

BMJ Open Body mass index and all-cause mortality in patients with newly diagnosed type 2 diabetes mellitus in South Korea: a retrospective cohort study

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ABSTRACT

Objectives The lower risk of death in overweight or obese patients, compared with normal-weight individuals, has caused confusion for patients with diabetes and healthcare providers. This study investigated the relationship between body mass index (BMI) and mortality in patients with type 2 diabetes.

Design A retrospective cohort study.

Setting We established a national population database by merging the Korea National Health Insurance (KNHI) claims database, the National Health Check-ups Database and the KNHI Qualification Database of South Korea.

Participants A total of 53 988 patients who were newly diagnosed with type 2 diabetes (E11 in International Classification of Diseases, 10th Edition) in 2007, had available BMI data, lacked a history of any serious comorbidity, received diabetes medication and did not die during the first 2 years were followed up for a median of 8.6 years.

Primary outcome measures All-cause mortality.

Results The mean BMI was 25.2 (SD 3.24) kg/m², and the largest proportion of patients (29.4%) had a BMI of 25–27.4 kg/m². Compared with a BMI of 27.5–29.9 kg/m² (the reference), mortality risk continuously increased as BMI decreased while the BMI score was under 25 (BMI <18.5 kg/m²: adjusted HR (aHR) 2.71, 95% CI 2.24 to 3.27; BMI 18.5–20.9 kg/m²: aHR 1.94, 95% CI 1.70 to 2.22; BMI 21–22.9 kg/m²: aHR 1.51, 95% CI 1.34 to 1.70; and BMI 23–24.9 kg/m²: aHR 1.14, 95% CI 1.01 to 1.28). For patients aged ≥65 years, the inverse association was connected up to a BMI ≥30 kg/m² group (aHR 0.76, 95% CI 0.59 to 0.98). However, the associations for men, patients aged <65 years and ever smokers resembled a reverse J curve, with a significantly greater risk of death in patients with a BMI ≥30 kg/m².

Conclusions This study suggests that, for patients with type 2 diabetes at a normal weight, distinct approaches are needed in terms of promoting muscle mass improvement or cardiorespiratory fitness, rather than maintaining weight status. Improved early diagnosis considering the inverse association between BMI and mortality is also needed.

INTRODUCTION

Worldwide, the numbers of people with obesity or overweight are increasing. In

Strengths and limitations of this study

- We performed a nationally representative population-based study using national big data on healthcare.
- This was a long-term, retrospective cohort study with a median follow-up time of 8.6 years.
- We performed a subgroup analysis according to smoking status and medication adherence, in addition to an overall analysis.
- Adjustments for unmeasured confounders were inadequate because of unavailable data.
- We excluded people with diabetes with unavailable body mass index data because they did not attend routine health check-ups.

2016, there were estimated to be 650 million adults aged ≥18 years with obesity (body mass index (BMI) ≥30 kg/m²), which was nearly threefold greater than the number in 1975. Moreover, the number of adults aged ≥18 years with overweight (BMI 25–29.9 kg/m²) is >1.9 billion, which comprises 39% of adults in this age range.¹ It has been reported that obesity and overweight are major risk factors of non-communicable diseases including cardiovascular disease, musculoskeletal disorders and cancer. Notably, they are also linked to premature death.¹

Obesity and overweight statuses are major risk factors for diabetes. A person with obesity or overweight has a greater risk for diabetes than a person with normal-weight BMI. A 1 kg/m² increase in BMI is connected with a 25% increase in the risk of developing diabetes.^{2–6} Because obesity promotes insulin resistance, normal weight is essential for diabetes prevention.⁷

However, recent studies of patients with diabetes have demonstrated an ‘obesity paradox’, such that patients with diabetes who have obesity or overweight have a lower risk of death, compared with patients with



diabetes who have normal-weight BMI.^{2 8–11} These results have shown that the maintenance of normal-weight BMI is important for diabetes prevention, but normal-weight BMI may be a risk factor for mortality among people with diabetes, compared with overweight and obesity. This is a source of confusion for patients and healthcare providers.² Additionally, some studies have highlighted weaknesses in prior investigations, including small sample size, short follow-up period and insufficient adjustment for confounding factors.¹²

This study examined the associations between BMI and risk of death to determine whether the obesity paradox is a stable phenomenon, and to explore its causes by means of a large-scale, long-term follow-up study involving patients with diabetes in Korea. Because the number of patients with diabetes is increasing in Korea due to changes in diet and lifestyle, careful investigation of the impact of obesity and overweight as a core component of diabetes management is expected to provide important policy-making guidance.

METHODS

Study design and data source

This retrospective cohort study included patients who were newly diagnosed with type 2 diabetes (E11, International Classification of Diseases, 10th Edition (ICD-10)) in 2007. The patients were followed for up to 8 years (until 2014). Newly diagnosed diabetes was defined as the absence of a prior record of diagnosis with diabetes (ICD-10 code E10–E14) within the preceding 2 years (2005–2006).

In this study, we established a linked database by merging medical procedure information (ie, date of diagnosis and prescription drugs) from the Korea National Health Insurance (KNHI) claims database, health screening information (ie, height, weight, smoking, alcohol consumption, physical activity, family history of diabetes, blood pressure and total cholesterol) from the National Health Check-ups Database and registration information (ie, sex, age, residence, income group and date of death) from the KNHI Qualification Database by using an encrypted resident registration number as a unique identifier.

The KNHI programme covers approximately 97% of the population as a compulsory social insurance scheme. The remaining 3% of the population is protected under the Medical Aid programme as public assistance for healthcare.^{13 14} The National Health Insurance Service (NHIS) acts as a single insurer and promotes health check-ups to detect diseases early and enhance public health accordingly.¹⁵

Study population

In 2007, a total of 432 665 patients were first diagnosed with type 2 diabetes (E11). Of these patients, 81 527 were excluded because they had no BMI records. Moreover, 294 485 patients were excluded because they had limited clinical information: 159 634 patients had ≤ 2

outpatient visits; 127 676 patients had no record of medication prescribed for diabetes in the year 2007; and 7175 patients were <35 years of age and much more likely to have type 1 diabetes.^{12 16} The KNHI claims database contains the information that providers submit to insurers when seeking reimbursements. However, the accuracy of the medical diagnoses has been questioned. Thus, we excluded patients with fewer than two ambulatory visits and those with no antidiabetic drug prescriptions.¹⁶ Additionally, 1407 patients were excluded because they had been diagnosed with ischaemic heart disease, cardiovascular disease or cancer before their diagnosis of diabetes. Finally, 1258 patients were excluded because they died during the first 2 years of follow-up.¹² Therefore, the study population comprised 53 988 patients with type 2 diabetes.

Study variables

The primary outcome of this study was all-cause mortality. Data concerning deaths from 1 January 2007 to 31 December 2014 were confirmed using the health insurance qualification database. The main independent variable was BMI, which was calculated using measurement records for height and weight on dates closest to the date of diabetes diagnosis in the health check-ups database (linked to the NHIS claims database of study participants). BMI values were categorised into seven groups (kg/m^2 : <18.5 , 18.5 – 20.9 , 21.0 – 22.9 , 23.0 – 24.9 , 25.0 – 27.4 , 27.5 – 29.9 (reference) and ≥ 30), in accordance with the WHO guidelines.^{17 18}

Covariates consisted of sex (male or female), age (35–44, 45–54, 55–64, 65–74 or 75+), income level (Medical Aid, deciles 1–2, deciles 3–4, deciles 5–6, deciles 7–8, deciles 9–10), residence (Seoul, metropolitan, or city and county), smoking status (never smoker, former smoker or current smoker), alcohol intake (never, 2–3 times/month, 1–2 times/week, 3–4 times/week or every day), physical activity (no activity, 1–2 times/week, 3–4 times/week, 5–6 times/week or every day), family history of diabetes mellitus (yes or no), medication adherence (adherence or non-adherence), systolic blood pressure (continuous variable) and total cholesterol (continuous variable). Income level, residence, smoking status, alcohol intake, physical activity, family history of diabetes mellitus, systolic blood pressure and total cholesterol data were extracted from health screening information collected at the first diagnosis.¹²

The income distributions of patients insured by the National Health Insurance (NHI) were divided into equal deciles (1–10), with the highest decile associated with the highest income level, apart from Medical Aid beneficiaries. Adherence to diabetes medication was evaluated by medication possession ratio (MPR). The MPR score for diabetes was expressed as the proportion of aggregate days a patient had access to diabetes medications during the study period ($\text{MPR} = \text{number of days in the study period covered by the supply of medication} / \text{number of days in the study period}$).¹⁶ MPR scores were calculated

using individual medication records prescribed for diabetes during a period of 1 year (365 days) since the first diagnosis, according to information in the NHIS claims database. The medication adherence group was defined as patients with MPR ≥ 0.80 .¹⁶

Statistical analysis

χ^2 tests and analysis of variance were performed to examine whether patients were differentially distributed in terms of socioeconomic status (sex, age, income and residence), health behavioural characteristics (smoking, drinking and physical activity) and medical care characteristics (MPR, family history, systolic blood pressure and total cholesterol) according to BMI category.

The relationship between BMI and mortality was evaluated through Cox proportional hazards analysis with adjustment for covariates. Additionally, a stratified analysis was performed according to sex (male or female), age (<65 or ≥ 65 years), smoking status (never smoker or ever smoker) and medication adherence (adherence or non-adherence). The results are shown as HRs and 95% CIs with two-tailed p values. All statistical analyses were performed using SAS V.9.3 (SAS).

RESULTS

Patient characteristics according to BMI

The mean BMI was 25.2 ± 3.24 kg/m² overall (n=53 988; 25.0 ± 3.04 kg/m² in men and 25.6 ± 3.46 kg/m² in women). When stratified according to BMI category the largest proportion of patients (29.4%; n=15 847) had a BMI of 25–27.4 kg/m². Additionally, 25.5% of patients (n=13 761) had a BMI of 23–24.9 kg/m² (table 1).

The BMI <18.5 kg/m² group contained a higher proportion of men (67.4%) than women, whereas the BMI ≥ 30 kg/m² group contained a higher proportion of women (57.7%) than men. Among patients with a BMI <18.5 kg/m², most were aged ≥ 65 years. The proportions of younger adults and women were higher in the high BMI groups. Patients in low-income families (Medical Aid, income deciles 1–2) (21.7%) made up a larger proportion of patients with BMI <18.5 kg/m² and patients in high-income families (income deciles 9–10) (30%) made up a larger proportion of patients with BMI 23–24.9 kg/m². The proportions of patients who resided in city and county, never drank alcohol and had no physical activity were highest among those with BMI <18.5 or ≥ 30 kg/m². With increasing BMI, the proportions of patients who were never smokers and who had MPR >80% increased. Mean systolic blood pressure (mm Hg) and mean total cholesterol (mg/dL) also increased with increasing BMI. Furthermore, patients with a family history of diabetes constituted the largest proportion among patients with BMI 21–22.9 kg/m² (22.5%) (table 1).

Relationship between BMI and mortality

During the median 8.6 years of follow-up (452 951 person-years), 4215 participants died. Our findings suggested an inverse association between BMI and mortality in patients

with type 2 diabetes and BMI <25 kg/m² (figure 1 and table 2). After adjusting for sex, age, income, residence, smoking status, alcohol intake, physical activity, family history of diabetes mellitus, medication adherence, systolic blood pressure and total cholesterol level, the mortality risk relative to a reference group (BMI 27.5–29.9 kg/m²) increased as the BMI decreased while the BMI score was under 25 (BMI <18.5 kg/m²: HR 2.71, 95% CI 2.24 to 3.27; BMI 18.5–20.9 kg/m²: HR 1.94, 95% CI 1.70 to 2.22; BMI 21–22.9 kg/m²: HR 1.51, 95% CI 1.34 to 1.70; and BMI 23–24.9 kg/m²: HR 1.14, 95% CI 1.01 to 1.28), but the trend was not significant afterwards (BMI 25–27.4 kg/m²: HR 1.10, 95% CI 0.98 to 1.24; BMI ≥ 30 kg/m²: HR 1.04, 95% CI 0.88 to 1.24) (table 2).

In patients aged ≥ 65 years, the inverse association between BMI and mortality risk was more evident. The mortality risk compared with the reference group (BMI of 27.5–29.9) in all groups with BMI less than 27.5 decreased as the BMI increased (BMI <18.5 kg/m²: HR 2.43, 95% CI 1.90 to 3.10; BMI 18.5–20.9 kg/m²: HR 1.84, 95% CI 1.56 to 2.18; BMI 21–22.9 kg/m²: HR 1.42, 95% CI 1.22 to 1.66; BMI 23–24.9 kg/m²: HR 1.16, 95% CI 1.00 to 1.34; and BMI 25–27.4 kg/m²: HR 1.07, 95% CI 0.92 to 1.24), and thus the mortality risk in the highest BMI group was lowest (BMI ≥ 30 kg/m²: HR 0.76, 95% CI 0.59 to 0.98). However, the associations for men and patients aged <65 years resembled a reverse J curve, with a significantly greater risk of death in patients with a BMI ≥ 30 kg/m² (men: HR 1.37, 95% CI 1.08 to 1.74; patients aged <65 years: HR 1.37, 95% CI 1.06 to 1.77) (table 2 and figure 1).

Subgroup analysis of the association between BMI and mortality according to smoking status (never or ever) and medication adherence (adherence or non-adherence) also showed similar inverse or reverse J curve association patterns (figure 2 and table 3). In the never smoker group, compared with BMI of 27.5–29.9, only while the BMI was under 23, mortality risk decreased significantly as BMI increased (BMI <18.5 kg/m²: HR 2.65, 95% CI 2.06 to 3.42; BMI 18.5–20.9 kg/m²: HR 1.70, 95% CI 1.44 to 2.02; and BMI 21–22.9 kg/m²: HR 1.41, 95% CI 1.22 to 1.63). The mortality risk was lowest in a BMI ≥ 30 kg/m² but was not significant (HR 0.94, 95% CI 0.76 to 1.16). However, in ever smokers, a reverse J curve of mortality risk was observed, with the risk for patients with BMI ≥ 30 kg/m² compared with BMI of 27.5–29.9 increased (HR 1.40, 95% CI 1.01 to 1.92) (table 3 and figure 2). In both the adherence group and the non-adherence group, the inverse association between BMI and mortality was significant only for the lower BMI groups than the reference group (adherence: BMI <18.5 kg/m²: HR 2.06, 95% CI 1.43 to 2.97; BMI 18.5–20.9 kg/m²: HR 1.87, 95% CI 1.51 to 2.31; and BMI 21–22.9 kg/m²: HR 1.44, 95% CI 1.20 to 1.74; non-adherence: BMI <18.5 kg/m²: HR 3.03, 95% CI 2.42 to 3.80; BMI 18.5–20.9 kg/m²: HR 2.00, 95% CI 1.69 to 2.38; BMI 21–22.9 kg/m²: HR 1.56, 95% CI 1.33 to 1.83; and BMI 23–24.9 kg/m²: HR 1.22, 95% CI 1.04 to 1.42). Although there were no statistical significances, the

Table 1 Baseline characteristics of the study participants, according to body mass index (BMI) categories

	BMI category (kg/m ²)					P value	
	<18.5	18.5–20.9	21–22.9	23–24.9	25–27.4		27.5–29.9
Patients, n (%)	636 (1.2)	3436 (6.4)	8440 (15.6)	13761 (25.5)	15847 (29.4)	7826 (14.5)	4042 (7.5)
Person-years, sum (%)	4890 (1.1)	27870 (6.2)	70144 (15.5)	115709 (25.5)	133649 (29.5)	66355 (14.6)	34334 (7.6)
Sex, n (%)							
Male	429 (67.4)	2145 (62.4)	5197 (61.6)	8488 (61.7)	9624 (60.7)	4242 (54.2)	1710 (42.3)
Female	207 (32.6)	1291 (37.6)	3243 (38.4)	5273 (38.3)	6223 (39.3)	3584 (45.8)	2332 (57.7)
Age, years, n (%)							
35–44	60 (9.4)	386 (11.2)	990 (11.7)	1829 (13.3)	2120 (13.4)	1211 (15.5)	815 (20.2)
45–54	151 (23.7)	1013 (29.5)	2625 (31.1)	4292 (31.2)	5205 (32.9)	2515 (32.1)	1311 (32.4)
55–64	173 (27.2)	928 (27.0)	2571 (30.5)	4261 (31.0)	4866 (30.7)	2343 (29.9)	1146 (28.4)
65–74	165 (25.9)	804 (23.4)	1740 (20.6)	2748 (20.0)	3046 (19.2)	1471 (18.8)	650 (16.1)
75+	87 (13.7)	305 (8.9)	514 (6.1)	631 (4.6)	610 (3.9)	286 (3.7)	120 (3.0)
Income level, n (%)							
Medical Aid	4 (0.6)	12 (0.4)	14 (0.2)	21 (0.2)	27 (0.2)	10 (0.1)	13 (0.3)
Deciles 1–2	134 (21.1)	592 (17.2)	1403 (16.6)	2194 (15.9)	2595 (16.4)	1256 (16.1)	697 (17.2)
Deciles 3–4	97 (15.3)	491 (14.3)	1169 (13.9)	1809 (13.2)	2023 (12.8)	1060 (13.5)	557 (13.8)
Deciles 5–6	115 (18.1)	657 (19.1)	1524 (18.1)	2448 (17.8)	2798 (17.7)	1515 (19.4)	805 (19.9)
Deciles 7–8	136 (21.4)	758 (22.1)	1940 (23.0)	3165 (23.0)	3683 (23.2)	1839 (23.5)	945 (23.4)
Deciles 9–10	150 (23.6)	926 (27.0)	2390 (28.3)	4124 (30.0)	4721 (29.8)	2146 (27.4)	1025 (25.4)
Residence, n (%)							
Seoul	101 (15.9)	564 (16.4)	1511 (17.9)	2482 (18.0)	2840 (17.9)	1317 (16.8)	659 (16.3)
Metropolitan	160 (25.2)	873 (25.4)	2315 (27.4)	3624 (26.3)	4002 (25.3)	1937 (24.8)	955 (23.6)
City and county	375 (59.0)	1999 (58.2)	4614 (54.7)	7655 (55.6)	9005 (56.8)	4572 (58.4)	2428 (60.1)
Smoking status, n (%)							
Never smoker	340 (54.8)	1926 (58.2)	5082 (62.1)	8512 (64.0)	10001 (65.2)	5104 (67.6)	2872 (74.3)
Former smoker	57 (9.2)	323 (9.8)	867 (10.6)	1505 (11.3)	1768 (11.5)	840 (11.1)	284 (7.4)
Current smoker	224 (36.1)	1059 (32.0)	2235 (27.3)	3292 (24.7)	3577 (23.3)	1611 (21.3)	708 (18.3)
Alcohol intake, n (%)							
Never	374 (59.8)	1912 (57.3)	4693 (56.8)	7636 (56.8)	8852 (57.2)	4576 (60.0)	2561 (65.6)
2–3 times/month	58 (9.3)	388 (11.6)	981 (11.9)	1761 (13.1)	1976 (12.8)	878 (11.5)	477 (12.2)
1–2 times/week	83 (13.3)	475 (14.2)	1361 (16.5)	2256 (16.8)	2677 (17.3)	1297 (17.0)	514 (13.2)
3–4 times/week	50 (8.0)	259 (7.8)	695 (8.4)	1078 (8.0)	1271 (8.2)	547 (7.2)	243 (6.2)
Every day	60 (9.6)	302 (9.1)	532 (6.4)	719 (5.4)	710 (4.6)	334 (4.4)	111 (2.8)
Physical activity, n (%)							
No activity	388 (63.7)	1905 (57.4)	4309 (52.4)	6914 (51.7)	7893 (51.3)	4135 (54.3)	2250 (57.6)

Continued

Table 1 Continued

	BMI category (kg/m ²)							P value
	<18.5	18.5-20.9	21-22.9	23-24.9	25-27.4	27.5-29.9	30+	
1-2 times/week	121 (19.9)	745 (22.4)	1958 (23.8)	3342 (25.0)	3909 (25.4)	1901 (25.0)	937 (24.0)	
3-4 times/week	40 (6.6)	315 (9.5)	900 (11.0)	1510 (11.3)	1862 (12.1)	762 (10.0)	352 (9.0)	
5-6 times/week	11 (1.8)	80 (2.4)	294 (3.6)	439 (3.3)	465 (3.0)	219 (2.9)	88 (2.3)	
Every day	49 (8.1)	276 (8.3)	761 (9.3)	1171 (8.8)	1265 (8.2)	598 (7.9)	277 (7.1)	
Medication adherence, n (%)								
Adherence (MPR ≥80%)	215 (33.8)	1429 (41.6)	3851 (45.6)	6327 (46.0)	7458 (47.1)	3709 (47.4)	1965 (48.6)	<0.001
Non-adherence (MPR <80%)	421 (66.2)	2007 (58.4)	4589 (54.4)	7434 (54.0)	8389 (52.9)	4117 (52.6)	2077 (51.4)	
Family history of DM, n (%)	108 (17.0)	736 (21.4)	1900 (22.5)	2950 (21.4)	3310 (20.9)	1548 (19.8)	834 (20.6)	<0.001
Systolic BP, mean (SD), mm Hg*	124.8 (19.6)	127.3 (18.0)	128.9 (17.6)	130.0 (17.1)	132.2 (17.2)	134.2 (17.3)	136.0 (17.3)	<0.001
Total cholesterol, mean (SD), mg/dL*	188.0 (43.2)	199.2 (45.1)	204.7 (44.5)	207.9 (44.2)	210.0 (43.0)	210.2 (42.7)	212.8 (42.8)	<0.001

X² test.

*Analysis of variance (ANOVA).

BP, blood pressure; DM, diabetes mellitus; MPR, medication possession ratio.

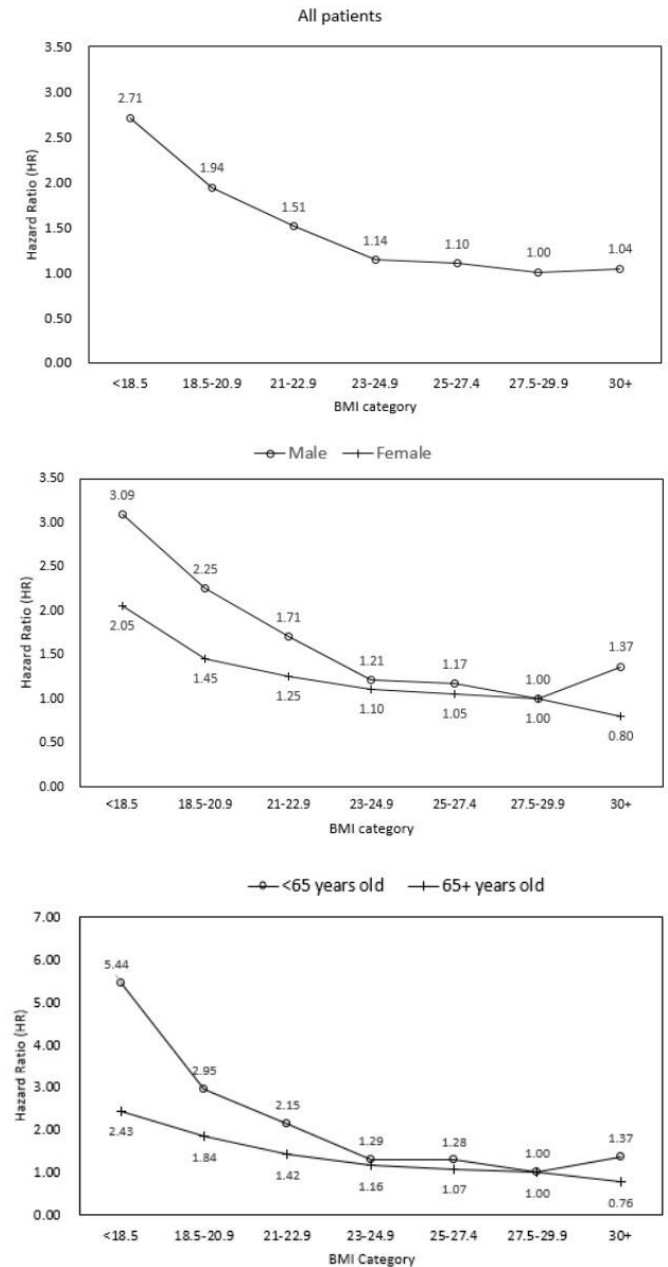


Figure 1 The adjusted HR for all-cause mortality among participants with incident type 2 diabetes, according to different levels of body mass index (BMI) at baseline.

adherence group showed the tendency for inverse association while the non-adherence group the tendency for a reverse J curve (adherence: HR 0.96, 95% CI 0.73 to 1.26; non-adherence: HR 1.10, 95% CI 0.87 to 1.39) (table 3 and figure 2).

DISCUSSION

Overweight and obesity have been reported as major risk factors for type 2 diabetes worldwide.^{19 20} Although there is general agreement concerning their effects on diabetes incidence, there is controversy regarding their impacts on mortality risk among people with diabetes. Some studies have reported an inverse association between BMI

Table 2 The adjusted HR for all-cause mortality among participants with incident type 2 diabetes, according to different levels of body mass index at baseline

	BMI category (kg/m ²)						
	<18.5	18.5–20.9	21–22.9	23–24.9	25–27.4	27.5–29.9	30+
All patients							
Death (n)	169	532	867	999	1030	427	191
Person-years	4890	27 870	70 144	115 709	133 649	66 355	34 334
HR (95% CI)	2.71 (2.24 to 3.27)	1.94 (1.70 to 2.22)	1.51 (1.34 to 1.70)	1.14 (1.01 to 1.28)	1.10 (0.98 to 1.24)	1.00	1.04 (0.88 to 1.24)
Male							
Death (n)	132	401	635	684	680	232	101
Person-years	3232	17 153	42 864	71 143	80 966	35 932	14 461
HR (95% CI)	3.09 (2.47 to 3.88)	2.25 (1.90 to 2.66)	1.71 (1.46 to 2.00)	1.21 (1.04 to 1.41)	1.17 (1.01 to 1.37)	1.00	1.37 (1.08 to 1.74)
Female							
Death (n)	37	131	232	315	350	195	90
Person-years	1658	10 717	27 280	44 566	52 683	30 423	19 872
HR (95% CI)	2.05 (1.41 to 2.99)	1.45 (1.16 to 1.83)	1.25 (1.03 to 1.52)	1.10 (0.92 to 1.32)	1.05 (0.88 to 1.26)	1.00	0.80 (0.62 to 1.04)
<65 years old							
Death (n)	71	189	337	345	396	155	104
Person-years	3084	19 428	52 350	88 480	103 950	51 964	27 929
HR (95% CI)	5.44 (4.04 to 7.32)	2.95 (2.37 to 3.68)	2.15 (1.76 to 2.61)	1.29 (1.06 to 1.57)	1.28 (1.05 to 1.55)	1.00	1.37 (1.06 to 1.77)
65+ years old							
Death (n)	98	343	530	654	634	272	87
Person-years	1806	8443	17 794	27 229	29 699	14 391	6405
HR (95% CI)	2.43 (1.90 to 3.10)	1.84 (1.56 to 2.18)	1.42 (1.22 to 1.66)	1.16 (1.00 to 1.34)	1.07 (0.92 to 1.24)	1.00	0.76 (0.59 to 0.98)

Adjusted for sex (male, female), age (35–44, 45–54, 55–64, 65–74, 75+), income level (Medical Aid, deciles 1–2, deciles 3–4, deciles 5–6, deciles 7–8, deciles 9–10), residence (Seoul, metropolitan, city and county), smoking status (never smoker, former smoker, current smoker), alcohol intake (never, 2–3 times/month, 1–2 times/week, 3–4 times/week, every day), physical activity (no activity, 1–2 times/week, 3–4 times/week, 5–6 times/week, every day), family history of diabetes mellitus (yes or no), medication adherence (adherence, non-adherence), systolic blood pressure (continuous variable) and total cholesterol (continuous variable).
 BMI, body mass index.;

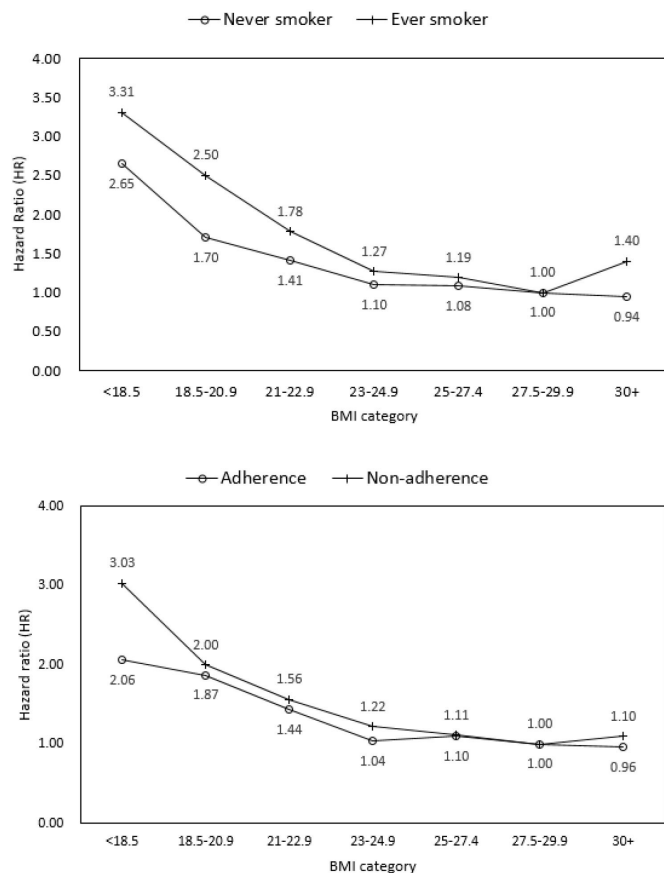


Figure 2 The adjusted HR for all-cause mortality among participants with incident type 2 diabetes, according to different levels of body mass index (BMI) at baseline, by smoking status and medication adherence.

and mortality, while other studies have shown U-shaped or V-shaped associations indicative of higher mortality in individuals with both lower and higher BMIs.²¹ Linear positive associations have also been described.¹² Since 2010, the obesity paradox has become evident in that better outcomes are present in overweight and obese patients with type 2 diabetes than in normal-weight patients with type 2 diabetes, and has been repeatedly published.^{2 22-24}

Some relatively recent studies have suggested that problems with research design contribute to the obesity paradox.^{2 12} These problems include short follow-up periods, small sample sizes and insufficient risk adjustment.^{2 12} Therefore, the present study investigated the obesity paradox in patients with type 2 diabetes using a long-term follow-up period of 8 years, and by controlling for major confounding variables to limit the problems involved in previous studies.

Patient mortality is impacted by disease severity and insufficient risk adjustment is likely to generate biased results in explorations of causal relationships with death. This study endeavoured to control for the effects of related risk factors. First, the cohort was limited to patients with newly diagnosed type 2 diabetes because it has been challenging to control for the differential impacts of disease

severity linked to different durations of illness in patients with an existing diagnosis.^{8 12 16} Second, this study excluded patients with severe comorbidities (eg, ischaemic heart disease, cardiovascular disease or cancer)² and patients who died within 2 years after diagnosis.^{12 25} Third, this study used an improved risk adjustment approach. In the model of association between BMI and mortality in patients with type 2 diabetes, disease severity characteristics (eg, systolic blood pressure and total cholesterol) were considered, as were sociodemographic (eg, sex, age and income group), health behavioural (eg, region, smoking status, drinking habits and physical activity) and health medical care (eg, prescription compliance and family history) characteristics.^{12 25} The results showed an inverse association between BMI and mortality, thereby confirming the existence of an obesity paradox in which the risk of death in patients with type 2 diabetes was lower in overweight (BMI 25.0–29.9 kg/m²) and obese (BMI ≥30 kg/m²) patients, compared with normal-weight patients (BMI 18.5–24.9 kg/m²).¹² This tendency was more evident in patients with type 2 diabetes who were female, aged ≥65 years and non-smokers.

The highest risk of death was observed in patients with BMI <18.5 kg/m². This high mortality rate was previously reported to be influenced by various underlying diseases and smoking status.^{2 25} Underweight patients were more likely to have comorbidities in addition to diabetes,²⁵ or to be smokers (a major risk factor for death).^{9 11} The BMI <18.5 kg/m² group contained larger proportions of smokers, patients aged ≥65 years, those with a low income (Medical Aid, income deciles 1–2) and those exhibiting medication non-adherence compared with the other groups.

There have been various reported causes for lower mortality among patients with diabetes who have overweight or obese BMI, compared with those who have normal-weight BMI. First, overweight or obese patients with diabetes could achieve a degree of disease control by improving their lifestyle (eg, by losing weight).^{8 9} The most frequently used approach to manage type 2 diabetes involves weight control through dietary modification and physical activity.⁸ Weight loss for blood sugar control should be a goal of disease management for overweight or obese patients with type 2 diabetes, but is not considered appropriate for patients with normal-weight BMI. Thus, distinct strategies are needed for normal-weight individuals with diabetes, but these are difficult to develop and implement.⁸ Second, earlier diabetes detection could be more likely in overweight or obese individuals than in normal-weight individuals^{2 9 10} because of a greater tendency to undergo health screenings to relieve concerns about overweight or obesity-related health problems, which could lead to early intervention.^{2 9} Third, genetic factors may play a role. Normal-weight patients with type 2 diabetes may be genetically susceptible to more severe disease, higher mortality risk or both.²⁶ In particular, single nucleotide polymorphism variants in *TCF7L2* and *CDKAL1* reportedly have some

Table 3 The adjusted HR for all-cause mortality among participants with incident type 2 diabetes, according to different levels of body mass index at baseline, by smoking status and medication adherence

	BMI category (kg/m ²)						
	<18.5	18.5–20.9	21–22.9	23–24.9	25–27.4	27.5–29.9	30+
Never smoker							
Death (n)	81	270	497	597	644	293	127
Person-years	2650	15741	42329	71660	84390	43259	24429
HR (95% CI)	2.65 (2.06 to 3.42)	1.70 (1.44 to 2.02)	1.41 (1.22 to 1.63)	1.10 (0.95 to 1.27)	1.08 (0.94 to 1.24)	1.00	0.94 (0.76 to 1.16)
Ever smoker							
Death (n)	80	246	349	373	354	122	55
Person-years	2137	11081	25673	40242	45035	20792	8394
HR (95% CI)	3.31 (2.47 to 4.43)	2.50 (2.00 to 3.13)	1.78 (1.44 to 2.19)	1.27 (1.03 to 1.57)	1.19 (0.97 to 1.47)	1.00	1.40 (1.01 to 1.92)
Adherence							
Death (n)	39	185	337	386	447	180	82
Person-years	1707	11754	32276	53468	63110	31508	16731
HR (95% CI)	2.06 (1.43 to 2.97)	1.87 (1.51 to 2.31)	1.44 (1.20 to 1.74)	1.04 (0.87 to 1.25)	1.10 (0.92 to 1.31)	1.00	0.96 (0.73 to 1.26)
Non-adherence							
Death (n)	130	347	530	613	583	247	109
Person-years	3183	16116	37868	62241	70540	34847	17602
HR (95% CI)	3.03 (2.42 to 3.80)	2.00 (1.69 to 2.38)	1.56 (1.33 to 1.83)	1.22 (1.04 to 1.42)	1.11 (0.95 to 1.30)	1.00	1.10 (0.87 to 1.39)

Adjusted for sex (male, female), age (35–44, 45–54, 55–64, 65–74, 75+), income level (Medical Aid, deciles 1–2, deciles 3–4, deciles 5–6, deciles 7–8, deciles 9–10), residence (Seoul, metropolitan, city and county), smoking status (never smoker, former smoker, current smoker), alcohol intake (never, 2–3 times/month, 1–2 times/week, 3–4 times/week, every day), physical activity (no activity, 1–2 times/week, 3–4 times/week, 5–6 times/week, every day), family history of diabetes mellitus (yes, no), medication adherence (adherence, non-adherence), systolic blood pressure (continuous variable) and total cholesterol (continuous variable).
 BMI, body mass index.;

associations with increasing risk of cancer in people with diabetes, primarily in the context of low BMI.^{10 27 28} Notably, patients with type 2 diabetes and BMI <25 kg/m² have greater disease severity, are more likely to require insulin therapy and experience higher mortality.^{2 29} Among overweight patients, the presence of overweight itself could lower the risk of mortality by stimulating metabolic reserve and preventing frailty, malnutrition and osteoporosis.⁹

Additional analysis was performed to examine the differences in the relationship between BMI and mortality according to patient characteristics (eg, sex, age at diagnosis, smoking status and medication adherence).^{12 21} The results demonstrated a reverse association for all classified groups, as described above. However, these results do not imply that weight control or weight loss is not essential for diabetes management or that weight gain is necessary.^{11 21} Obesity is reportedly associated with the onset of various diseases (eg, cancer and cardiocerebrovascular disease).^{30 31} Weight control or loss remains important because of the increased risk of mortality linked to related diseases associated with obesity in patients with diabetes.^{11 21} Obese patients who were male, aged <65 years and were smokers showed higher risks of death in our study. Thus, at early stages after the diagnosis of diabetes, even weight control alone could be effective for diabetes control, but failure to address obesity could increase the risk of death. Overall, overweight or obese patients with type 2 diabetes were likely to have a lower risk of mortality than normal-weight patients because people with overweight and obesity have greater accessibility to early diagnosis and effective disease management. Thus, weight loss alone is insufficient for the management of diabetes in normal-weight individuals and a tailored approach is needed for these patients.^{2 8}

Enhanced muscle mass is considered important for diabetes management,² because sarcopenic obesity has been observed in normal-weight patients with diabetes.¹⁰ Among normal-weight individuals, reduced muscle mass might increase the risk of death.² Greater muscle strength is associated with lower risk of death. Therefore, the maintenance of normal weight among patients with diabetes should also involve efforts to increase muscle mass. Although these individuals would experience slight weight gain due to the increased muscle mass, the risk of death would be reduced.² Furthermore, normal-weight patients with diabetes should strive to improve their cardiorespiratory fitness through aerobic activities.^{8 32} Cardiorespiratory fitness reportedly has a greater impact on the risk of death, compared with weight status.³³ Therefore, efforts to maintain normal weight should involve both calorie supplementation and continued cardiorespiratory fitness through aerobic activities.⁸ Finally, genetic factors influencing diabetes must be considered.⁸ The risk of diabetes is associated with family history, and overweight or obese patients are more likely to undergo screening if they have a family history of diabetes.^{2 9} Despite the maintenance of normal weight, patients with a family history of diabetes

should focus on early diagnosis and management through periodic screening tests.

This study had a few limitations. First, obesity was defined as BMI ≥ 30 kg/m². If that broad categorisation were stratified into a few subgroups, the risk of death would presumably increase more among patients with severe obesity.²¹ However, because patients with BMI ≥ 30 kg/m² only constituted 7.5% of the patients with diabetes in this study and had the lowest risk of death, this subgrouping is not expected to drastically influence the results. Second, we could not identify the causes of death among the participants. NHIS data solely include information related to the retention or loss (death or immigration) of eligibility status as beneficiaries, but not causes of death. Many previous studies have used all-cause mortality as an outcome variable.^{12 21 25} In future studies, more detailed analysis is needed to determine clearly why normal-weight patients with diabetes had comparatively higher mortality. Third, this study did not consider changes in BMI. Notably, we used BMI information at the time of diagnosis. In the future, examining the risk of death according to changes in BMI after diabetes diagnosis might clarify whether the reduced risk of death in overweight or obese patients with diabetes is attributable to weight loss or other factors. Fourth, although we controlled for many covariates, residual confounding may still exist. Collider bias attributable to unmeasured factors may explain the inverse association between BMI and death in people with diabetes.³⁴ Two previous studies considered that the obesity paradox in people with diabetes is a reverse association caused by insufficient adjustment for potential confounding variables (including smoking status); the obesity paradox disappeared after controlling for the unmeasured factors.^{12 35} In an effort to resolve this problem, we included various confounding factors (eg, smoking status) in the analysis, but these factors did not include diabetes-related genes or fat accumulation in the liver or pancreas; additional analysis may be required.³⁶ However, our argument is not that obesity protects against mortality in people with diabetes but rather that people with diabetes who are not obese require more appropriate management compared with current management strategies. We found that patients in the lowest BMI category (<18.5 kg/m²) exhibited the lowest rate of medication adherence (33.8%); thus, they require better management. In contrast, adherence was better in patients with a higher BMI (27.5–29.9: 47.4%; ≥ 30 kg/m²: 48.6%). Connectedly, we had no HbA1c test results to assess the adequacy of diabetes management, so we were not able to confirm whether the higher risk of death in lower BMI groups compared with the reference group was due to inadequate control of diabetes. However, that lower BMI groups had low adherence suggested there could have been gaps with effective management of diabetes as aforementioned (table 1). Fifth, people with diabetes with unavailable BMI data (because they did not attend national health check-ups) were excluded. This may have distorted the



association between BMI and mortality risk. However, when comparing demographic characteristics between those who did and those who did not attend check-ups, the proportions of women and patients aged 34–44 and ≥ 65 years were only slightly higher among attendees than non-attendees. Thus, we have no evidence of large-scale exclusion of a specific group. We suggest that exclusion of the non-attendees did not greatly affect the results. Sixth, Our study basically referred to the WHO expert consultation on population-specific cut-off points for BMI in use.¹⁸ A WHO expert consultation suggested that Asian populations have different associations between BMI, percentage of body fat and health risks than do European populations and recommended to make a decision of adding further potential points of 23, 27.5, 32.5 and 37.5 kg/m² to the WHO cut-off points under each country's context.¹⁸ In this study, we did not simply use 18.5–24.9 kg/m² for the BMI range of normal weight but subdivided into 18.5–20.9, 21.0–22.9 and 23.0–24.9. For the BMI range of overweight as well, by dividing into 25.0–27.4 and 27.5–29.9 instead of 25.0–29.9, we tried to apply more appropriate cut-off points for BMI of Asians. Therefore, we think it is difficult to question that the cut-off points for BMI in this study would have been biasing the results on the inverse association between BMI and mortality in Korea diabetics. Last, we did not diagnose the proportional hazard (PH) assumption based on the specificity of our data because this model had mostly time-dependent covariates which were associated with chronic care management, and would change the risk for death as outcome during the follow-up period. If censoring is absent or censoring is independent of tested covariates, average HRs are valid and interpretable as such because PH violation alone could not automatically lead to biased estimates and non-proportionality would not be an issue.³⁷ In this study, censoring was independent because all patients were followed up by the NHI administrative data. In addition, we transformed all covariates into stratified variables and did subgroup analysis for main interest covariates. Nevertheless, it might still be that HRs due to higher mortality associated with lower BMI groups might be higher in the earlier years of the follow-up period such that estimates would represent underestimates in the earlier and overestimates in the later.

Despite these limitations, our findings are meaningful because we are the first to investigate the long-term relationship between BMI and mortality in patients with type 2 diabetes; we used information from a national insurance database. Few similar studies have been performed in Asia. We controlled for various confounders and performed subgroup analyses. Few studies have evaluated the association between BMI category and mortality in different subgroups.

CONCLUSION

In conclusion, this study shows an inverse association between BMI and mortality in patients with type 2 diabetes.

However, we do not suggest that weight gain is appropriate when seeking to reduce mortality risk in people with diabetes. We simply suggest that people with diabetes who are not obese require more appropriate management. Therefore, disease management for normal-weight patients should not simply follow the approach used for overweight or obese patients. For normal-weight patients, tailored approaches should be implemented to focus on early diagnosis and promote improvement of muscle mass or cardiorespiratory fitness, rather than maintenance of weight status. Importantly, normal-weight patients with diabetes had lower medication adherence, which suggests that more thorough medication guidance is needed. The reverse J curve indicated that the mortality risk was higher for men with a BMI ≥ 30 kg/m², patients aged < 65 years and smokers. Weight management remains important for people with diabetes.

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