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Original article

## Association between BMI and risk of severe hypoglycaemia in type 2 diabetes



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### ABSTRACT

**Aim.** – This study aimed to assess the association between body mass index (BMI) and the development of severe hypoglycaemia in patients with type 2 diabetes (T2D), using nationwide data for the entire South Korean population.

**Methods.** – The association between BMI and severe hypoglycaemia was retrospectively examined from claims and National Health examination data registered between 2002 and 2015. A total of 1,366,692 subjects assigned clinical codes for T2D and prescribed antihypoglycaemic agents were included. The primary outcome was an episode of severe hypoglycaemia after the baseline health examination.

**Results.** – A total of 37,682 subjects (2.7%) experienced a new severe hypoglycaemic event during the follow-up period (mean: 8.6 years). An inverse J-shaped association was observed between BMI and severe hypoglycaemic events. The association between low BMI and high risk of severe hypoglycaemia was similar in subjects who had never smoked, did not consume alcohol, did not use insulin and had no major comorbidities, after adjusting for multiple confounding variables. This association was also found to be intensified in men, young people aged 30–49 years, those with major comorbidities and insulin users.

**Conclusion.** – BMI and severe hypoglycaemia were found to be inversely associated. Thus, those who fall into the category of having low BMI and high risk of severe hypoglycaemia should be warned about the risk of having a hypoglycaemic event and be properly informed about hypoglycaemia to minimize the risk of fatal hypoglycaemia-related outcomes.

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### Introduction

The 2012 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement emphasized the complexity of glycaemic control and the importance of individualized diabetes care [1]. In the recent trend towards such personalization of diabetes care, hypoglycaemia has been considered a major barrier to optimal glucose control to prevent diabetes complications. One recent survey of global opinion leaders in diabetes showed that “the risk of hypoglycaemia from treatment” and “the risk associated with hypoglycaemia” are important factors that need to be considered when setting a given

patient's glycaemic target [2]. Severe hypoglycaemia is defined as an episode in which the subject's blood glucose levels are extremely low, to the point of requiring the assistance of someone else for treatment [3]. Severe hypoglycaemia reduces the quality of life, increases medical costs and can even lead to various fatal outcomes [4]. Thus, identifying the barriers to proper treatment of hypoglycaemia is an important and crucial issue in the management of type 2 diabetes (T2D).

Obesity and underweight have been widely recognized as important risk factors militating against good health [5]. Yet, the obesity paradox, the medical hypothesis proposing that obese and overweight patients with cardiovascular disease (CVD) appear to have better survival prognoses, has been suggested [6]. Since then, many studies have been performed to analyze the association between body mass index (BMI) and increased risks for various diseases and mortality. However, the effects of being either underweight or overweight on the risk of severe hypoglycaemia

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have been controversial. Some studies have shown that lower BMI is associated with an increased risk of severe hypoglycaemia [7,8] but, as large-scale studies to elucidate the association between BMI and severe hypoglycaemia have been conducted only in Caucasian patient groups at high risk of CVD, it remains uncertain whether the findings of such studies can be applied to other populations including other ethnicities. Furthermore, no studies have analyzed the risk of severe hypoglycaemia based on BMI categories.

For this reason, the present study aimed to investigate the association between BMI and risk of severe hypoglycaemia using insurance claims data for the entire South Korean population. Another objective was to compare the associations in various weight-related subgroups to quantify the risk of severe hypoglycaemia associated with incremental increases in BMI.

## Materials and methods

### Study population

The Catholic Medical Centre Ethics Committee approved the study, which was conducted in compliance with the Declaration of Helsinki. This nationwide retrospective study was conducted from 2002 to 2015, using the Korean National Health Insurance (NHI) Claims Database maintained by the Korean National Health Insurance Service (NHIS), a government-affiliated agency under the Korean Ministry of Health and Welfare. This database comprises various subdatasets, including those for qualification, health insurance claims, health checkups and death-related information, provided by the Korean NHI and Medical Aid programmes [9]. The NHI programme is a compulsory social insurance scheme that covers approximately 97% of the entire population, while the remaining 3% are covered under the Medical Aid programme. NHI subscribers are recommended to undergo standardized general medical checkups once every 2 years. These checkups generally assess smoking status, alcohol consumption, physical activity, income level, measurements of height, weight and blood pressure, and various laboratory tests.

Using the claims database, subjects who had undergone a health examination at least once between 2005 and 2008 were identified. From these, those who were aged > 30 years and had their body weight measured were selected. Both International Classification of Diseases, Tenth Edition (ICD-10) codes and medication prescriptions were used to define the diseases of interest. Patients with T2D were defined as those assigned codes such as E11 and E14 by the diagnostic clinic in both inpatient and outpatient claims datasets, and then prescribed oral hypoglycaemic agents or insulin [10]. A total of 24651 subjects without T2D and aged < 30 years were excluded, as were also 1622 people who were lacking BMI data. In addition, as a previous history of severe hypoglycaemia is one of the more important risk factors for a subsequent severe hypoglycaemic event, 2971 subjects with severe hypoglycaemic events in the 3 years prior to health examination (in other words, 3 years before the study baseline point) were also excluded to ensure a washout period to avoid the effects of the previous severe hypoglycaemic event. Thus, the final study sample included 1,366,692 subjects (Figs. S1 and S2; see [supplementary materials associated with this article online](#)).

### Definition of variables

The primary endpoint of our study was an episode of severe hypoglycaemia during the follow-up period. Patients with severe hypoglycaemia were defined as those assigned diagnostic clinical codes for hypoglycaemia (E1163, E1363, E1463, E160, E161, E162)

from either the inpatient or emergency room claims dataset. Further information on smoking status (never smoked, former smoker, current smoker), drinking habits [never drank alcohol, moderate drinker ( $\leq 1$  drink/day), heavy drinker ( $> 1$  drink/day)] and physical activity (no exercise, 1–2 times a week,  $\geq 3$  times a week) were obtained using a standard questionnaire during the health examination. Socioeconomic status (SES) was categorized into three groups (lower 30%, mid 40%, upper 30%) based on income levels. Hypertension was defined by ICD-10 codes I10–I13 and I15 and the prescription of antihypertensive drugs, or systolic and diastolic blood pressure  $\geq 140$  mmHg and  $\geq 90$  mmHg, respectively. Antidiabetic agents included those from six drug classes (biguanide, sulphonylurea,  $\alpha$ -glucosidase inhibitor, thiazolidinedione, meglitinide, insulin) dispensed during the study baseline period (2005–2008). Of these antidiabetic agents, insulin and sulphonylurea are strongly associated with the development of hypoglycaemia and, thus, these two classes were included in our analysis.

In addition, for all study subjects, their medical histories (identified by ICD-10 codes), including chronic obstructive pulmonary disease (COPD; J43–J44), all types of cancer (C00–C97), liver cirrhosis (K704, K746), end-stage renal disease (ESRD; N18, N19, Z49, Z905, Z94; procedure codes Z992, R380, O7011–7020, O7017, O7075) and CVD (I21, I22, I63, I64), were also recorded [11,12]. BMI was calculated as weight divided by the square of height ( $\text{kg}/\text{m}^2$ ) and categorized into five groups, based on BMI recommendations of the World Health Organization (WHO) for Asian populations: underweight,  $< 18.5$   $\text{kg}/\text{m}^2$ ; normal weight,  $18.5$ – $22.9$   $\text{kg}/\text{m}^2$ ; overweight,  $23.0$ – $24.9$   $\text{kg}/\text{m}^2$ ; obese class I,  $25.0$ – $29.9$   $\text{kg}/\text{m}^2$ ; and obese class II,  $\geq 30$   $\text{kg}/\text{m}^2$ .

### Statistical analysis

Statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC, USA). Restricted cubic spline curves were used to test and visualize non-linear relationships between BMI and risk of severe hypoglycaemia, using the 'Hmisc' package of the R Project for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria). The results for continuous data are presented as means  $\pm$  standard deviation (SD), while categorical data are presented as number (n) and percentage (%) of the total data. Statistical analyses were also performed using one-way analysis of variance (ANOVA) for continuous variables and the chi-squared test for categorical variables to compare baseline values. Also evaluated was the potential interaction between baseline BMI, severe hypoglycaemia and the major variables. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional-hazard models to analyze the association between severe hypoglycaemia and other variables: age as a categorical variable (30–49 years, 50–64 years,  $> 65$  years); gender (male, female); smoking status (never smoked, former smoker, current smoker); alcohol consumption (never drinker, moderate drinker, heavy drinker); physical activity (no exercise, 1–2 times a week,  $\geq 3$  times a week); SES (lower 30%, mid 40%, upper 30%); major comorbidities (major diseases, including COPD, cancer, liver cirrhosis, ESRD, CVD); fasting plasma glucose (FPG) as a continuous variable; use of insulin and sulphonylurea; and BMI.

These datasets were complete for all 1,366,692 subjects included in our analysis except for those lacking data on smoking status (33,106 cases, 2.4% of total subjects) and alcohol consumption (32,556 cases, 2.4% of total subjects), and were included in the baseline comparison and crude Cox regression analyses (except for smoking status and alcohol consumption), but not in the multivariable Cox regression analysis. *P* values  $< 0.05$  were considered statistically significant.

## Results

### Association of BMI and severe hypoglycaemia

#### Study population characteristics

A total of 1,366,692 subjects were followed from baseline up to the end of the study period (mean follow-up duration:  $8.6 \pm 2.0$  years). Subjects' mean age was  $57.7 \pm 11.7$  years, of whom 59.3% were male, and their mean BMI was  $24.9 \pm 3.2$  kg/m<sup>2</sup>. Table 1 presents their baseline characteristics stratified by BMI categories. Those with higher BMIs tended to be younger, with a higher ratio of women to men, and were also less likely to be smokers, to exercise regularly and to use insulin, but more likely to have hypertension and CVD. On the other hand, rates of prevalence of COPD, cancer, liver cirrhosis and ESRD were higher in subjects with lower BMIs.

#### Severe hypoglycaemic events in all T2D patients

The mean time to a severe hypoglycaemic event from enrolment was  $5.1 \pm 2.7$  years. During the follow-up period, the incidence of such events was 3.2/1000 patient-years. The affected patients were older and included a smaller proportion of current smokers (Table 2), whereas their prevalence rates for hypertension, COPD, cancer, CVD, liver cirrhosis and ESRD were higher during the follow-up period.

Fig. 1 shows the relationship between BMI and risk of severe hypoglycaemia. The lowest risk found with BMI scores in the 25.0–29.9 kg/m<sup>2</sup> (obese class I) category which, after adjusting for potential confounders, was an inverse relationship (Table S1; see supplementary materials associated with this article online), whereas the highest risk of severe hypoglycaemia was found in patients in the lowest BMI (underweight) category.

In addition, this association between BMI and severe hypoglycaemia was retained on further analyses stratified by subgroups. However, the association between low BMI and severe hypoglycaemia was weaker among subjects aged > 65 years and in women, but showed a steeper curve in men and among those aged 30–49 years (Fig. 1, Table S1). These relationships were similar among subjects who had never smoked, did not consume alcohol and did not use insulin (Fig. 2, Table S1). The associations of BMI with severe hypoglycaemia according to gender, age, smoking, alcohol consumption and use of insulin were significant (all  $P < 0.001$  for interaction), whereas those by SES ( $P = 0.232$  for interaction), physical activity ( $P = 0.186$  for interaction) and sulphonylurea use ( $P = 0.411$  for interaction) were not.

On analyzing the association between BMI and risk of severe hypoglycaemia within subgroups stratified by major chronic medical comorbidity status (Table S1), the highest rate of severe

**Table 1**  
Baseline characteristics according to body mass index (BMI) category.

	BMI (kg/m <sup>2</sup> )					P
	<18.5	18.5 to <23.0	23.0 to <25.0	25.0 to <30.0	≥30.0	
Total subjects (n)	22,724	355,378	353,679	549,651	85,260	<0.001
Age (years)						<0.001
30–49	20	24	24	27	34	
50–64	31	43	47	47	43	
≥65	49	34	29	27	23	
Gender (male)	61	60	62	60	46	<0.001
Smoking status						<0.001
Never smoked	59	63	65	67	72	
Former smoker	7.9	9.2	11	11	8.2	
Current smoker	34	28	25	23	20	
Alcohol consumption						<0.001
Never drinker	65	61	59	59	64	
Moderate drinker	7.6	10	11	11	9.5	
Heavy drinker	28	29	31	31	27	
Physical activity						<0.001
None	67	53	49	50	56	
1–2 times a week	16	22	24	25	24	
≥3 times a week	17	25	27	25	20	
Socioeconomic status						<0.001
Lower 30%	34	32	30	30	32	
Mid 40%	37	37	37	37	39	
Upper 30%	29	31	33	33	29	
Glucose-lowering medication						<0.001
Insulin	12	8.9	7.3	6.4	6.3	
Sulphonylurea	40	49	52	51	51	
Metformin	30	37	39	38	39	
Thiazolidinedione	4.4	5.8	6.5	7.0	8.7	
Acarbose	15	16	14	12	12	
Meglitinide	3.6	3.3	2.9	2.5	2.4	
Hypertension	41	48	56	64	74	<0.001
Systolic blood pressure (mmHg)	125 ± 19	128 ± 18	131 ± 17	133 ± 17	136 ± 17	<0.001
Diastolic blood pressure (mmHg)	77 ± 11	78 ± 11	80 ± 11	82 ± 11	84 ± 11	<0.001
COPD	15	10	9.2	9.2	9.6	<0.001
Cancer	3.9	2.6	2.0	1.8	1.7	<0.001
Cardiovascular disease	12	12	13	14	15	<0.001
Liver cirrhosis	1.9	1.2	0.9	0.7	0.6	<0.001
End-stage renal disease	0.3	0.2	0.1	0.1	0.1	<0.001
Fasting plasma glucose (mmol/L)	8.7 ± 3.3	8.4 ± 2.9	8.2 ± 2.7	8.2 ± 2.6	8.2 ± 2.6	<0.001

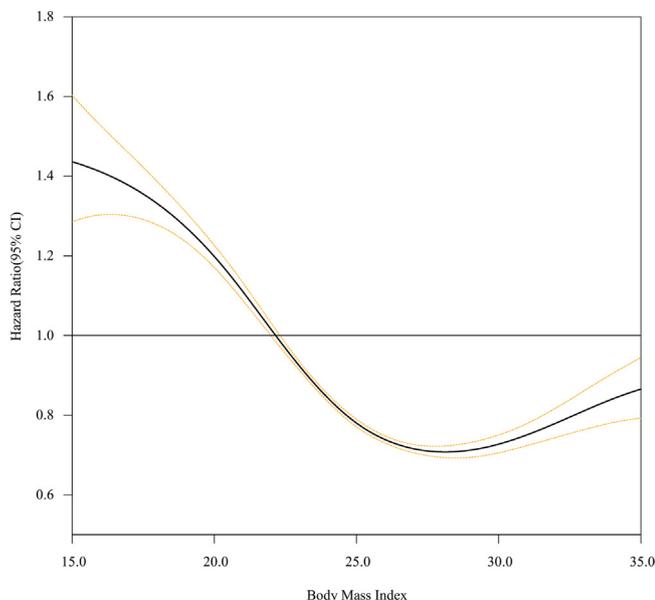
Values are presented as % or means ± standard deviation (SD).  
COPD: chronic obstructive pulmonary disease.

**Table 2**  
Baseline parameters in study participants with (+) and without (–) severe hypoglycaemia.

	Severe hypoglycaemia (–)	Severe hypoglycaemia (+)	P
Participants (n)	1,329,010	37,682	
Body mass index (kg/m <sup>2</sup> )	24.9 ± 3.2	24.3 ± 3.4	<0.001
Age (years)			<0.001
30–49	26	6.1	
50–64	46	32	
≥65	28	62	
Gender (male)	60	45	<0.001
Smoking status (%)			<0.001
Never smoked	65	75	
Former smoker	10	7.3	
Current smoker	25	18	
Alcohol consumption (%)			<0.001
Never drinker	59	75	
Moderate drinker	10	6.1	
Heavy drinking	31	19	
Physical activity (%)			<0.001
None	51	63	
1–2 times a week	24	15	
≥3 times a week	25	22	
Socioeconomic status (%)			0.02
Lower 30%	31	31	
Mid 40%	37	36	
Upper 30%	32	33	
Glucose-lowering medication			
Insulin	7.3	9.6	<0.001
Sulphonylurea	52	14	<0.001
Metformin	39	12	<0.001
Thiazolidinedione	6.8	2.1	<0.001
Acarbose	14	7.3	<0.001
Meglitinide	2.8	2.6	0.01
Hypertension (%)	57	73	<0.001
SBP (mmHg)	131 ± 17	134 ± 19	<0.001
DBP (mmHg)	80 ± 11	80 ± 11	<0.001
COPD (%)	9.3	16	<0.001
Cancer (%)	2.1	2.4	<0.001
Cardiovascular disease (%)	15	28	<0.001
Liver cirrhosis (%)	0.9	1.5	<0.001
ESRD (%)	0.1	0.5	<0.001
FPG (mmol/L)	8.3 ± 2.7	8.4 ± 3.4	<0.001

Values are expressed as % or means ± standard deviation (SD).

SBP/DBP: systolic/diastolic blood pressure; COPD: chronic obstructive pulmonary disease; ESRD: end-stage renal disease; FPG: fasting plasma glucose.

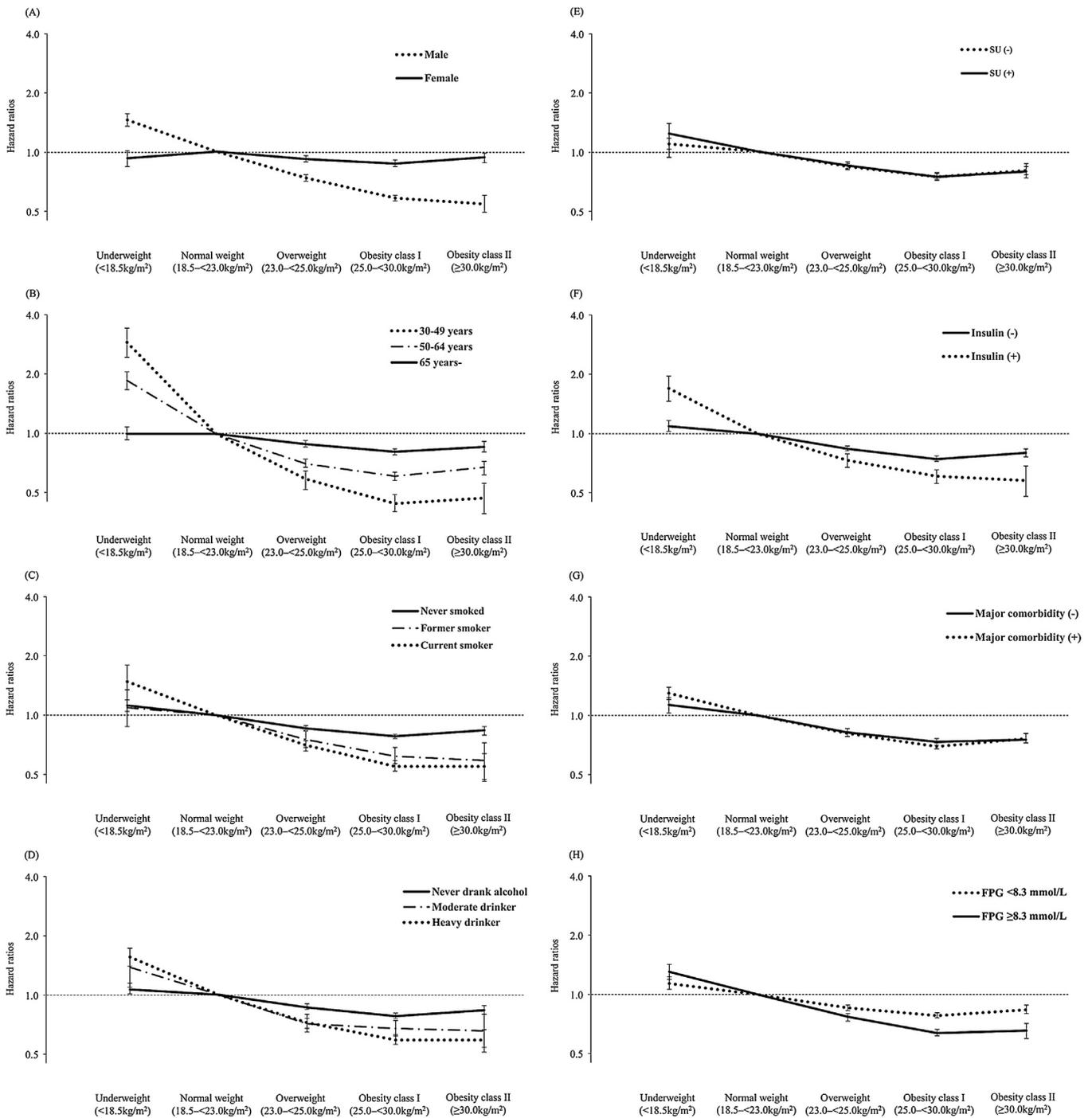


**Fig. 1.** Restricted cubic spline curve of body mass index (BMI) and risk of severe hypoglycaemia in the total studied population.

hypoglycaemia was found in subjects in the lowest BMI (underweight) class, whereas the adjusted HR was lowest in the obese class I group for all chronic diseases. In fact, the association between low BMI and severe hypoglycaemia increased in those with at least one or more major comorbidities ( $P < 0.001$  for interaction), and in those with poor glycaemic control (FPG  $\geq 8.3$  mmol/L;  $P < 0.001$  for interaction) and with liver cirrhosis ( $P = 0.011$  for interaction). In addition, a similar association curve was observed between BMI and risk of severe hypoglycaemia within the subgroup of participants with no major chronic medical diseases.

## Discussion

This long-term retrospective study has demonstrated that BMI and the incidence of severe hypoglycaemic events are significantly associated. In general, there was an inverse J-shaped association between BMI and severe hypoglycaemic events in Korean patients with T2D. An increased risk of severe hypoglycaemia in subjects with BMI  $< 18.5$  kg/m<sup>2</sup> compared with the reference range (BMI 18.5– $< 23.0$  kg/m<sup>2</sup>) was also found, whereas the lowest risk was found in the obese class I group (BMI 25.0– $< 30.0$  kg/m<sup>2</sup>). Further subgroup analyses stratified by smoking, alcohol consumption and



**Fig. 2.** Subgroup analyses for severe hypoglycaemic risk by (A) gender, (B) age, (C) smoking status, (D) drinking habits, (E) use of sulphonylurea (SU), (F) use of insulin, (G) presence of major comorbidity and (H) fasting plasma glucose (FPG).

chronic comorbidity status did not change the general association trend between low BMI and severe hypoglycaemia, whereas the degree of risk did vary across age, gender, smoking, alcohol consumption, medication use and comorbidity subgroups.

In general, Asians tend to have lower BMIs and higher ratios of body fat content for the same BMI compared with Western populations [13]. Also, obese Asians are vulnerable to insulin resistance, and have greater risks of diabetes, hypertension, dyslipidaemia and CVD [13]. Based on this evidence, the WHO has proposed lower optimal BMI cut-off points for obesity in Asian compared with Caucasian populations [14]. Our present study findings, which applied the WHO criteria for obesity in Asians, are

consistent with the results of previous analyses in Western countries [7,8] and show that the risk of severe hypoglycaemia was higher in the underweight category compared with all the other BMI categories.

One possible explanation for our findings for the association between BMI and severe hypoglycaemia is the ‘reverse causation’ bias, wherein weight loss due to chronic disease may distort the independent relationship between underweight and risk of hypoglycaemia. To evaluate and control for such confounding or reverse causation bias, our subjects were stratified by major chronic disease at baseline. As a result, in subjects with no major comorbidities, the same relationship between BMI and development of severe

hypoglycaemia was found. It was also evident that the association between BMI and severe hypoglycaemia varied according to type of chronic disease: for example, in patients with liver cirrhosis, low BMI was significantly associated with an increased risk of severe hypoglycaemia. However, our subgroup analysis of ESRD was limited by the small number of subjects in each BMI category and, thus, the precise risk trend in that disease group could not be determined.

Previous studies have already identified the association between BMI and severe hypoglycaemia in T2D. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, higher BMI ( $\geq 30.0 \text{ kg/m}^2$  vs  $< 25.0 \text{ kg/m}^2$ ) was associated with lower risk of severe hypoglycaemia (HR: 0.65, 95% CI: 0.50–0.85;  $P < 0.001$ ) [7]. The Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified-Release Controlled Evaluation (ADVANCE) trial, another large-scale study of patients with T2D and high CVD risk, also demonstrated that each  $1.0 \text{ kg/m}^2$  increase in BMI resulted in a 5% decrease in risk of severe hypoglycaemia [8]. Of those conducted in Asian populations, a recent large-scale study by the Hong Kong Diabetes Registry investigated the association between BMI and severe hypoglycaemia. In this case, Kong et al. [15] similarly found that a  $1.0 \text{ kg/m}^2$  increase in BMI was associated with a 5% lower risk of severe hypoglycaemia. However, both the ACCORD and ADVANCE trials were designed to include patients with high CVD risk, while the Hong Kong Diabetes Registry study did not exclude patients with chronic disorders, such as cancer, and chronic liver and kidney diseases. Therefore, the noteworthy limitation in these studies was a reverse causation bias.

A previous study had proposed the hypothesis that normal-weight people with diabetes have a different genetic susceptibility to the disorder, one associated with more severe and advanced diabetes [16,17]. Indeed, subjects with the metabolically obese normal-weight phenotype may be prone to exposure to other diseases and are 'genetically loaded' towards developing other comorbidities. They may also have a greater risk of severe hypoglycaemia compared with the metabolically healthy obese phenotype group [16]. However, a lower BMI may partially reflect the effects of malnutrition, which is associated with a greater risk of hypoglycaemia [18]. In addition, in patients with low body weight, insulin secretion capacity may also be decreased [19,20]. Thus, the use of insulin treatment may be more common in patients with diabetes and low body weight, and could be the cause of more hypoglycaemic events. In our study, more subjects with low-to-normal BMI were using insulin compared with those in the obese categories at baseline, and insulin use showed an intensified-effect change in the relationship between low BMI and severe hypoglycaemia.

In our study, diabetes patients with low or even normal weight and those of younger age were at greater risk of severe hypoglycaemia compared with obese patients, and the magnitude of the risk in younger subjects with low BMI was considerably higher than that of older subjects with low BMI. Yet, older patients with diabetes may have more risk factors for severe hypoglycaemia, such as cognitive, renal and hepatic impairment and/or polypharmacy [4,21,22] whereas, in contrast, younger patients have fewer other major risk factors of severe hypoglycaemia. In addition, a low BMI may have considerably greater impact on the development of severe hypoglycaemia in younger patients, who are also more likely to comply with recommendations for intensive glycaemic control [1,23].

In our analysis of the relationship between BMI and severe hypoglycaemia, the association was stronger in men than in women. To the best of our knowledge, studies of this relationship based on gender differences have never been conducted. On examining male and female BMI distributions by age, insulin treatment and comorbidities, no clear explanation of our gender

differences in the development of severe hypoglycaemia were found. The association between low BMI and severe hypoglycaemia increased in smokers and heavy drinkers, both of which were related to other severe comorbidities closely related to the development of severe hypoglycaemia. In contrast, SES and physical activity had no effect on the relationship between BMI and severe hypoglycaemia.

Finally, low BMI was strongly associated with severe hypoglycaemia in subjects with poorly controlled glycaemic levels (FPG  $> 8.3 \text{ mmol/L}$ ), which may have been due to either the efficacy of the antihypoglycaemic agent or the possibility that this group may have included more patients with high-risk factors for severe hypoglycaemia, including longer diabetes duration, older age, polypharmacy and the presence of diabetes complications.

In our study, the risk of severe hypoglycaemia was slightly increased in the obesity class II group (BMI  $\geq 30 \text{ kg/m}^2$ ) compared with obesity class I (BMI  $25.0$ – $29.9 \text{ kg/m}^2$ ). In general, more intensive glycaemic control and higher medication dosages, which can potentially influence hypoglycaemia, may be prescribed for severely obese patients because of insulin resistance [23,24]. In addition, severe obesity associated with various conditions, including kidney dysfunction and autonomic neuropathy, may also attenuate the defence mechanism behind hypoglycaemia [25–27]. However, more research is needed to confirm this association.

Our study has several limitations. First, as it was based on a medical claims database, the misclassification of diagnoses is possible. Second, it has a potential for selection bias: a health examination at least once every 2 years is recommended, but not compulsory, by the NHI for all subscribers to health insurance. As a consequence, the subjects included in our study may have been healthier or simply more concerned about their health than other people. Third, the claims database included no detailed information on diabetes patients' history, such as duration of disease, medication dosages and beta-cell function.

On the other hand, the strength of our study lies in the fact that all relevant medical data for the South Korean population were included in the analyses. Furthermore, to the best of our knowledge, this was the largest population-based analysis of the association between BMI and severe hypoglycaemia to date.

## Conclusion

Our results indicate an inverse J-shaped relationship between BMI and risk of severe hypoglycaemia. In particular, underweight T2D patients who are young and male with chronic comorbidities and using insulin appear to be at greater risk of severe hypoglycaemia. Thus, patients who meet these criteria should be specifically warned of the risk of hypoglycaemic events and properly taught about hypoglycaemia, and how to self-adjust their medication doses if they are receiving intensive treatment for diabetes. This will minimize the risk of severe hypoglycaemic events and fatal hypoglycaemia-related outcomes.

## Authors' contributions

J.-S.Y. wrote the manuscript and interpreted data. Y.-M.P. contributed to review of the manuscript and statistical problems. K.H. analyzed data. S.-A.C. contributed to discussions. Y.-B.A. reviewed the manuscript. S.-H.K. interpreted data, reviewed and edited the manuscript and contributed to discussions.

## Disclosure of interest

The authors declare that they have no competing interest.

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## Appendix A. Supplementary data

Supplementary data (Figs. S1 and S2, Table S1) associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.diabet.2018.03.006>.

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