Original article

Low normal fasting glucose and risk of accidental death in Korean adults: A prospective cohort study

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A B S T R A C T

Aim. – This study aimed to prospectively examine whether low normal glucose levels and hypoglycaemia are associated with increased mortality due to external causes, especially unintentional accidents.

Methods. – A total of 345,318 normoglycaemic Korean adults who had undergone health examinations during 2002–2003 were followed-up to 2013. To avoid potential biases related to glucose-lowering medication use, those with known diabetes or hyperglycaemia were excluded.

Results. – During 3.6 million person-years of follow-up, 1293 participants died because of unintentional accidents. Hazard ratios (HRs) for these accidental deaths were 1.26 (95% CI: 1.11–1.42), 1.60 (1.21–2.11) and 3.07 (1.37–6.85) for fasting serum glucose (FSG) levels of 70–79, 55–69 and < 55 mg/dL (3.9–4.4, 3.05–3.83 and < 3.05 mmol/L), respectively, compared with 80–99 mg/dL (4.44–5.5 mmol/L). FSG levels < 80 mg/dL were associated with an approximately 30% higher mortality due to accidents: specifically, 40% were non-fall-related injury; 50% were automobile-related; and 80% were motorcycle-related. The associations were weak (approximately 10% higher mortality, with $P > 0.05$ for each cause) for deaths due to traffic accidents (pedestrians, pedal cyclists), falls, intentional self-harm and physical assault. The population attributable risks for FSG levels < 80 mg/dL were 10% (95% CI: 2–18%) for non-fall-related injury, 11% (6–17%) for car accidents and 17% (6–27%) for motorcycle accidents.

Conclusion. – FSG levels of 70–79 mg/dL (3.9–4.4 mmol/L) as well as < 70 mg/dL are risk factors for accidental death. Appropriate management of the impact of FSG levels < 80 mg/dL might reduce unintended deaths due to non-fall-related injury, and automobile and motorcycle accidents, by ≥ 10%.

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Introduction

Hypoglycaemia is a common complication in diabetes patients taking glucose-lowering treatments. Based on evidence from physiological changes and driving simulations during induced hypoglycaemia in patients with diabetes, hypoglycaemia is known to impair cognitive function and driving performance and, therefore, could be considered a potential cause of automobile accidents and other unintentional injury [1,2]. However, few population-based studies, if any, have examined whether and to what extent hypoglycaemia is associated with a higher incidence of automobile accidents and injuries or deaths. In addition, in people without diabetes, low glucose levels during health checkups are never deemed to be hypoglycaemia [3]. Furthermore, as impaired cognitive function and glucose counter-regulation is generally considered to manifest only at very low levels of blood glucose [4,5], levels of 70–79 mg/dL (3.9–4.4 mmol/L) have rarely been cause for concern in both the general and diabetes populations in terms of risk of unintentional accidents. Indeed, the potential impact of low normal glucose levels on the risk of accidental deaths has never been examined.

Thus, the aim of the present large-scale prospective cohort study of 345,318 participants without hyperglycaemia was to examine whether low blood glucose levels, including hypoglycaemia and, more specifically, levels < 80 mg/dL (4.44 mmol/L), are indeed associated with unintentional deaths such as motorcar accidents. To focus more closely on the impact of lower fasting glucose levels, and to avoid any potential interactions and biases related to glucose-lowering medication use, patients with known diabetes or hyperglycaemia were excluded from this study.

Methods

Study population and follow-up

The National Health Insurance Service (NHIS) provides compulsory health insurance for 97% of the Korean population. Our study cohort (n = 514,886) consisted of a 10% random sample of NHIS beneficiaries, aged 40–79 years in 2002, who underwent health examinations during 2002–2003. In total, 169,568 people were excluded because of missing information on metabolic risk factors or health screening dates (n = 1853), a history of known diabetes at baseline (n = 21,766) and fasting serum glucose (FSG) levels ≥ 100 mg/dL (n = 145,949). When assessing the impact of low normal fasting glucose levels on external causes of death, those with diabetes were excluded to focus more closely on the impact of lower normal fasting glucose levels, and to avoid potential interactions and biases related to glucose-lowering medication use in diabetes patients. Death from external causes in 345,318 people up to 31 December 2013 was assessed from Korean national death records, and the International Classification of Diseases 10th Revision (ICD-10) was used to define death due to external causes (Table 1). The NHIS can provide these data without specific informed consent from participants according to Korean law [6]. The study was approved by the Institutional Review Board of the Catholic Kwandong University in Gangneung, South Korea. Anonymized data were provided for analysis to the authors in 2016 by the NHIS [6], and analyzed during 2016–2017.

Data collection

FSG was measured at local participating hospitals using enzymatic methods [7]. Body mass index (BMI) was calculated by weight in kilograms divided by the square of height in metres (kg/m^2), measured to the nearest kg and cm, respectively. Patients' self-reported smoking history, alcohol use frequency and physical activity were collected via questionnaire, while income status was based on the NHIS database of beneficiary status. Health examinations and data collection followed a standard protocol officially registered by the Ministry of Health and Welfare. More details on data collection through NHIS health screenings can be found elsewhere [8–10].

Table 1
Subtypes of external causes of death (and ICD-10 codes) analyzed in the study.

Total external causes of death (V01–Y89)
Unintentional accidents (V01–X59)
Transport accidents (V01–V99)
Transport accidents involving pedestrians or pedal cyclists (V01–V19)
Automobile (or car) accidents (V20–V89)
Motorcycle accidents (V20–V29)
Non-motorcycle accidents (V30–V89)
Falls (W00–W19)
Non-fall-related accidental injury (W20–W99, X00–X59)
Intentional self-harm (X60–X84)
Assault or event of undetermined intent (X85–Y09, Y10–Y34)

ICD-10: International Classification of Diseases, 10th Revision

Statistical analysis

FSG concentrations were categorized into either four or five groups (< 55, 55–69, 70–79, 80–99 [or 80–89 and 90–99] mg/dL) as well as two more general groups (< 80 mg/dL ['low normal FSG'] and 80–99 mg/dL ['high normal FSG']). Cut-off points at 55 mg/dL, 70 mg/dL and 80 mg/dL were chosen for clinically significant hypoglycaemia [11], hypoglycaemia [12] and optimal levels [10], respectively. For each categorical analysis, the highest FSG group was used as reference. Glucose levels can be converted to the International System of Units (mmol/L) by multiplying mg/dL values by 0.0555. FSG was also analyzed as a continuous variable.

Hazard ratios (HRs) for death due to external causes for the various fasting glucose categories were calculated using Cox proportional-hazards models stratified by age at baseline (40–44, 45–54, 55–64, 65–74, 75–80 years). The multivariable model was adjusted for the following variables: age at baseline (continuous variable, within each age group); gender; smoking status (current smoker, former smoker, never-smoker, missing data [n = 14,857]); alcohol use frequency [none, 2 days/month–2 days/week, 3–7 days/week, missing data (n = 6447)]; physical activity (at least once a week: yes, no); income status (deciles); and BMI (< 18.5, 18.5–24.9, 25–29.9, ≥ 30 kg/m^2).

Subgroup analyses of various categories of fasting glucose and subcategories of external causes of death served as sensitivity analyses. Subgroup analyses for transport accidents were performed by testing for interactions to assess differences in estimates of relative risk across person-specific characteristics, including age, gender and alcohol-drinking behaviour. The population attributable risk (PAR) for low normal FSG was also estimated [13]. This indicates the proportion of deaths from external causes that might be prevented if the impact of low normal FSG were eliminated from the study population.

All P-values were two-sided, and all analyses used SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

General characteristics

During the 3.6 million person-years of follow-up of 345,318 participants (48.7% women), 2731 people died of external causes: 1293 were accidental (802 from transport accidents, 210 from falls and 281 from non-fall-related unintentional injury) and 1091 were from intentional self-harm. At baseline, the mean (standard deviation, SD) age was 52.3 (9.5) years. Also, those with lower normal FSG levels were more likely to be current smokers, and less likely to be obese and to report less frequent alcohol use and less physical activity than those with higher normal FSG levels (Table 2). Specifically, there were 484, 8545, 78,862, 130,142 and 127,285 people in FSG categories < 55, 55–69, 70–79, 80–89 and 90–99 mg/dL, respectively.

Fasting glucose and risk of mortality from unintentional accidents

In those with FSG levels < 100 mg/dL, a decrease in FSG was generally associated with a higher risk of death from external causes and its subcategories (Fig. 1). Compared with people with FSG levels of 80–99 mg/dL (Table 3), the HRs for accidental deaths were 1.26, 1.60 and 3.07 with FSG at 70–79, 55–69 and < 55 mg/dL, respectively, and, for transport accidents, 1.29, 1.53 and 3.36, respectively. Each decrease of 10 mg/dL in FSG was associated with a 20–30% greater mortality due to various subcategories of unintentional accidents, except for falls and transport accidents involving pedestrians and pedal cyclists, whereas the correspond-

Table 2
Characteristics of participants according to fasting serum glucose (FSG) categories.

Variables	Characteristics	Total (n = 345,318)		Low normal FSG[a] (n = 87,891)		High normal FSG[b] (n = 257,427)	
Age (years)		52.3	±9.5	52.0	±9.6	52.3	±9.5
FSG (mg/dL)		85.5	±8.6	74.0	±4.6	89.4	±5.5
Gender	Women	168,228	(48.7)	42,886	(48.8)	125,342	(48.7)
	Men	177,090	(51.3)	45,005	(51.2)	132,085	(51.3)
Smoking status	Never-smoker	227,215	(65.8)	57,662	(65.6)	169,553	(65.9)
	Past smoker	27,361	(7.9)	6377	(7.3)	20,984	(8.2)
	Current smoker	75,885	(22.0)	20,574	(23.4)	55,311	(21.5)
	Missing data	14,857	(4.3)	3278	(3.7)	11,579	(4.5)
Alcohol use frequency, days	None/rarely	197,231	(57.1)	51,191	(58.2)	146,040	(56.7)
	2/month–2/week	107,303	(31.1)	26,847	(30.5)	80,456	(31.3)
	3–7/week	34,337	(9.9)	8378	(9.5)	25,959	(10.1)
	Missing data	6447	(1.9)	1475	(1.7)	4972	(1.9)
Physical activity	≥ 1 times/week	140,429	(40.7)	34,577	(39.3)	105,852	(41.1)
Income status, deciles	< 4 (low income)	78,298	(22.7)	21,211	(24.1)	57,087	(22.2)
	4–7	110,686	(32.1)	28,764	(32.7)	81,922	(31.8)
	> 7 (high income)	156,334	(45.3)	37,916	(43.1)	118,418	(46.0)
Body mass index, kg/m²	< 18.5	8775	(2.5)	2618	(3.0)	6157	(2.4)
	18.5–24.9	225,460	(65.3)	59,337	(67.5)	166,123	(64.5)
	25–29.9	103,006	(29.8)	24,157	(27.5)	78,849	(30.6)
	≥ 30	8077	(2.3)	1779	(2.0)	6298	(2.4)

Data are means ± standard deviation or n (%). P < 0.001 for each variable except gender (P = 0.594), calculated by Chi² test and one-way analysis of variance between FSG groups; to convert glucose to mmol/L, multiply mg/dL by 0.0555.
[a] < 80 mg/dL.
[b] 0–99 mg/dL.
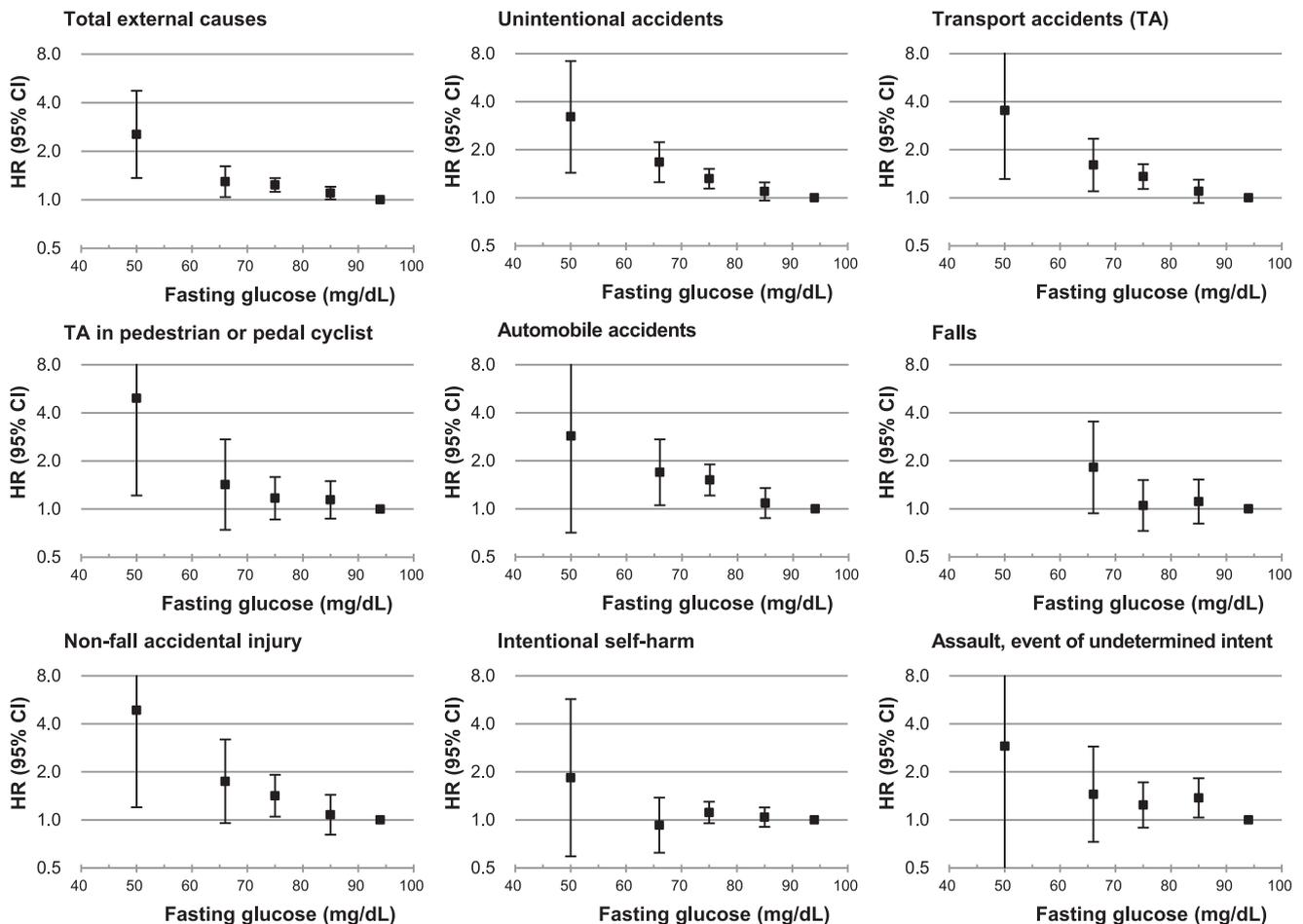
Fig. 1. Hazard ratios (HRs) for deaths due to external causes across five categories of baseline fasting serum glucose (FSG): < 55, 55–69, 70–79, 80–89, 90–99 (reference) mg/dL. Medians served as the representative value in each FSG category. HRs and 95% confidence intervals (CIs) were calculated using Cox proportional-hazard models stratified by age after adjusting for age, gender, smoking status, alcohol use frequency, income status and body mass index. No deaths by falls were observed with FSG < 55 mg/dL. To convert glucose to mmol/L, multiply mg/dL by 0.0555.

Table 3
Hazard ratios (HRs) for deaths due to external causes associated with fasting serum glucose (FSG) levels.

Causes of death	FSG category (mg/dL)	Deaths (n)	Crude death rate[a]	P	HR (95% CI)	Per 10-mg/dL lower FSG	
						P	HR (95% CI)
Total external causes	< 55	10	2046	0.005	2.42 (1.30–4.51)	< 0.001	1.12 (1.08–1.17)
	55–69	87	978	0.056	1.23 (0.99–1.53)		
	70–79	711	863	< 0.001	1.18 (1.08–1.28)		
	80–99	1923	716		1.00 (Reference)		
Unintentional accidents	< 55	6	1228	0.006	3.07 (1.37–6.85)	< 0.001	1.17 (1.11–1.25)
	55–69	52	584	0.001	1.60 (1.21–2.11)		
	70–79	350	425	< 0.001	1.26 (1.11–1.42)		
	80–99	885	330	1.00	1.00 (Reference)		
Transport accidents	< 55	4	818	0.016	3.36 (1.26–8.98)	< 0.001	1.20 (1.11–1.29)
	55–69	30	337	0.023	1.53 (1.06–2.21)		
	70–79	221	268	0.001	1.29 (1.11–1.51)		
	80–99	547	204		1.00 (Reference)		
Transport accidents involving pedestrians or pedal cyclists	< 55	2	409	0.032	4.61 (1.14–18.58)	0.117	1.11 (0.97–1.26)
	55–69	10	112	0.381	1.33 (0.70–2.51)		
	70–79	71	86	0.523	1.09 (0.83–1.43)		
	80–99	210	78		1.00 (Reference)		
Automobile accidents	< 55	2	409	0.155	2.74 (0.68–11.00)	< 0.001	1.25 (1.14–1.38)
	55–69	19	214	0.040	1.62 (1.02–2.58)		
	70–79	149	181	< 0.001	1.45 (1.20–1.77)		
	80–99	327	122		1.00 (Reference)		
Motorcycle accidents	< 55	1	205	0.162	4.07 (0.57–29.12)	0.001	1.33 (1.13–1.56)
	55–69	8	90	0.045	2.09 (1.02–4.29)		
	70–79	55	67	0.002	1.70 (1.23–2.37)		
	80–99	101	38		1.00 (Reference)		
Non-motorcycle accidents	< 55	1	205	0.467	2.07 (0.29–14.71)	0.001	1.22 (1.08–1.37)
	55–69	11	124	0.278	1.40 (0.76–2.56)		
	70–79	94	114	0.018	1.34 (1.05–1.70)		
	80–99	226	84		(Reference)		
Falls	< 55	0	0	–	–	0.514	1.05 (0.90–1.23)
	55–69	10	112	0.095	1.73 (0.91–3.27)		
	70–79	48	58	0.978	1.00 (0.72–1.38)		
	80–99	152	57		1.00 (Reference)		
Non-fall-related accidental injury	< 55	2	409	0.030	4.69 (1.16–18.87)	0.004	1.21 (1.06–1.38)
	55–69	12	135	0.082	1.68 (0.94–3.01)		
	70–79	81	98	0.020	1.36 (1.05–1.77)		
	80–99	186	69		1.00 (Reference)		
Intentional self-harm	< 55	3	614	0.309	1.80 (0.58–5.59)	0.070	1.06 (0.99–1.14)
	55–69	26	292	0.629	0.91 (0.61–1.34)		
	70–79	272	330	0.216	1.09 (0.95–1.25)		
	80–99	790	294		1.00 (Reference)		
Assault or event of undetermined intent	< 55	1	205	0.373	2.44 (0.34–17.43)	0.124	1.11 (0.97–1.27)
	55–69	9	101	0.562	1.22 (0.62–2.38)		
	70–79	64	78	0.762	1.04 (0.79–1.39)		
	80–99	197	73		1.00 (Reference)		

HRs and 95% confidence intervals (CIs) calculated using Cox proportional-hazards models stratified by age after adjusting for age, gender, smoking status, alcohol use frequency, income status and body mass index; to convert glucose to mmol/L, multiply mg/dL by 0.0555.

[a] Per 1,000,000 person-years.

ing associations for intentional self-harm and physical assault were weak (approximately 10% higher mortality) and statistically non-significant ($P > 0.05$).

Low normal FSG levels (< 80 mg/dL) were associated with an approximately 30% greater mortality from unintentional accidents (HR: 1.30, 95% CI: 1.16–1.47), 48% from car accidents, 76% from motorcycle accidents and 42% from non-fall-related accidental injuries compared with high normal FSG levels (Fig. 2). When FSG levels < 70 mg/dL — the range considered hypoglycaemic in diabetes — were excluded, the associations of low normal FSG levels (70–79 mg/dL) remained unchanged except for a modest decrease in HR (from 1.48 to 1.45 for death by car accidents).

Subgroup analysis

In subgroup analyses, the risk of death in a transport accident associated with low normal FSG increased with advancing age (Fig. 2): 1.12 (40–59 years); 1.48 (60–69 years); and 1.84 (70–80 years). These associations did not differ by gender, alcohol use frequency, smoking history, physical activity status, income status or BMI. Also, the association of low normal FSG with death due to
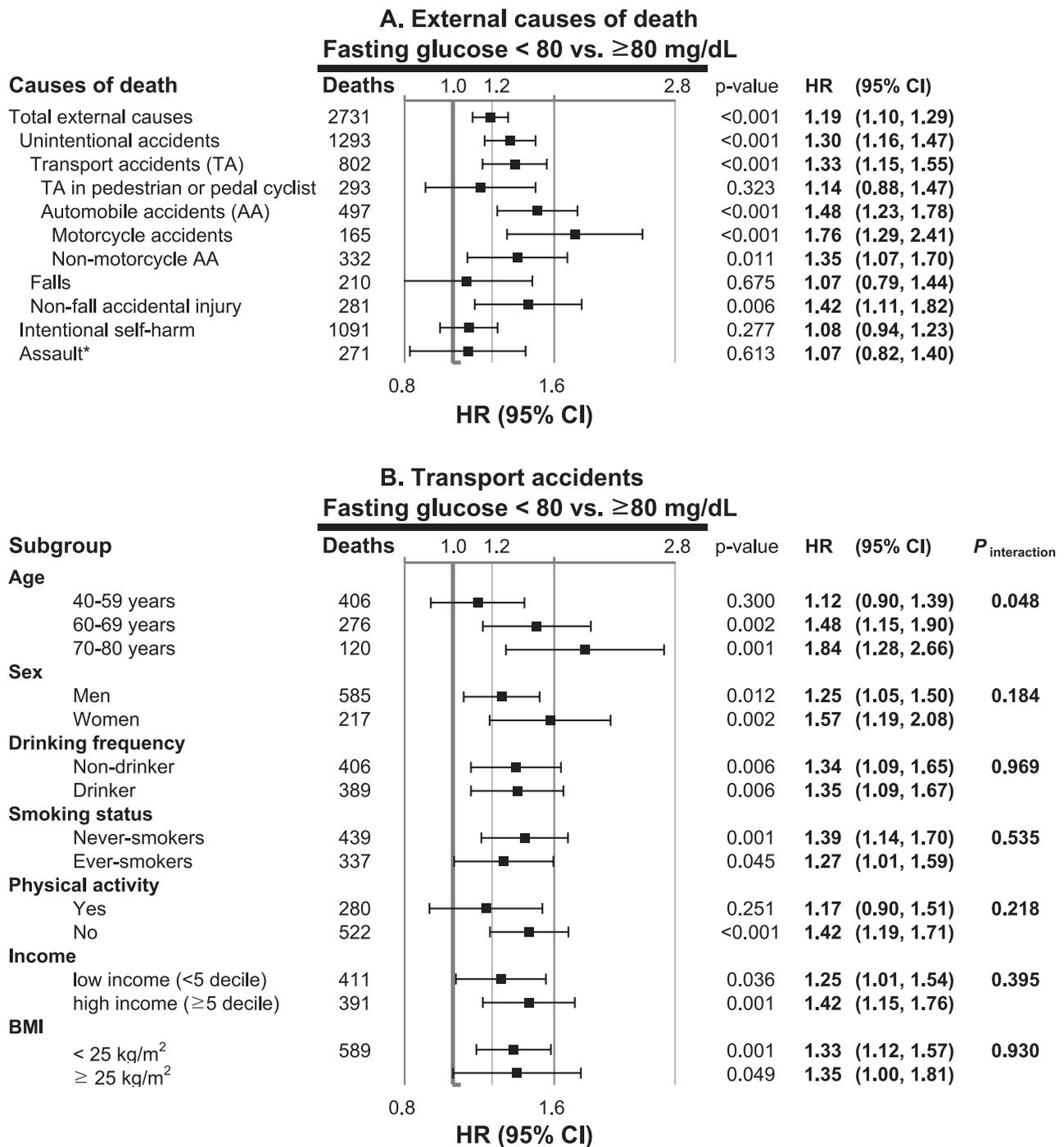
automobile accidents was stronger in people aged ≥ 60 years than in those aged < 60 years (HR: 1.83 vs. 1.22, respectively; $P = 0.034$ for interaction), particularly for non-motorcycle vehicular accidents.

Population attributable risk

The PAR for low normal FSG levels was 7.4% (95% CI: 4.0–10.8%) for accidental deaths: 10.0% (2.4–17.5%) for non-fall-related injury; 7.9% (3.7–12.1%) for transport accidents; 11.1% (5.6–16.5%) for automobile accidents; and 16.8% (6.4–26.8%) for motorcycle accidents. In those aged ≥ 60 years, the PAR was 17.7% for car accidents.

Discussion

This large-scale prospective study of people without diabetes or hyperglycaemia has clearly shown that low normal FSG levels (< 80 mg/dL) are associated with a 30% higher mortality due to unintentional accidents (HR: 1.30), particularly those involving automobiles (48%, HR: 1.48) and motorcycles (76%), and non-fall-

A. External causes of death
Fasting glucose < 80 vs. ≥80 mg/dL

Causes of death	Deaths		p-value	HR	(95% CI)
Total external causes	2731		<0.001	1.19	(1.10, 1.29)
Unintentional accidents	1293		<0.001	1.30	(1.16, 1.47)
Transport accidents (TA)	802		<0.001	1.33	(1.15, 1.55)
TA in pedestrian or pedal cyclist	293		0.323	1.14	(0.88, 1.47)
Automobile accidents (AA)	497		<0.001	1.48	(1.23, 1.78)
Motorcycle accidents	165		<0.001	1.76	(1.29, 2.41)
Non-motorcycle AA	332		0.011	1.35	(1.07, 1.70)
Falls	210		0.675	1.07	(0.79, 1.44)
Non-fall accidental injury	281		0.006	1.42	(1.11, 1.82)
Intentional self-harm	1091		0.277	1.08	(0.94, 1.23)
Assault*	271		0.613	1.07	(0.82, 1.40)

HR (95% CI)

B. Transport accidents
Fasting glucose < 80 vs. ≥80 mg/dL

Subgroup	Deaths		p-value	HR	(95% CI)	$P_{interaction}$
Age						
40-59 years	406		0.300	1.12	(0.90, 1.39)	0.048
60-69 years	276		0.002	1.48	(1.15, 1.90)	
70-80 years	120		0.001	1.84	(1.28, 2.66)	
Sex						
Men	585		0.012	1.25	(1.05, 1.50)	0.184
Women	217		0.002	1.57	(1.19, 2.08)	
Drinking frequency						
Non-drinker	406		0.006	1.34	(1.09, 1.65)	0.969
Drinker	389		0.006	1.35	(1.09, 1.67)	
Smoking status						
Never-smokers	439		0.001	1.39	(1.14, 1.70)	0.535
Ever-smokers	337		0.045	1.27	(1.01, 1.59)	
Physical activity						
Yes	280		0.251	1.17	(0.90, 1.51)	0.218
No	522		<0.001	1.42	(1.19, 1.71)	
Income						
low income (<5 decile)	411		0.036	1.25	(1.01, 1.54)	0.395
high income (≥5 decile)	391		0.001	1.42	(1.15, 1.76)	
BMI						
< 25 kg/m^2	589		0.001	1.33	(1.12, 1.57)	0.930
≥ 25 kg/m^2			0.049	1.35	(1.00, 1.81)	

HR (95% CI)

Fig. 2. Hazard ratios (HRs) associated with low normal fasting serum glucose (FSG < 80 mg/dL) compared with high normal FSG (80–99 mg/dL) for accidental deaths. HRs and 95% confidence intervals (CIs) were calculated by Cox proportional-hazard models, using the same method as in Fig. 1. AA: automobile accidents; BMI: body mass index. *: includes physical assault or events of undetermined intent (X85–Y34). To convert glucose to mmol/L, multiply mg/dL by 0.0555.

related injuries (42%), than FSG levels 80–99 mg/dL. Excluding people with FSG < 70 mg/dL only slightly changed these associations with low normal FSG except for a modest decrease in the relevant HRs. FSG levels < 100 mg/dL were progressively inversely related to the risk of accidental death. The effect of low normal FSG on mortality due to car accidents was greater in those aged ≥ 60 years (the elderly) than in their younger counterparts. Indeed, these elderly with low normal FSG (< 80 mg/dL) compared with those with high normal FSG had an 83% increased mortality risk from automobile accidents (HR: 1.83, P < 0.001), whereas middle-

aged adults (40–59 years) with low normal FSG had only a 22% greater risk (HR: 1.22, P = 0.135) than their counterparts. PARs associated with low normal FSG levels were ≥ 10% for deaths from non-fall-related injuries and automobile accidents, particularly motorcycle accidents.

Despite concerns over hypoglycaemia-related car accidents and other unintentional injury in people with drug-treated diabetes [1,2], the impact of low fasting glucose levels on these accidental injuries, and especially death due to these accidents, have rarely been examined previously in either the general or diabetic

populations. Furthermore, non-diabetic subjects with low glucose concentrations on health screening are generally not considered hypoglycaemic and, thus, are given no hypoglycaemia-related guidance for road safety and other injuries. In fact, in non-diabetics, the evaluation and management of hypoglycaemia is only recommended for those in whom the Whipple triad is documented (symptoms of hypoglycaemia, low glucose concentrations and resolution of those symptoms with glucose administration) [3].

Our present findings have demonstrated that FSG levels < 55 mg/dL and 55–69 mg/dL, as revealed by health screening, are associated with higher risks of mortality at around 200% and 60%, respectively, due to unintentional accidents than for FSG levels of 80–99 mg/dL. Furthermore, in the present study, people with FSG at 70–79 mg/dL (23% of participants) had, on average, an approximately 30% greater risk of accidental death (HR: 1.26), with about 50% due to automobile accidents (HR: 1.45), 70% from motorcycle accidents (HR: 1.70) and 40% from non-fall-related injuries (HR: 1.36) than those with FSG 80–99 mg/dL. This is a novel finding. To the best of our knowledge, no previous research has ever examined the potential effects of low normal FSG levels (particularly 70–79 mg/dL) on accidental deaths, including motor vehicles.

Our present results provide evidence that low normal fasting glucose levels detected at health checkups increase the risk of death due to unintentional accidents even in those without diabetes. This suggests that low normal fasting glucose levels found at health checkups should not be overlooked, but instead considered conditions that require attention and management for public health and safety reasons related to unintended accidents, including vehicular accidents.

Considering the inverse dose-response relationship of FSG and mortality due to unintended accidents, in our opinion, the mechanism behind the effects of FSG levels 70–79 mg/dL are similar to those of hypoglycaemia. In people without diabetes, cognitive function and glucose counter-regulation have been shown to be impaired at FSG levels 50–54 mg/dL (2.8–3.0 mmol/L) [4,5]. However, several important cognitive functions, such as working memory, a core executive function related to decision-making and appropriate behaviours [14], may start to deteriorate at higher FSG levels and be even more severely impaired [5,15,16]. In addition, in cases of mild cognitive impairment where a person's absolute ability seems unaffected, it may simply take longer to complete certain tasks [5]. Therefore, the impact of low normal glucose levels may be greatest at those moments when appropriate decisions, judgments and actions need to be taken quickly, such as in cases of transport accidents, and the consequence of any mistakes could be life-threatening. In contrast, the impact may be less in cases of falls or non-transport-related accidents, where relatively more time is available and the consequence of mishaps is less severe than in automobile accidents. Furthermore, in our study, the associations of low normal glucose were stronger in elderly than in middle-aged people. Several cognitive abilities, such as processing speed, visuospatial construction skills and executive function, including working memory, decline with age [17], and this decline combined with the impact of low normal glucose levels may be increased with advancing age. These findings bolster the possibility that the impact of low normal glucose levels reflects hypoglycaemia-related functional impairment.

Previous studies conducted in diabetes patients have shown that driving skills are impaired at FSG levels 61–72 mg/dL (3.4–4.0 mmol/L) and that driving itself requires significant metabolic resources [18,19]. Thus, the authors of those studies have recommended that drivers with drug-treated diabetes should "not start driving when their blood glucose is < 90 mg/dL (5 mmol/L) without first treating their blood glucose, and immediately stop driving and eat fast-acting carbohydrates if their blood glucose level is < 72 mg/dL (4 mmol/L)". This recommendation has been included in the driving-related guidelines for diabetes patients [1,20,21], and our present findings provide population-based evidence to support these recommendations. However, for those free of diabetes but with a history of FSG levels < 80 mg/dL at health checkups, our findings suggest that a similar recommendation for these people not to drive while fasting (such as after overnight fasting) without first breaking their fast may also be prudent.

The progressive excess mortality with FSG levels < 80 mg/dL enhances the probability that low normal glucose levels may be a causal factor for unintentional injury, including transport accidents. Our estimated PARs indicate that around 7% of deaths from unintentional accidents, 10% from non-fall-related injury, 11% from automobile accidents and 17% from motorcycle accidents could be prevented if the impact of low normal glucose levels were eliminated. In 2015, around 1.5 million people died in transport accidents and another 1.8 million died because of other unintended injury worldwide [22]; in fact, road-related injuries have risen in rank to become the leading cause of global disability from 1990 and 2005 to 2015 [23]. Assuming causality and a similar magnitude of associations between our Korean and other national populations, it appears that a substantial number of lives all over the world could be saved, and disability prevented, if the impact of low normal glucose levels is managed appropriately. Although more studies are yet needed to confirm causality, the underlying mechanisms and magnitude of associations in other ethnic or regional populations, non-diabetic people with low normal glucose levels at health checkups are likely to benefit from information regarding the potential risks of low normal glucose levels with respect to automobile accidents and other unintentional injuries just as much as patients with diabetes [2,24].

Our study has several limitations. First, the effects of low normal glucose levels in car drivers may have been underestimated, as deaths caused by motor vehicle accidents also include passengers (around 50% of deaths are estimated to be the drivers in Korea). Second, information on important confounders, such as driving exposure, was not available [25]. However, as all our participants were normoglycaemic, confounders such as driving exposure may not have been substantially different across all our FSG categories. Nevertheless, not adjusting for such confounders is a limitation. Third, in people exposed to road traffic, the risk of death in traffic accidents can be considered a function of several elements: a risk factor might influence crash involvement, crash severity, severity of post-crash outcomes (poor post-impact care, poor prognosis) or all of the above [26]. If hypoglycaemia impairs driving performance, it may also increase the number of crashes (crash involvement). If hypoglycaemia impairs judgment regarding, say, seatbelt use, then crashes may also be more serious (crash severity). If hypoglycaemia at the time of a crash slows the wound-healing process, especially before arriving at the hospital, then crash outcomes may be more fatal (post-crash outcome). Also, this study could not confirm whether the number, severity or post-crash outcome of accidents was influenced in the low normal glucose groups. Finally, the fact that our study participants were Korean, a homogeneous ethnic group, affects the generalizability of our findings to other populations, as the magnitude of the associations may vary in regional and ethnic populations for a variety of reasons, including different distributions of individual, environmental and cultural risk factors related to unintentional accidents [26,27].

Conclusion

An inverse dose-response relationship was found between FSG and risk of mortality due to unintentional accidents in the FSG

range $<$ 100 mg/dL ($<$ 5.55 mmol/L), and low normal FSG levels $<$ 80 mg/dL ($<$ 4.44 mmol/L) proved to be a risk factor for accidental deaths. However, appropriate management of the impact of low normal glucose levels have the potential to reduce the number of deaths from several types of unintentional accidents, such as non-fall-related injuries, and automobile and motorcycle accidents, by $\geq$ 10%.

Contribution statement

SWY conceived the study concept and design, acquired the data, analyzed the data and wrote the first draft of the manuscript. SWY, YJW and JJY interpreted the data and contributed to critical revision of the manuscript. All authors read and approved the final submitted version of the manuscript. SWY is the study guarantor.

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Disclosure of interest

The authors declare that they have no competing interest.

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