Complex interaction of fasting glucose, body mass index, age and sex on all-cause mortality: a cohort study in 15 million Korean adults

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Abstract

Aims/hypothesis The aim of this work was to examine whether synergistic associations with mortality exist for BMI and fasting blood glucose (FBG) and to identify FBG–BMI combined subgroups with higher mortality according to sex and age.

Methods A total of 15,149,275 Korean adults participated in health examinations during 2003–2006 and were followed up until December 2018. Mortality HRs of 40 FBG–BMI combined groups were assessed by Cox proportional hazards models.

Results During a mean 13.7 years of follow-up, 1,213,401 individuals died. A J-shaped association was seen between FBG and all-cause mortality for all BMI categories. Those with BMI <20 kg/m² had the highest mortality for any given FBG level, followed by those with BMI 20–22.4 kg/m². The detrimental effect of elevated FBG was greater among leaner individuals than more corpulent individuals. Moreover, the synergistic adverse effects of hyperglycaemia and leanness was stronger in younger adults than in older adults. Compared with the reference group (overweight with normoglycaemia), age- and sex-adjusted HRs of the leanest with normoglycaemia (BMI <20 kg/m² and FBG 4.4–5.2 mmol/l), overweight with diabetes (BMI 25–27.4 kg/m² and FBG ≥10.0 mmol/l) and leanest with diabetes (BMI <20 kg/m² and FBG ≥10.0 mmol/l) were 1.29, 2.59 and 11.18, respectively, in those aged 18–44 years and 1.56, 1.72 and 2.87, respectively, in those aged 75–99 years. The identification of BMI–FBG subgroups associated with higher mortality was not straightforward, illustrated by the group with FBG 6.1–6.9 mmol/l and BMI 20–22.4 kg/m² having a similar or higher mortality compared with the group with FBG 7.0–9.9 mmol/l and BMI ≥22.5 kg/m². In women aged <45 years with FBG <6.9 mmol/l, those with BMI ≥27.5 kg/m² had the highest mortality, whereas individuals with BMI <20 kg/m² had the highest mortality for each given FBG level in other age and sex groups.

Conclusions/interpretation Leanness and hyperglycaemia interact together to increase mortality in a supra-multiplicative manner, especially in younger adults; the interactions of BMI, FBG, sex and age with mortality are complex.

Keywords Age · Body mass index · Diabetes mellitus · Hyperglycaemia · Obesity · Sex · Thinness

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Research in context

What is already known about this subject?

- Lean diabetes has been highlighted as an emerging pathological condition; however, the joint effects of low BMI and hyperglycaemia are not clear

What is the key question?

- Do synergistic effects of leanness and hyperglycaemia exist and do the combined associations of fasting blood glucose (FBG) and BMI differ by sex and age?

What are the new findings?

- The adverse effects of hyperglycaemia on mortality were more marked in leaner individuals than in more corpulent individuals
- Strong synergistic (supra-multiplicative) adverse effects of hyperglycaemia and leanness were found, particularly in younger men and middle-aged women
- FBG–BMI subgroups with high mortality were different according to sex and age

How might this impact on clinical practice in the foreseeable future?

- Sophisticated management according to detailed metabolic profiles of each individual, including FBG and BMI as well as sex and age, may be needed for achieving better health

Abbreviations

FBG Fasting blood glucose

NHIS National Health Insurance Service

Introduction

Diabetes is pandemic and is a growing healthcare burden worldwide [1, 2]. Recently, lean diabetes (people with diabetes and a low BMI [$<25 \text{ kg/m}^2$]) has been highlighted as an emerging pathological condition [3, 4] and has been reported to have a higher mortality than excessive weight or even grade I obese diabetes [4–7]. However, people with low BMI (lean/normal weight, particularly BMI $<22\text{--}23 \text{ kg/m}^2$) also had higher mortality than overweight people in the general population [8, 9]. Thus, the joint effects of low BMI and hyperglycaemia on mortality are not clear.

In recent cohort studies among 13 million Koreans, associations between fasting blood glucose (FBG) and mortality were similar when comparing men and women across the age groups [10], whereas associations between BMI and mortality were substantially modified by age and sex [9]. Few studies, if any, have examined whether the joint effect of FBG and BMI on mortality differs by age and sex. Furthermore, lean diabetes has been reported to be more frequent in men and younger adults [4, 5]. In most previous studies of lean diabetes, leanness was roughly defined as BMI $<25 \text{ kg/m}^2$ [4, 5] and known diabetes was generally the only glycaemic state examined [4–7].

Through a population-based prospective cohort study of over 15 million Korean adults, we examined the combined association of FBG and BMI with mortality and analysed whether their combined effects differ by age and sex, using detailed categories of FBG (eight groups) and BMI (five or seven groups) to identify subgroups with a higher mortality. Specifically, we examined the age- and sex-specific associations between lean diabetes and mortality and addressed the question of whether lean diabetes is associated with a higher mortality in men vs women and/or younger vs older adults, relative to their counterparts with normoglycaemia. Our results enable more informed decisions, allowing targeted and individualised management.

Methods

Study population and follow-up The National Health Insurance Service (NHIS) provides compulsory health insurance, covering 97% of the Korean population [9]. Our study population comprised of 15,325,916 Korean adults aged 18–99 years who underwent routine health examinations for the NHIS during 2003–2006. Individuals with missing or extreme values for FBG, BP, total cholesterol or BMI were excluded ($n = 175,562$), as were 1079 with a missing or incorrect date for the health examination. The final study population consisted of 15,149,275 participants, followed up until 31 December 2018 through the NHIS database of beneficiary status, with participants' deaths being ascertained from the

Resident Register of Korea [9]. This study was approved by the Institutional Review Board of Catholic Kwandong University, the Republic of Korea (IRB no. CKU-19-01-0202). Informed consent was waived because the study used anonymised data from the NHIS, according to a strict confidentiality protocol.

Data collection A venous blood sample was taken after the participant had fasted for more than 6 h. Serum was centrifuged within 2 h of blood sampling and was stored at (2–8°C) before testing; samples were tested within 24 h of sampling. Serum FBG and total cholesterol were assayed using enzymatic methods [10]. BP was measured with the participant in a seated position using a standard mercury sphygmomanometer. BMI was calculated by measured weight in kilograms divided by the square of measured height in metres (kg/m^2) [9]. Smoking history, alcohol use and known cardiovascular diseases and cancer were self-reported via a questionnaire. Health examination and data collection followed an official standard government protocol. External quality control of clinical chemistry procedures in hospitals, such as FBG measurement, was regularly performed by the Korean Association of Quality Assurance for Clinical Laboratory [11].

Statistical analysis For mortality analyses, individuals were assigned to one of eight groups according to FBG concentration: hypoglycaemia (<3.9 mmol/l [<70 mg/dl]); low normal (3.9–4.4 mmol/l [70–79 mg/dl]); optimal (4.44–5.2 mmol/l [80–94 mg/dl]); high normal (5.3–5.5 mmol/l [95–99 mg/dl]); low prediabetes (5.6–6.06 mmol/l [100–109 mg/dl]); high prediabetes (6.1–6.9 mmol/l [110–125 mg/dl]); low FBG diabetes (7.0–9.9 mmol/l [126–179 mg/dl]); and high FBG diabetes (≥ 10.0 mmol/l [≥ 180 mg/dl]). People with diabetes but with well-controlled blood glucose were grouped according to their FBG levels at the baseline health examination. Individuals were also assigned to one of five groups according to their BMI: very lean (<20 kg/m^2); low normal weight (20–22.4 kg/m^2); high normal weight (22.5–24.9 kg/m^2); overweight (25–27.4 kg/m^2); and obese (≥ 27.5 kg/m^2). To evaluate the joint effects of FBG and BMI, we combined the eight FBG groups and five BMI categories into 40 groups. As a reference group, we used people with an optimal FBG of 4.44–5.2 mmol/l and BMI of 25–27.4 kg/m^2 , as this group had the lowest mortality.

HRs for FBG and BMI categories, with respect to the reference group, were calculated using Cox proportional hazards models after adjustment for age and sex. For this adjustment, age was initially stratified as a categorical variable at baseline (18–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, 85–99 years, when applicable) and was further adjusted as a continuous variable within each age group [9, 10]. The HRs were determined for the entire study population (aged 18–

99 years) and for each sex- and age-stratified group (18–44, 45–54, 55–64, 65–74, 75–99 years). For multivariable-adjusted analyses, the following additional adjustment variables were used: income status (first [low income], second, third and fourth quartile), smoking status (current smoker, former smoker, never smoker, and missing information [$n = 357,470$]), frequency of alcohol use (monthly or less, 2 days/month to 2 days/week, 3–7 days/week, and missing information [$n = 261,262$]), physical activity (performing exercise with light sweating at least once a week; yes and no), systolic BP (continuous variable), serum total cholesterol (<5.17 , 5.17–6.18, ≥ 6.20 mmol/l), known cardiovascular disease and known cancer. Assuming linear associations for FBG ≥ 5.6 mmol/l, HRs per 1 mmol/l increase in FBG were also calculated.

A restricted cubic spline transformation of the FBG–mortality association used five predefined knots (3.9, 4.7, 5.6, 6.7 and 7.8) to evaluate the non-linear associations [10].

Subgroup analyses by sex and age, as well as various categorical, spline and linear analyses, served as sensitivity analyses. Cochran's Q statistic was used as the interaction test to examine the difference in the effect size of FBG between sex, age and BMI groups.

All p values were two-sided. All analyses used SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline demographic findings Overall, 15,149,275 participants were included in the cohort (mean age 45.3 ± 14.5 years, 45.6% women). Mean $\pm$ SD BMI and FBG was 23.5 ± 3.2 kg/m^2 and 5.3 ± 1.5 mmol/l, respectively. Detailed demographic characteristics of the participants grouped according to BMI are shown in electronic supplementary material (ESM) Table 1.

Combined effects of FBG and BMI on all-cause mortality

During a mean of 13.7 ± 2.3 years (median 14.3 years) of follow-up, 1,213,401 individuals died. For all BMI categories, a J-shaped association was seen between FBG and overall mortality, after adjustment for age, sex (when applicable) and other confounders (Fig. 1 and ESM Figs 1, 2). The lowest HR was observed for FBG 4.44–5.2 mmol/l for all BMI categories, except for those with BMI ≥ 27.5 kg/m^2 (FBG 5.3–5.5 mmol/l). The J-shaped associations were similar in men and women, but men had higher HRs than women in the BMI <20 kg/m^2 and 20–22.4 kg/m^2 groups (Fig. 1).

People with BMI <20 kg/m^2 had the highest mortality for any given FBG level, followed by those with BMI 20–22.4 kg/m^2 (ESM Table 2). The lowest HRs were observed in people with BMI 25–27.4 kg/m^2 . The detrimental effect of elevated FBG was greater among leaner individuals. In the age- and sex-adjusted analysis, for the optimal FBG range

Fig. 1 HRs for all-cause mortality in 40 FBG–BMI categories. Sex and age-adjusted HRs (95% CIs) for all-cause mortality in (a) all participants, (b) men and (c) women were plotted on a logarithmic scale. BMI thresholds are in kg/m^2 . Reference group: FBG 4.44–5.2 mmol/l and BMI 25–27.4 kg/m^2

(4.44–5.2 mmol/l), the HR for all-cause mortality was 1.66, 1.21, 1.02, 1 (reference) and 1.12 for BMI <20, 20–22.4, 22.5–24.9, 25–27.4 and ≥ 27.5 kg/m^2 , respectively. In the high prediabetes range (FBG 6.1–6.9 mmol/l) the HRs were 2.20, 1.59, 1.28, 1.19 and 1.28 for the respective BMI groups, while in the high FBG diabetes range (FBG ≥ 10.0 mmol/l) corresponding HRs were 4.77, 3.13, 2.46, 2.17 and 2.21.

People in the high prediabetes group (FBG 6.1–6.9 mmol/l) with BMI <22.5 kg/m^2 had similar or higher mortality than those in the low FBG diabetes group (FBG 7.0–9.9 mmol/l) with BMI ≥ 22.5 kg/m^2 . These findings remained robust after controlling for various confounders (ESM Table 2).

When we repeated the same analyses with BMI divided into seven categories (56 FBG–BMI categories; BMI <18.5, 18.5–20.9, 21–22.9, 23–24.9, 25–27.4, 27.5–29.9 and ≥ 30 kg/m^2), similar results were observed (ESM Fig. 1). Sensitivity analyses that excluded those who died within the first 3 years and those with cancer at baseline also showed similar results (ESM Figs 3, 4).

Age- and sex-specific association of FBG–BMI with all-cause mortality Results of age- and sex-stratified analyses are shown in Figs 2, 3. An adverse association of very lean (BMI <20 kg/m^2) and high FBG diabetes was clear in young men (aged 18–44 years) and in middle-aged men and women (45–64 years): the HRs increased more steeply as FBG increased in the lower BMI groups than in the higher BMI groups. Conversely, with advancing age, the gap (difference in mortality HRs) between lower and higher BMI groups became smaller (Figs 2, 3 and ESM Fig. 2). Compared with the reference group (overweight with normoglycaemia), age- and sex-adjusted HRs of the leanest with normoglycaemia (BMI <20 kg/m^2 and FBG 4.4–5.2 mmol/l), overweight with diabetes (BMI 25–

27.4 kg/m^2 and FBG ≥ 10.0 mmol/l) and leanest with diabetes (BMI <20 kg/m^2 and FBG ≥ 10.0 mmol/l) were 1.29, 2.59 and 11.18, respectively, in those aged 18–44 years and 1.56, 1.72 and 2.87, respectively, in those aged 75–99 years (ESM Table 2). Among young women (aged 18–44 years) with FBG <7.0 mmol/l, the group with BMI ≥ 27.5 kg/m^2 displayed the highest mortality, whereas the very lean individuals had the highest mortality for each given FBG level among other sex and age groups. In addition, among individuals aged <65 years, the HRs for all-cause mortality were similar for those with BMI 22.5–24.9 kg/m^2 and those with BMI 25–27.4 kg/m^2 who were in the normoglycaemic range (<5.6 mmol/l); however, for individuals who were in the hyperglycaemic range (≥ 6.1 mmol/l), the HRs for the BMI 22.5–24.9 kg/m^2 groups surpassed those for the BMI 25–27.4 kg/m^2 groups, more markedly in men.

We further explored the shape of the association with a spline model (Fig. 4). In the lower FBG ranges (<5.0 mmol/l), the CIs associated with FBG generally overlapped between age groups in each BMI subgroup. However, in the prediabetes and diabetes FBG ranges, the slope of association was steeper in the younger adults. This age-specific association was more evident in the groups with lower BMI.

Assuming linear associations within the FBG range 5.6–11.1 mmol/l, the slope of the associations were examined using HRs per 1 mmol/l increase in FBG. The gradient of the associations generally decreased with increasing age for both men and women in each BMI subgroup ($p_{\text{interaction}}[\text{age}] < 0.001$ in each sex–BMI subgroup, except for men with BMI ≥ 27.5 kg/m^2 [$p = 0.042$]). Meanwhile, leaner individuals had steeper linear associations in the younger and middle-aged groups (except women aged <45 years) but not in elderly

Fig. 2 HRs for all-cause mortality in 40 FBG–BMI categories by age among men. Age-adjusted HRs (95% CIs) for all-cause mortality in men aged (a) 18–99 years, (b) 18–44 years, (c) 45–54 years, (d) 55–64 years,

(e) 65–74 years and (f) 75–99 years were plotted on a logarithmic scale. BMI thresholds are in kg/m^2 . Reference group: FBG 4.44–5.2 mmol/l and BMI 25–27.4 kg/m^2

adults (aged ≥ 65 years). As an example, in men aged 18–44 years the HR for each 1 mmol/l increase in FBG was 1.29 and 1.09, respectively, for those with BMI $<20 \text{ kg}/\text{m}^2$ and BMI $\geq 27.5 \text{ kg}/\text{m}^2$ ($p_{\text{interaction}} [\text{BMI}] < 0.001$), whereas the corresponding HRs were 1.10 and 1.08, respectively, in those aged 75–99 years ($p_{\text{interaction}} [\text{BMI}] = 0.764$; ESM Table 3).

Discussion

In this cohort involving over 15 million Korean adults, we found that the association between hyperglycaemia and mortality was stronger in leaner individuals than in more corpulent individuals. This increase in the adverse effects of

Fig. 3 Age-adjusted HRs for all-cause mortality in 40 FBG–BMI categories by age among women. Age-adjusted HRs (95% CIs) for all-cause mortality in women aged (a) 18–99 years, (b) 18–44 years, (c) 45–

54 years, (d) 55–64 years, (e) 65–74 years and (f) 75–99 years were plotted on a logarithmic scale. BMI thresholds are in kg/m^2 . Reference group: FBG 4.44–5.2 mmol/l and BMI 25–27.4 kg/m^2

hyperglycaemia in leaner people was more prominent in younger adults, particularly young men and middle-aged women, than in older adults. The identification of FBG–BMI subgroups with higher mortality in each sex–age group was not straightforward, because of the complex interaction of BMI, FBG, sex and age.

Age- and sex-specific association of FBG–BMI with all-cause mortality The effects of hyperglycaemia on mortality were more deleterious in leaner than in more corpulent individuals, relative to those of normoglycaemic individuals with corresponding BMIs. The hyperglycaemia-induced increase in mortality was more marked in younger adults and less

Fig. 4 Multivariable-adjusted HRs for all-cause mortality by BMI and age. Restricted cubic splines of FBG with five knots were used, with a reference value of 5.0 mmol/l. HRs were plotted on a logarithmic scale and were calculated by Cox models, after adjusting for age at baseline,

sex, smoking status, frequency of alcohol consumption, household income, level of physical activity, BMI, systolic BP, total cholesterol, known cardiovascular disease and cancer

prominent in the elderly (Fig. 5). The fact that lean individuals with diabetes have higher mortality than those who are overweight, or display grade I obesity, has been reported recently [6, 7, 12]. The novel finding of our study was the differential age- and sex-specific effect of lean diabetes: the adverse association was more marked in younger individuals. The combined effect of leanness and hyperglycaemia in younger individuals seems to be supra-multiplicative, surpassing the

simple product of the individual risks for leanness and hyperglycaemia. Conversely, in the elderly, although individuals with leaner hyperglycaemia had higher mortality than those with more obese hyperglycaemia, their estimated HR was similar to that for lean normoglycaemia when compared with more obese normoglycaemia (multiplicative joint effects).

This indicates that other pathogenic mechanisms might underlie lean hyperglycaemia, especially in younger adults.

Fig. 5 Supra-multiplicative effect of leanness and hyperglycaemia, particularly in younger adults. Age- and sex-adjusted HRs for all-cause mortality in (a) the overall population aged 18–99 years, (b) younger adults aged 18–44 years and (c) older adults aged 75–99 years. BMI

thresholds are in kg/m^2 . Reference group: with FBG 4.44–5.2 mmol/l and BMI 25–27.4 kg/m^2 . HRs and CIs are presented in more detail in ESM Table 2

Interestingly, a sex-specific difference in mortality was observed in younger adults (aged <45 years). In our study, young men had a more evident supra-multiplicative association compared with young women. Considering that younger individuals are less frequently affected by comorbidities, the possibility of reverse causality is relatively low. Currently, the precise mechanism for poor prognosis in lean hyperglycaemia, not to mention this age- and sex-specific FBG–BMI association, is not clear. In the literature, early beta cell failure (impaired insulin secretion and action) has been implicated in lean diabetes [4, 5, 13]. Since skeletal muscle is a major organ that takes up glucose from the blood by insulin signalling in a dose-dependent manner, lean individuals, who generally have low muscle mass, possibly have lower insulin-stimulated glucose disposal [14]. With ageing, the general population also experiences loss of muscle mass to some degree and men have more skeletal muscle than women [15, 16]. So, the effects of leanness in younger men (even at the same BMI) might differ from those in elderly men or younger women. According to the Korea Nutritional Health and Nutritional Examination Survey data, men have been shown to lose appendicular muscle mass sharply after their 40s, whereas women gradually gain muscle mass until their 50s and then lose muscle mass gradually [15]. This partially supports the current findings. Indeed, the adverse effect of lean hyperglycaemia in women was more evident in those aged 45–54 years compared with those aged 18–44 years in the current study. Our results could be partly explained by there being a higher proportion of type 1 diabetes in younger adults with hyperglycaemia and leanness. The prevalence of type 1 diabetes (defined as those assigned ICD-10 code E10 [http://apps.who.int/classifications/icd10/browse/2016/en] on a visit to a clinic and issued with an insulin prescription within 1 year before or 2 months after baseline health

examination) was only 0.1% ($n = 22,286$) in the study population. Moreover, among lean people with hyperglycaemia, the prevalence did not differ substantially across age groups (e.g. 6.8% [18–44 years] vs 5.2% [65–74 years] in people with BMI <20 kg/m^2 and FBG ≥ 10.0 mmol/l). Male predominance and/or male-specific risk exaggeration among the lean hyperglycaemic population could also be explained by both an unhealthy lifestyle and a genetic susceptibility [4, 5, 14]. However, since the findings remained robust after adjusting for behavioural factors, including smoking, alcohol consumption and physical activity, genetic factors and/or body composition-related factors are more likely to be responsible. Further studies are needed to clarify the exact mechanisms.

Complex relationship of FBG–BMI strata with mortality The metabolic profile of each individual is multi-dimensional in nature. Indeed, not all obese individuals develop diabetes. The interpretation of how mortality HRs are associated with FBG–BMI subgroups is not straightforward because of the complex interaction of BMI, FBG, sex and age. For example, the mortality in normoglycaemic individuals was comparable for those with BMI 22.5–24.9 kg/m^2 vs BMI 25–27.4 kg/m^2 . However, for individuals with FBG in the hyperglycaemic range (≥ 6.1 mmol/l), the risk for BMI 22.5–24.9 kg/m^2 was greater than that for BMI 25–27.4 kg/m^2 . People with high prediabetes and low normal weight had similar or higher mortality than people with low FBG diabetes and BMI ≥ 22.5 kg/m^2 . In young women aged <45 years, obesity (BMI ≥ 27.5 kg/m^2) was associated with the highest mortality among the BMI groups in normoglycaemic individuals, although the lowest BMI group (<20 kg/m^2) had the worst mortality for each given FBG level in other sex and age groups. Finally, obese diabetes had higher mortality than

overweight diabetes in all age groups, except for very elderly (≥ 75 years).

Therefore, different management approaches (e.g. risk information, patient monitoring) may be required according to underlying BMI–FBG–(sex)–age categories. Hyperglycaemia in lean people (lean diabetes and prediabetes), especially in younger (male) individuals, should be considered as an alarming sign that may warrant proactive management. In those with lean hyperglycaemia, lifestyle modification, such as regular exercise, to increase their muscle mass may be beneficial [17–22]. More clinical trials are needed to provide better informed lifestyle counselling for those with lean hyperglycaemia. Lean diabetes encompasses individuals with normal weight (BMI 18.5–24.9 kg/m²) and is frequently encountered in Asians. Lean diabetes is not just a simple state of lacking a single risk factor (excess adiposity). Rather, it is a pathological condition with higher mortality risk than diabetes in individuals who are overweight or even display class I obesity. Even high prediabetes (FBG 6.1–6.9 mmol/l) in individuals with low normal weight (BMI 20–22.4 kg/m²) had comparable or greater mortality than low FBG diabetes (FBG 7.0–9.9 mmol/l) with greater BMI (≥ 22.5 kg/m²). Proper attention and management should be provided to those with lean hyperglycaemia.

Caution is needed when we interpret the results with regard to the mortality risk in obese individuals. Obesity (≥ 27.5 kg/m²) was associated with substantial mortality in individuals within the optimal FBG ranges, with the exception of those who were elderly (aged ≥ 65 years). Particularly, this association was prominent in younger (female) adults. Young women and men (aged 18–44 years) with obesity (BMI ≥ 27.5 kg/m²) correspond to the worst and second-worst group, respectively, for those with FBG at least below 6.1 mmol/l. This implies that obesity itself is an important risk factor in younger adults even in a metabolically healthy state. In the era of precision medicine, more sophisticated management according to detailed metabolic profiles of each individual, including FBG and BMI as well as sex, age and ethnicity, may be needed for achieving better health.

Strengths and weaknesses of the study The clear strengths of our study are the prospective design in a general population, the large number of participants and the complete follow-up of deaths. However, there are several limitations. Due to the observational nature of the study design, we cannot draw any conclusions about direct causality. The estimated risk based on a single measurement of FBG and BMI might underestimate the true association. There might be residual confounding factors, although we rigorously adjusted for possible confounding factors. The BMI categories used in the current study might not be ideal for other countries. Considering that Asians (including Koreans) have a relatively low BMI compared with western people, the estimated risks

for obesity mainly represent those in the high overweight group (BMI 27.5–29.9 kg/m²) and with grade I obesity. A lack of detailed information on cause-specific mortality and medication use during the follow-up is another limitation of our study. Finally, as our participants were entirely Korean, some results might not extrapolate to other ethnicities.

Conclusions In this cohort involving over 15 million Korean adults, the association between hyperglycaemia and mortality was stronger in leaner individuals than in more corpulent individuals. The combined adverse effects of hyperglycaemia and leanness seem to be supra-multiplicative, particularly in younger men and middle-aged women. Furthermore, our data showed that the interpretation of mortality associated with FBG–BMI subgroups is not straightforward because of the complex interaction between BMI, FBG, sex and age. Additional studies are needed to corroborate our findings and to elucidate the mechanisms underlying the complex relationship between FBG, BMI, age and sex.

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Data availability The data that support the findings of this study are available from NHIS [10]. Restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available.

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Contribution statement SWY conceived the study concept and design. SWY and HK acquired data. SWY and JY performed statistical analyses. SWY, MHJ, SJA, BB, JY and HK analysed and interpreted the data. MHJ and SWY wrote the first draft. SJA, BB, JY and HK revised the article critically for important intellectual content. All authors have read and approved the final submitted version of the manuscript. SWY is the study guarantor and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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