 1174)	T3 (21, 31] (n = 1132)	*p* for trend
New cases of T2DM, n		51	34	24	
Mean follow-up, years		3.60	3.54	3.40	
Person-years of follow-up		4348	4153	3850	
Incidence rate per 1000 person-year		11.73	8.19	6.23	
Model 1	HR (95 % CI)	1.00 (ref)	0.70 (0.45–1.08)	0.54 (0.33–0.87)	
	p value	–	0.109	0.012	0.010
Model 2	HR (95 % CI)	1.00 (ref)	0.74 (0.48–1.15)	0.49 (0.29–0.83)	
	p value	–	0.177	0.008	0.007
Model 3	HR (95 % CI)	1.00 (ref)	0.75 (0.47–1.21)	0.49 (0.28–0.83)	
	p value	–	0.236	0.010	0.012
Model 4	HR (95 % CI)	1.00 (ref)	0.71 (0.47–1.07)	0.47 (0.30–0.75)	
	p value	–	0.101	0.001	0.002

Model 1: Adjusted for age and sex.
Model 2: Adjusted for age, sex, BMI, WC, systolic BP, diastolic BP, FPG, total cholesterol, HDL cholesterol, and triglycerides.
Model 3: Adjusted for age, sex, BMI, WC, systolic BP, diastolic BP, FPG, total cholesterol, HDL cholesterol, triglycerides, smoking status, alcohol intake, regular exercise, hypertension, dyslipidemia, chronic kidney disease, and total energy intake.
Model 4: Adjusted for age, sex, BMI, WC, systolic BP, diastolic BP, FPG, total cholesterol, HDL cholesterol, triglycerides, smoking status, alcohol intake, regular exercise, hypertension, dyslipidemia, chronic kidney disease, total energy intake, and follow up duration.
Abbreviations: T2DM, type 2 diabetes mellitus; BMI, body mass index; WC, waist circumference; BP, blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; Ref, reference.

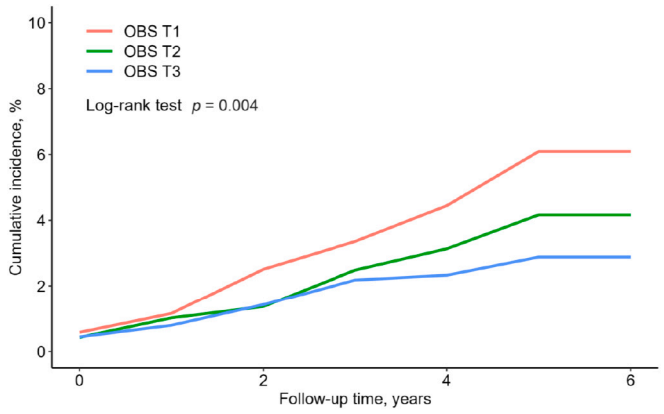

Fig. 2. Reverse Kaplan–Meier curves of the cumulative new-onset T2DM according to the OBS tertiles.
The T3 group had a significantly lower cumulative incident T2DM compared with the T1 group after adjusting for confounders (log-rank test, $p = 0.004$).

et al., 2014), gamma glutamyltransferase (Cho et al., 2018), and F2-isoprostanes (Mao and Bostick, 2021), regardless of whether each factor was weighted (Mao and Bostick, 2021). Thus, the OBS is sufficiently valid to assess oxidative balance involved in the T2DM incidence.

We performed univariable analyses to determine the effect of each component of the OBS on the development of T2DM. Of the non-dietary OBS factors, lower BMI was associated with a significantly lower incidence of T2DM in both the univariable and multivariable analyses. This result is consistent with previous findings that obesity contributes to T2DM development by increasing insulin resistance through multiple mechanisms (Bellary et al., 2021). Of the dietary OBS factors, the HRs (95 % CIs) were significantly reduced in the highest intake group (T3) compared with the lowest intake group (T1) for dietary fiber, niacin (vitamin B3), pyridoxine (vitamin B6), total folate (vitamin B9), vitamin C, calcium, and zinc. According to Chandalia et al., dietary fiber prevents the diffusion of glucose, delays gastric emptying, and increases insulin sensitivity (Chandalia et al., 2000). In addition, according to a recent report by Li et al., the short-chain fatty acids produced by the breakdown of dietary fiber by the gut microbiota not only stabilize the gut microbiome but also promote the secretion of satiety hormones (ie. glucagon-like peptide-1 and peptide YY), thereby reducing insulin resistance and facilitating glycemic control (Li et al., 2020). In accordance with Deshmukh et al., vitamins may play a pivotal role in the prevention of T2DM because they are key components of glucose metabolism (Deshmukh et al., 2020). Dietary niacin intake may also be involved in diabetes prevention by upregulating the activity of the gene SIRT1, which protects cells against oxidative stress and aging (Liu et al., 2023). Pyridoxine acts as an antioxidant by inhibiting the formation of ROS and advanced glycation end products, and there is evidence that pyridoxine deficiency in the body plays a role in some forms of glucose tolerance (Deshmukh et al., 2020). Folate reduces oxidative stress, improves endothelial dysfunction, and regulates DNA methylation of genes involved in insulin signaling, which may play a role in the prevention of diabetes (Deshmukh et al., 2020). In one study, folate intake was significantly associated with lower levels of homocysteine, insulin, and C-reactive protein (Deshmukh et al. 2020; Zhu et al., 2020). Moreover, by reducing intracellular ROS and reactive nitrogen species, vitamin C attenuates the activity of stress signaling pathway factors, such as nuclear factor kappa B, c-Jun N-terminal kinase, and p38 mitogen-activated protein kinase, which are known to interfere with insulin signaling (Mason et al., 2022).

According to Dubey et al., overall deficiencies or excesses of essential minerals and trace elements are associated with imbalances in glucose homeostasis and insulin resistance (Dubey et al., 2020). Calcium homeostasis plays an important role in insulin resistance and secretion by mediating the regulation of calcium metabolism (Dubey et al., 2020). Zinc is involved in insulin hexamer formation, storage, and secretion by β cells, and there is evidence that it protects against the progression of insulin resistance and diabetes (Dubey et al., 2020).

There are several limitations in this study. First, the KoGES dataset did not include follow-up information related to the dietary OBS items, so only baseline survey data were used in the analysis. Disease progression and lifestyle changes over time may alter both the OBS itself and the incidence of T2DM and should be considered in further studies. Second, we applied the same weight to each OBS component, which may inaccurately reflect the contribution of each component. However, according to Lakkur et al., no significant differences were found between weighted and unweighted OBS in their association with various cancers and mortality in previous studies (Lakkur et al., 2014). Thus, we considered using an unweighted OBS is sufficient for this study. The OBS is sufficiently valid to assess oxidative balance. Third, the OBS only included dietary and non-dietary lifestyle factors. KoGES data did not include information on endogenous factors, such as individual pro- and anti-inflammatory cytokines and their associated genes that contribute to oxidative balance. However, past research has shown that even if the OBS includes only dietary and lifestyle factors, it reflects a variety of biomarkers of oxidative stress (Cho et al., 2018; Mao and Bostick, 2021). Fourth, The KoGES-HEXA cohort used in this study had only one follow-up, which may have led to inaccurate timing of T2DM diagnosis. Additionally, the cohort's short mean follow-up of 3.5 years resulted in fewer cases of new-onset T2DM, which may have reduced statistical power. This brief duration of the study may account for why smoking

status, physical activity, and alcohol consumption did not have a significant impact on the incidence of T2DM in the univariable analysis. Nonetheless, we observed statistically significant results indicating the impact of OBS on T2DM morbidity. Finally, the markers included in the OBS may affect T2DM development in the older adult population through a variety of interacting mechanisms in addition to the effects of oxidative stress. For example, resistance exercise has a protective effect against diabetes by improving insulin resistance in the muscle and liver, whereas obesity can contribute to T2DM through altered pancreatic hormone secretion, impaired glucose uptake in skeletal muscle, and worsening hepatic insulin resistance (Bellary et al., 2021; Park et al., 2023). Despite the above limitations, this study has the clear strength of identifying the impact of dietary and non-dietary lifestyle factors on the incidence of T2DM in older adults in a large population-based prospective cohort followed for a mean of 3.5 years.

5. Conclusion

In conclusion, we expect that the OBS is a reliable indicator of the T2DM incidence in adults aged 60 years or older. Our study suggests that maintaining an appropriate body weight through healthy lifestyle modification in elderly has the potential to lower the incidence of T2DM. Our findings suggest that the OBS may be an additional useful tool for assessing the T2DM incidence in the older adult population.

CRediT authorship contribution statement

Mid-Eum Moon: Writing – review & editing, Writing – original draft, Conceptualization. **Dong Hyuk Jung:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Seok-Jae Heo:** Writing – review & editing, Formal analysis. **Byoungjin Park:** Methodology, Data curation. **Yong Jae Lee:** Supervision, Methodology.

Declaration of competing interest

None of the authors have conflicts of interest to declare that could be perceived as prejudicing the impartiality of this study.

Data availability

The data cannot be shared due to regulations by the Korea Disease Control and Prevention Agency. However, additional analyses can be performed upon reasonable request to the corresponding author.

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Ethics approval

This study involving human participants was conducted in accordance with the ethical principles of the Declaration of Helsinki and approved by the Institutional Review Board of Yongin Severance Hospital (IRB number: 9-2023-0045).

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