BMI and All-Cause Mortality in Normoglycemia, Impaired Fasting Glucose, Newly Diagnosed Diabetes, and Prevalent Diabetes: A Cohort Study

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OBJECTIVE

This study examined associations between BMI and mortality in individuals with normoglycemia, impaired fasting glucose (IFG), newly diagnosed diabetes, and prevalent diabetes and identified BMI ranges associated with the lowest mortality in each group.

RESEARCH DESIGN AND METHODS

A total of 12,815,006 adults were prospectively monitored until 2013. Diabetes status was defined as follows: normoglycemia (fasting glucose <100 mg/dL), IFG (100–125 mg/dL), newly diagnosed diabetes (≥126 mg/dL), and prevalent diabetes (self-reported). BMI (kg/m^2) was measured. Cox proportional hazards model hazard ratios were calculated after adjusting for confounders.

RESULTS

During a mean follow-up period of 10.5 years, 454,546 men and 239,877 women died. U-shaped associations were observed regardless of diabetes status, sex, age, and smoking history. Optimal BMI (kg/m^2) for the lowest mortality by group was 23.5–27.9 (normoglycemia), 25–27.9 (IFG), 25–29.4 (newly diagnosed diabetes), and 26.5–29.4 (prevalent diabetes). Higher optimal BMI by worsening diabetes status was more prominent in younger ages, especially in women. The relationship between worsening diabetes status and higher mortality was stronger with lower BMI, especially at younger ages. Given the same BMI, people with prevalent diabetes had higher mortality compared with those with newly diagnosed diabetes, and this was more striking in women than men.

CONCLUSIONS

U-curve relationships existed regardless of diabetes status. Optimal BMI for lowest mortality became gradually higher with worsening diabetes for each sex and each age-group.

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Individuals with diabetes who are classified by BMI (kg/m^2) as overweight (25–29.9) or obese (≥30) have been associated with lower mortality (an "obesity paradox") compared with those classified as normal weight (1–4), with a few exceptions (5,6). However, these associations were observed primarily in people with prevalent diabetes. Optimal BMI for longevity remains unsettled, especially in people with incident diabetes (5), where the influence of diabetes duration and weight change secondary to

diabetes progression and treatment was minimized, and in never smokers, where smoking-related confounding was minimized (1,5).

Overweight or obesity has generally been associated with the lowest mortality in people with diabetes. However, it is unclear whether the BMI range associated with lowest mortality is higher in people with diabetes than it is in the general population, because studies have also shown that overweight compared with normal weight is associated with decreased risk of death in general populations (7,8). In addition, some researchers suggest that the optimal BMI may be higher in people with manifest chronic disease (3,4,9–11). If such a distinction exists, one might expect the optimal BMI to be greater as disease severity increases; in the case of diabetes, from normoglycemia to impaired fasting glucose (IFG), to newly diagnosed diabetes, and to prevalent diabetes. However, higher BMI according to diabetes severity has not been previously examined.

We monitored a large prospective cohort study (n = 12,815,006) that included individuals with known prevalent diabetes (n = 359,645) and newly diagnosed diabetes (n = 546,232) to elucidate the association between BMI and mortality and to identify optimal BMI for longevity according to diabetes status (normoglycemia, IFG, newly diagnosed diabetes, and prevalent diabetes). We also examined whether associations by diabetes status differ by sex and age, as a previous report showed that the association between BMI and mortality substantially varies by sex and age (12). We also explored associations in never smokers.

RESEARCH DESIGN AND METHODS

Study Population and Duration of Follow-up

The Korean Metabolic Risk Factor (KOMERIT) study was designed to evaluate associations between various metabolic risk factors and mortality in people aged 18–99 years who underwent routine health examinations between 2001 and 2004, courtesy of the National Health Insurance Service (NHIS) of Korea, which provides insurance coverage for 97% of the Korean population. Of the 12,845,017 beneficiaries, 26,346 individuals who were missing baseline information for serum glucose, blood pressure, total cholesterol, date of health examination,

or BMI were excluded, as were 3,665 people with weight <30 kg, BMI ≥50 kg/m^2 or height <130 cm (for age <55 years) or <110 cm (for age ≥55 years). The final study population (n = 12,815,006) was monitored through December 2013 for survival (12). Information on specific causes of death was unavailable. This study was approved by the Institutional Review Board of Kwandong University, Republic of Korea.

Measures

Cardiometabolic measures collected at baseline included fasting serum glucose, total cholesterol, and blood pressure. Height and weight were measured to the nearest centimeter and kilogram, respectively (12). BMI was calculated as weight in kilograms divided by the square of height in meters. Also collected were self-reported smoking history, alcohol use, and prevalent diabetes status (using a questionnaire that read, "Have you ever been diagnosed with or treated for diabetes?"). Fasting glucose levels (mg/dL) were used to categorize nonprevalent diabetes status as normoglycemia (<100), IFG (100–125), or newly diagnosed diabetes (≥126). Baseline disease status, including cancer, heart disease, and stroke, was assessed using the same questionnaire as for diabetes. Health examination and data collection used a standard protocol, the Health Examination Practice Guide, publicly available from the Ministry of Health and Welfare.

Statistical Analysis

BMI ranges (kg/m^2) were grouped as <17.5, 17.5–18.9, 19.0–20.4, 20.5–21.9, 22.0–23.4, 23.5–24.9, 25.0–26.4 (reference), 26.5–27.9, 28.0–29.4, 29.5–30.9, and ≥31.0. The reference BMI was selected based on previous research in East Asians showing BMI of 25–27 was associated with the lowest risk of mortality (13). BMI was further grouped into four standard categories of <18.5, 18.5–24.9 (reference), 25.0–29.9, and ≥30 for between-study comparisons (7).

Hazard ratios (HRs) for BMI ranges relative to the reference group were calculated using Cox proportional hazards models stratified by age (years) at baseline (18–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and 85–99) after adjustment for age at baseline as a continuous variable (within each age-group), sex (when applicable), smoking status (current smoker, former smoker, never smoker, and missing

information [n = 636,655]), frequency of alcohol use (monthly or less, 2 days/month–2 days/week, 3–7 days/week, and missing information [n = 493,992]), and physical activity at least once a week (yes or no). Metabolic mediators including systolic blood pressure, serum total cholesterol, and fasting glucose were not included in the main analysis but were included in the sensitivity analysis.

We examined associations separately, by diabetes status. To evaluate the combined effects of diabetes status and BMI, we combined 11 BMI categories and 4 categories of diabetes status into 44 groups and set normoglycemic people with BMI 25–26.4 kg/m^2 as the reference group. We stratified by sex and age (18–44, 45–54, 55–64, 65–74, and 75–99 years), because a previous study reported that associations between BMI and mortality differed by sex and age in this population (12). The effect modification (change in optimal BMI) between BMI and diabetes status for each sex and each age-group was assessed by introducing a linear interaction term (diabetes status × BMI), assuming quadratic association between BMI and mortality. The P value of the quadratic interaction term, when it was included, was >0.05 in both sexes at all ages combined.

Subgroup analyses were performed among never smokers and individuals without prevalent cancer, heart disease, or stroke, after excluding the first 3 years of follow-up. The subgroup analyses also served as a sensitivity analysis.

Sex- and age-standardized death rates per 100,000 person-years were calculated, as previously reported (12), and are presented in Supplementary Table 1. All P values were two-sided, and SAS 9.4 software (SAS Institute, Inc., Cary, NC) was used in all analyses.

RESULTS

Of the 12,815,006 people studied, 43.1% were women. During 134.9 million person-years of follow-up, 454,546 men and 239,877 women died (Supplementary Table 1). At baseline, the mean ± SD age was 44.4 ± 14.2 years.

Characteristics by Diabetes Status

Baseline diabetes status was as follows: 73.4% normoglycemia, 19.5% IFG, 4.3% newly diagnosed diabetes, and 2.8% prevalent diabetes. Mean age and BMI increased with worsening diabetes (Table 1). As
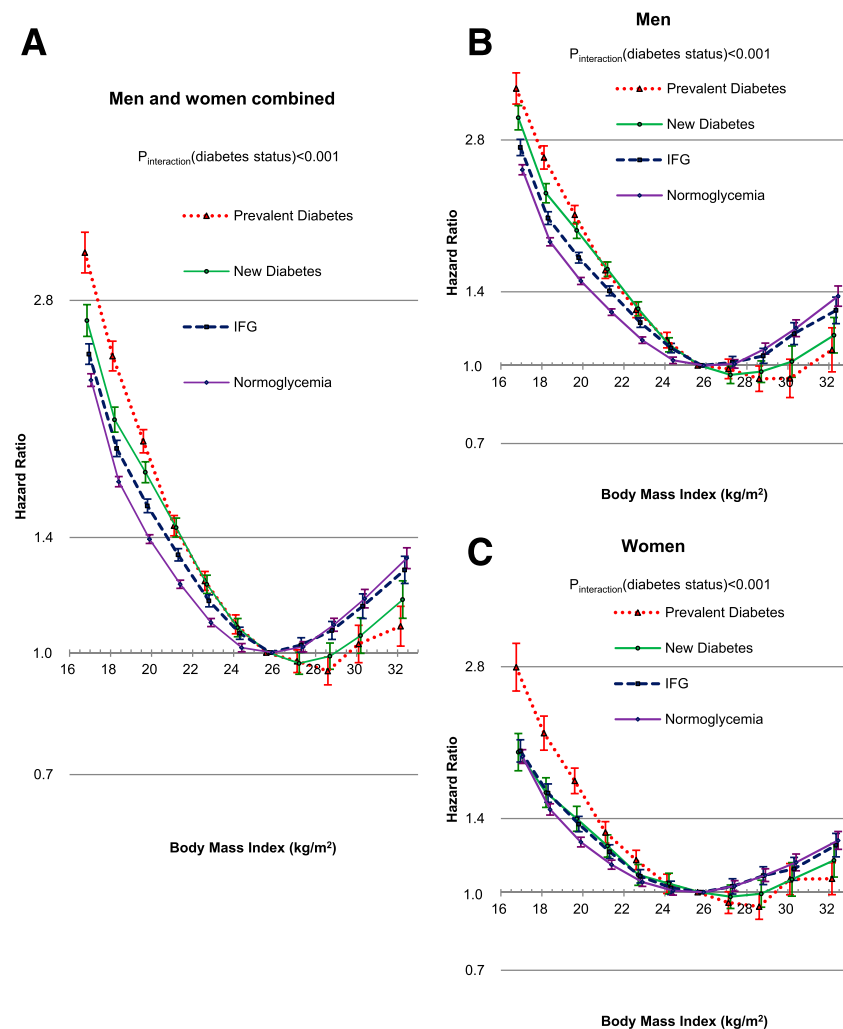
Table 1—Characteristics of participants according to diabetes status

Variable	Total N = 12,815,006	Normoglycemia n = 9,403,894	IFG n = 2,505,235	Newly diagnosed diabetes n = 546,232	Prevalent diabetes n = 359,645
Age, years	44.4 ± 14.2	42.5 ± 13.9	47.7 ± 13.8	52.5 ± 13.3	56.8 ± 12.1
BMI, kg/m^2	23.5 ± 3.2	23.2 ± 3.1	24.1 ± 3.2	24.7 ± 3.3	24.5 ± 3.2
SBP, mmHg	124.1 ± 17.3	122.3 ± 16.6	127.9 ± 17.7	133.1 ± 19.0	131.5 ± 18.8
FSG, mg/dL	94.9 ± 31.0	84.8 ± 8.6	108.0 ± 6.6	133.1 ± 19.0	131.5 ± 18.8
Total cholesterol, mg/dL	194.2 ± 49.0	191.2 ± 44.8	201.1 ± 56.6	208.5 ± 64.8	201.2 ± 58.3
Sex					
Men	7,292,064 (56.9)	5,155,811 (54.8)	367,232 (67.2)	1,567,046 (62.6)	201,975 (56.2)
Women	5,522,942 (43.1)	4,248,083 (45.2)	179,000 (32.8)	938,189 (37.4)	157,670 (43.8)
Smoking status					
Current smoker	3,653,334 (28.5)	2,626,812 (27.9)	182,435 (33.4)	756,268 (30.2)	87,819 (24.2)
Former smoker	1,099,436 (8.6)	759,271 (8.1)	52,186 (9.6)	249,647 (10.0)	38,332 (10.7)
Never smoker	7,425,581 (57.9)	5,527,669 (58.8)	283,945 (52.0)	1,389,340 (55.5)	224,627 (62.5)
Missing	636,655 (5.0)	490,142 (5.2)	27,666 (5.1)	109,980 (4.4)	8,867 (26.8)
Alcohol consumption, frequency (days)					
≤1/month	6,102,884 (47.6)	4,490,767 (47.8)	252,841 (46.3)	1,142,796 (45.6)	216,480 (60.2)
2/month–2/week	4,980,284 (38.9)	3,743,434 (39.8)	185,155 (33.9)	955,218 (38.1)	96,477 (26.8)
3–7/week	1,237,846 (9.7)	791,794 (8.4)	84,861 (15.5)	321,116 (12.8)	40,075 (11.1)
Missing	493,992 (3.9)	377,899 (4.0)	23,375 (4.3)	86,105 (3.4)	6,613 (1.8)
Physical activity					
≥1 times/week	5,158,300 (40.3)	3,744,925 (39.8)	1,032,589 (38.1)	211,600 (33.9)	169,186 (26.8)
Self-reported comorbidity					
Cancer, heart disease, stroke	202,464 (1.6)	120,449 (1.3)	46,594 (1.9)	16,676 (3.1)	18,745 (5.2)

Data are expressed as mean ± SD or n (%). FSG, fasting serum glucose; SBP, systolic blood pressure. P values, which were calculated by χ^2 tests and one-way ANOVA between diabetes status groups, were <0.001 for each variable. To convert cholesterol from mg/dL to mmol/L, multiply by 0.0259. To convert glucose from mg/dL to mmol/L, multiply by 0.0555.

expected, systolic blood pressure, fasting glucose, and total cholesterol levels were higher in IFG and diabetes groups compared with normoglycemia. Current smokers and those who drink alcohol ≥3 days per week were most commonly associated with newly diagnosed diabetes, whereas heart disease, stroke, or cancer was more commonly observed in individuals with prevalent diabetes. BMI at baseline was positively associated with higher systolic blood pressure, fasting glucose, and total cholesterol (Supplementary Table 2).

BMI and Mortality by Diabetes Status

Regardless of diabetes status, mortality risk increased at both ends of the BMI categories (Fig. 1A), with a U-shaped association. The optimal BMI (kg/m^2) for longevity was 23.5–27.9 (normoglycemia), 25–27.9 (IFG), 25–29.4 (newly diagnosed diabetes), and 26.5–29.4 (prevalent diabetes) (Fig. 1A and presented as 44 BMI-diabetes status categories in Supplementary Fig. 1). Compared with optimal BMI in individuals with normoglycemia, optimal BMI was higher in association with worsening diabetes status (P < 0.001 for interaction between BMI

and diabetes status); the difference (kg/m^2) was <1.5 for IFG, ~1.5 for newly diagnosed diabetes, and 1.5–3 for prevalent diabetes, regardless of sex (Fig. 1A).

BMI and Mortality by Diabetes Status, Age, and Sex

In men, optimal BMI (kg/m^2) ranges for longevity were 25–27.9 (normoglycemia), 25–27.9 (IFG), 26.5–29.4 (newly diagnosed diabetes), and 28–30.9 (prevalent diabetes) (Fig. 1B). In women, optimal BMI ranges were 23.5–27.9 (normoglycemia), 23.5–27.9 (IFG), 25–29.4 (newly diagnosed diabetes), and 26.5–29.4 (prevalent diabetes) (Fig. 1C). Given the same BMI, mortality risk increased with worse diabetes status in both men (Fig. 2) and women (Fig. 3) of different ages (the results of all participants are presented in Supplementary Fig. 2). In women, however, mortality in prevalent diabetes relative to newly diagnosed diabetes was much higher than was found in men (Figs. 2 and 3). Higher mortality associated with newly diagnosed and prevalent diabetes was more profound with lower BMI, and this was more evident at younger ages (18–54 years) (Figs. 2 and 3). For example, in men with BMI 19–20.4 kg/m^2 who

were aged 18–44 years, HRs were 1.38 (normoglycemia), 1.91 (IFG), 3.87 (newly diagnosed diabetes), and 4.69 (prevalent diabetes) compared with men with normoglycemia and BMI 25–26.4. In men with BMI 28–29.4 who were aged 65–74 years, HRs were 1.01, 1.09, 1.36, and 1.53, respectively, and in men aged 65–74 years with BMI 19–20.4, HRs were 1.46, 1.59, 2.29, and 2.65, respectively (Fig. 2).

In the subgroup analyses, overall associations were generally similar to the main analysis, after excluding participants with heart disease, stroke, or cancer (Supplementary Fig. 3 and Supplementary Table 3), ever smokers (Supplementary Fig. 4 and Supplementary Table 3), and/or death within the first 3 years of follow-up (Supplementary Fig. 5 and Supplementary Table 3). Similar results were observed when men (Supplementary Table 4) and women (Supplementary Table 5) were analyzed separately. The results after adjustment for mediators of potential effects of BMI, such as systolic blood pressure, fasting glucose, and total cholesterol, also did not differ from the main analysis according to diabetes status (normoglycemia, IFG, newly diagnosed diabetes, and

A

Men and women combined

$P_{interaction}$(diabetes status)<0.001

B

Men

$P_{interaction}$(diabetes status)<0.001

C

Women

$P_{interaction}$(diabetes status)<0.001

Figure 1—HRs for mortality in 11 BMI categories by diabetes status and sex for men and women (A), men (B), and women (C). BMI categories (kg/m^2): <17.5, 17.5–18.9, 19.0–20.4, 20.5–21.9, 22.0–23.4, 23.5–24.9, 25.0–26.4 [reference], 26.5–27.9, 28.0–29.4, 29.5–30.9, and ≥31.0. The midpoint was used as a representative value for each BMI category except for both ends (16.9 and 32.3), for which the median of all participants was used. HRs and 95% CIs were calculated using Cox proportional hazards models stratified by baseline age (18–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and 85–99 years) after adjustment for age at baseline as a continuous variable (within each age-group), sex, smoking history, alcohol use, and physical activity.

prevalent diabetes (Supplementary Tables 6–9, respectively).

CONCLUSIONS

This large prospective cohort of 12.8 million adults clearly demonstrated that optimal BMI for longevity was higher with worsening diabetes regardless of sex and age, except perhaps in individuals aged 75 years or older. Although previous studies reported various (U-curve, L-curve, or inverse linear) types of associations between BMI and mortality in diabetes (2,3,5,14–16), we observed a consistent U-shaped relationship regardless of diabetes status in each sex and all age-groups.

Difference in Optimal BMI With Worsening Diabetes Status

Across all age-groups, there was a difference of ~1.5 kg/m^2 in optimal BMI between newly diagnosed diabetes and normoglycemia. Several previous studies suggested a larger difference, with optimal BMI ≥5 kg/m^2 higher in people with diabetes compared with the general population or populations without diabetes (2–4,16). Most of these investigations were performed in the context of prevalent diabetes (4,6,8,14–17). According to our results, however, prevalent diabetes was associated with a greater difference in optimal BMI (1.5–3 kg/m^2) than was newly

diagnosed diabetes (~1.5 kg/m^2). Further, previous studies compared older (usually ≥60 years) people with diabetes with substantially younger general populations or with BMI values that were assessed decades earlier when mean BMI was substantially lower than in recent years (3,8,16–18). Owing to the small numbers of participants, crude BMI categories in many previous studies make it difficult to detect mild differences (analysis according to the World Health Organization BMI categories in Supplementary Tables 10 and 11).

The Nurses' Health Study (NHS) reported results of people with incident diabetes and also all participants in the same population. The mortality rate was lowest at BMI 19–26.9 kg/m^2 among all subjects (19), while there was no difference in mortality risk for those with a BMI of 27.5–29.9 kg/m^2 (HR 1.0 [95% CI 0.83–1.19]) compared with the reference group (22.5–24.9 kg/m^2) in individuals with type 2 diabetes (5). It might be interpreted that BMI ranges associated with the lowest mortality changed at ~3 kg/m^2 with increasing age and incident diabetes, in accordance with our results. However, directly comparing our findings with those of the NHS is difficult because of the differences in the analytical populations (all participants rather than those with normoglycemia in Manson et al. [19]) and follow-up time. Few previous studies examined sex- and age-specific associations with diabetes status (5,15). Higher optimal BMI with worsening diabetes was more apparent in women, especially at younger ages. Higher optimal BMI with advancing age was more apparent in normoglycemia than in prevalent diabetes, where it was subtle.

Potential Mechanism for Higher Optimal BMI With Worsening Diabetes

Greater BMI indicates increased muscle or fat, or both. Growing evidence suggests that higher muscle quantity and quality are associated with better survival (20,21). Aging and chronic diseases, including diabetes, are associated with reduced lean body mass, especially muscle mass (11,22), and loss of muscle mass and function with advancing age was greater in people with versus without diabetes (22,23).

Previous studies have suggested that adipose tissue may provide some protective benefit, especially in people with disease (10,11,20,24). Some studies suggest
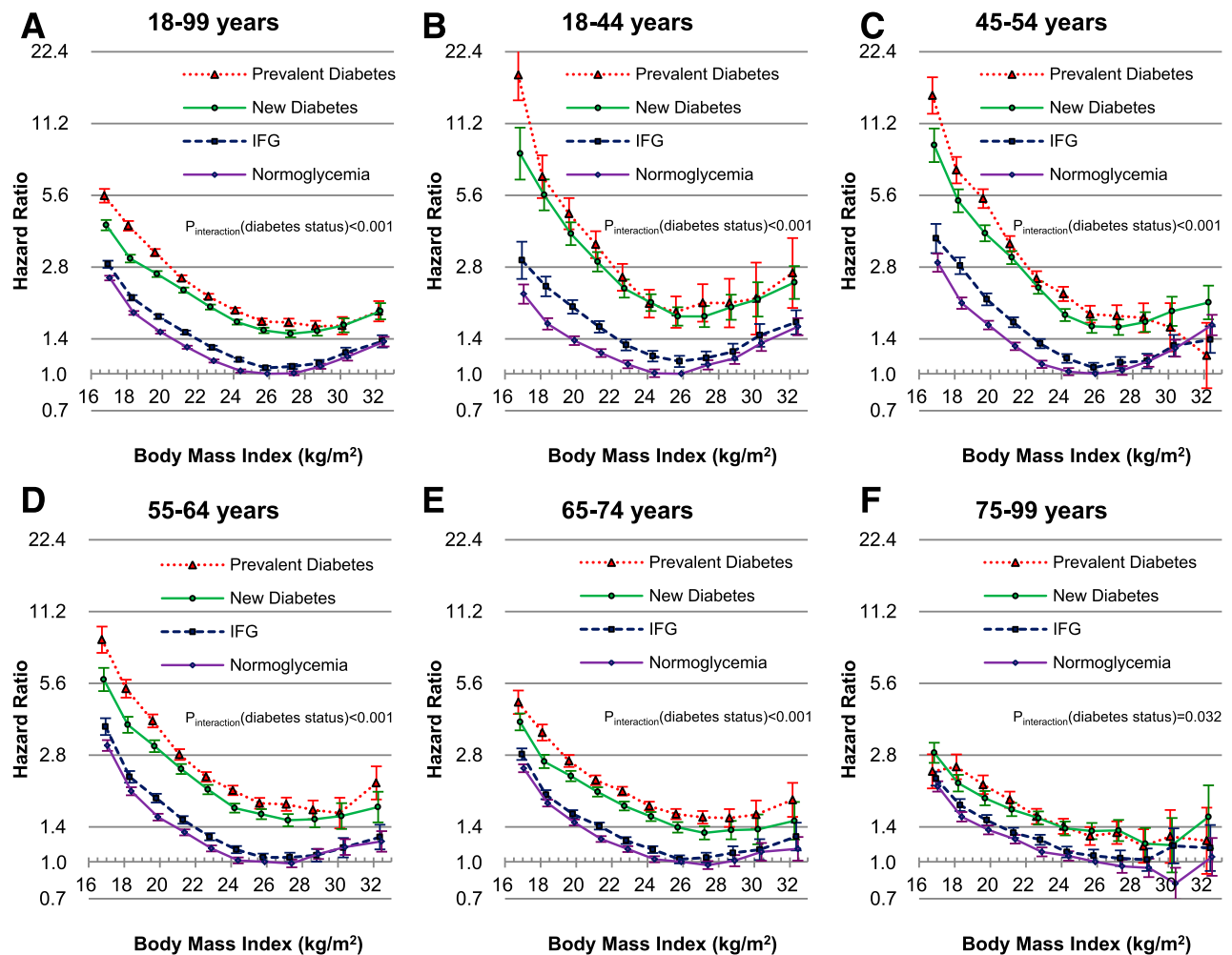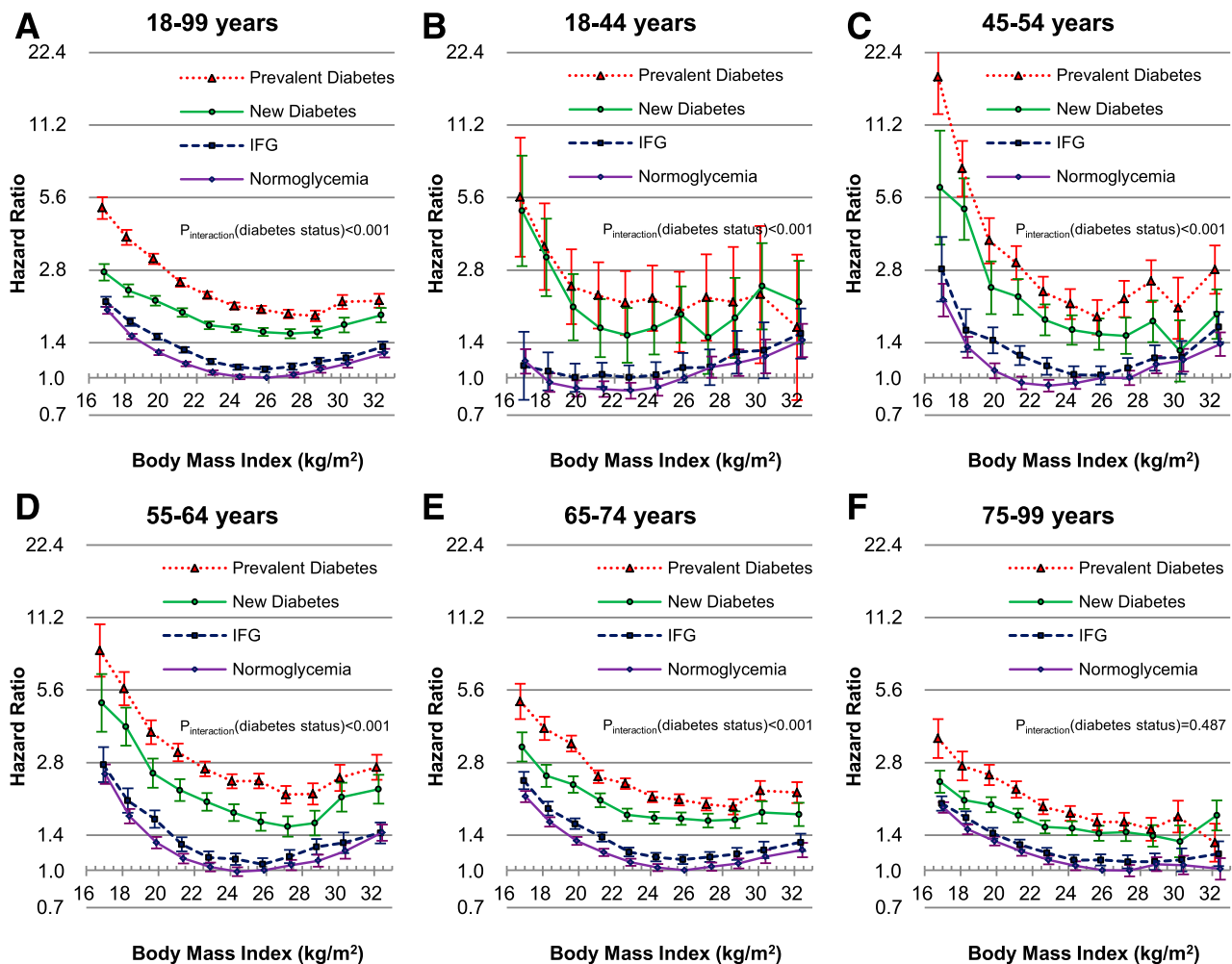
Figure 2—HRs for mortality in 44 BMI–diabetes status combined categories by age in men: 18–99 years (*A*), 18–44 years (*B*), 45–54 years (*C*), 55–64 years (*D*), 65–74 years (*E*), and 75–99 years (*F*). BMI categories (kg/m²): <17.5, 17.5–18.9, 19.0–20.4, 20.5–21.9, 22.0–23.4, 23.5–24.9, 25.0–26.4, 26.5–27.9, 28.0–29.4, 29.5–30.9, and ≥31.0. Normoglycemic people with BMI 25–26.4 were the reference group. The midpoint was used as a representative value for each BMI category, except for both ends (16.9 and 32.3), for which the median of all participants was used. HRs and 95% CIs were calculated using Cox proportional hazards models stratified by baseline age (18–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and 85–99 years) after adjustment for age at baseline as a continuous variable (within each age-group), smoking status, alcohol use, and physical activity.

that adipose tissue serves as a metabolic reservoir, protecting other tissues from lipotoxicity and ectopic fat accumulation as well as buffering the influx of dietary fats (25,26). As diabetes worsens, circulating levels of glucose and fatty acids increase, causing chronic complications. In a person with a good capacity to transport this excess energy into fat tissues, body fat will increase while the individual remains metabolically stable (healthy). However, the exact role of adiposity in the association between BMI and mortality, especially according to disease status, has not yet been elucidated. In addition, a recent study reported that body fat distribution, rather than BMI, was associated with the risk of incident cardiovascular events (27), although few studies, if any,

have examined whether the role of body fat differs by distribution site according to diabetes status. Further studies are needed to determine the differential role of adipose tissue, according to its distribution, on clinical outcomes such as mortality.

Reverse causality or confounding by smoking history has been considered a possible explanation of the different optimal BMIs according to diabetes status and a U-curve association between BMI and mortality (5). However, with exclusion of individuals who died during the first 3 years of follow-up, ever smokers, and those with known heart disease, stroke, or cancer, the primary findings did not substantially change (Supplementary Tables 3–5 and Supplementary Figs. 3–5).

In addition, differences in optimal BMI according to diabetes status were more apparent at younger ages, when undetected comorbid illness was least common; thus, reverse causation or smoking-related confounding is unlikely to wholly explain our results.

Because excess adiposity is associated with the development of diabetes, some researchers have suggested that individuals with a lower BMI at diabetes diagnosis may have other risk factors for overall death (2). However, people with diabetes and normal weight had lower blood pressure and total cholesterol levels compared with those who were overweight or obese (Supplementary Table 12). Genetic variants associated specifically with lean diabetes have been

Figure 3—HRs for mortality in 44 BMI–diabetes status combined categories by age in women: 18–99 years (*A*), 18–44 years (*B*), 45–54 years (*C*), 55–64 years (*D*), 65–74 years (*E*), and 75–99 years (*F*). BMI categories (kg/m²): <17.5, 17.5–18.9, 19.0–20.4, 20.5–21.9, 22.0–23.4, 23.5–24.9, 25.0–26.4, 26.5–27.9, 28.0–29.4, 29.5–30.9, and ≥31.0. Normoglycemic individuals with BMI 25–26.4 were the reference group. The midpoint was used as a representative value for each BMI category, except for both ends (16.9 and 32.3), for which the median of all participants was used. HRs and 95% CIs were calculated using Cox proportional hazards models stratified by baseline age (18–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and 85–99 years) (if applicable) after adjustment for age at baseline as a continuous variable (within each age-group), smoking history, alcohol use, and physical activity.

suggested (28). It is of interest to examine whether those variants are associated with poorer survival.

Patterns of Association Between BMI and Mortality by Diabetes Status, Age, and Sex

As diabetes status worsened, mortality increased. This effect was strongest with lower BMI, especially at younger ages. There are several possible explanations. First, this may be the effect of potential unmeasured confounders; for example, young and lean people with newly diagnosed diabetes may be genetically predisposed to poor prognosis. Previous studies have shown lower mass and greater failure of β-cells in lean people (29,30). Second, younger people may have no

comorbidities; thus, mortality associated with diabetes could be greater in this group. However, this does not explain why the association is stronger at lower BMI. Third, type 1 diabetes may be more prevalent in young and lean individuals. However, evidence is growing that young-onset type 2 diabetes is associated with greater complications and mortality compared with type 1 diabetes (31,32). In addition, the percentage of type 1 diabetes in young adults (20–39 years old) with diabetes was estimated to be below 10% in the Korean population (33,34). Thus, a potentially higher proportion of type 1 diabetes in young adults than in older adults may not totally explain the observed findings. Our observation, that in young-onset diabetes, normal weight

and underweight contribute more to reduced longevity compared with overweight and obesity, requires elucidation. Because young-onset diabetes is a major health issue requiring immediate action, further research to better understand underlying mechanisms are needed to improve the health of young people with diabetes.

Mortality in prevalent diabetes relative to newly diagnosed diabetes was higher in women than in men. Although the mechanism is unclear, differences in the biological response to hyperglycemia and cardiometabolic risk factors between sexes, along with poorer compliance and management in women with diabetes, may explain these findings (35,36). Further research to explore sex differences

and their underlying mechanisms is needed to better manage patients with diabetes.

Study Strengths and Limitations

Our study revealed that the association between BMI and mortality changed as diabetes worsened. We analyzed specific BMI ranges and conducted stratified analyses by sex, age, and smoking status. The study's prospective design and long follow-up period are definite strengths. Data were analyzed after adjusting for potential confounders, including smoking history and physical activity level. Effects of additional adjustment of metabolic mediators, such as blood pressure, fasting glucose, and total cholesterol, were also examined. In sensitivity analyses, exclusion of participants with comorbid conditions and those who died within the first 3 years of follow-up strengthened the analyses, as did the objective measurement of BMI.

Notwithstanding, the study has some limitations, which may be addressed by further investigation. One limitation is the lack of information on specific causes of death. Another is that we did not examine other measures of adiposity or skeletal muscle mass. Also, information relevant to diabetes, such as duration, type, severity, or treatment, was not examined. Regarding the type of diabetes, according to a recent research report, among adults aged 20–39 years with diabetes, the percentage of type 1 diabetes was <10% (33). Therefore, we surmise that most people with diabetes in our study generally have type 2 diabetes, even those aged 18–44 years. This analysis was based on a single baseline BMI measurement, which limited our ability to evaluate the effect of changing BMI on mortality. We also cannot rule out that our observed difference may be partially explained by collider stratification bias (37). And last, although we posited explanations for our findings, we could not completely exclude reverse causality or the effects of unmeasured confounding factors. The homogenous ethnic population may be considered a limitation for generalizability, but we consistently observed U-curve associations and higher optimal BMI with worsening diabetes status independent of sex and age. Participants likely had varying body shapes, cardiometabolic profiles, and comorbidities according to sex and age, which

contributes to increase generalizability including to other ethnic populations.

Summary

In this large prospective study, we observed a similar U-curve association between BMI and mortality, regardless of diabetes status, sex, and age. We also observed increasing mortality risk with worsening diabetes status, which was more prominent as BMI was lower, especially at younger ages. The optimal BMI for longevity became gradually higher with worsening diabetes status in each sex and all age-groups group, except perhaps for people aged ≥75 years.

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