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Improvement in Age at Mortality and Changes in Causes of Death in the Population with Diabetes: An Analysis of Data from the Korean National Health Insurance and Statistical Information Service, 2006 to 2018

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Background: Diabetes is a leading cause of death that is responsible for 1.6 million annual deaths worldwide. However, the life expectancy and age at death of people with diabetes have been a matter of debate.

Methods: The National Health Insurance Service claims database, merged with death records from the National Statistical Information Service in Korea from 2006 to 2018, was analyzed.

Results: In total, 1,432,567 deaths were collected. The overall age at death increased by 0.44 and 0.26 year/year in the diabetes and control populations, respectively. The disparity in the mean age at death between the diabetes and control populations narrowed from 5.2 years in 2006 to 3.0 years in 2018 ($P<0.001$). In a subgroup analysis according to the presence of comorbid diseases, the number and proportion of deaths remained steady in the group with diabetes only, but steadily increased in the groups with diabetes combined with dyslipidemia and/or hypertension. Compared to the control population, the increase in the mean death age was higher in the population with diabetes. This trend was more prominent in the groups with dyslipidemia and/or hypertension than in the diabetes only group. Deaths from vascular disease and diabetes decreased, whereas deaths from cancer and pneumonia increased. The decline in the proportion of deaths from vascular disease was greater in the diabetes groups with hypertension and/or dyslipidemia than in the control population.

Conclusion: The age at death in the population with diabetes increased more steeply and reached a comparable level to those without diabetes.

Keywords: Mortality; Diabetes mellitus; Cardiovascular diseases; Neoplasms; Epidemiology

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INTRODUCTION

With the current rapid increase in the incidence of obesity and prevailing sedentary lifestyles, diabetes mellitus is one of the most common and fastest-growing metabolic disorders, and its prevalence has almost doubled in older population groups [1,2]. Diabetes is also a leading cause of death that is responsible for 1.6 million annual deaths worldwide [3]. Although mortality and disability from diabetes vary by country and the mortality burden of metabolic diseases has shifted from developed countries to developing countries, diabetes still ranks as the seventh and eighth leading cause of death in the United States and European countries, respectively [4,5]. In South Korea, diabetes accounts for 17.1 deaths per 100,000 population and ranks as the sixth leading cause of death [6].

Although atherosclerotic cardiovascular disease (ASCVD) has been the leading cause of mortality among patients with diabetes, a recent study has provided strong evidence that the rate of ASCVD-related complications declined more than the case for other types of morbidity from 1990 to 2010 [7]. Since rosiglitazone use was reported to be associated with a higher occurrence of ASCVD, the ASCVD safety of diabetes medications has been emphasized in addition to the ability of medications to control glycemia. More recently marketed diabetes medications, including sodium glucose co-transporter 2 inhibitors and glucagon-like peptide 1 receptor agonists to control glycemia, have also reduced the number of deaths from ASCVD [8-10]. However, it remains unclear whether the availability of these newer medications has led to changes in mortality, particularly in Asian populations. Therefore, we investigated whether the recent mortality trends in people with diabetes have changed and compared these trends between individuals with and without diabetes in the general population, using data from the National Health Insurance database maintained by the Korean National Health Insurance Service (NHIS), as well as mortality records and statistics from the National Statistical Information Service (NSIS).

METHODS

Data source

This nationwide cohort study utilized insurance claims data collected from the Korean NHIS. The NHIS is the single compulsory insurer in the Korean public health insurance sector that provides health insurance, manages the enrollment of the insured and their dependents, collects contributions, and sets medical fee payment schedules [11]. The Korean NHIS provided claims data after de-identification; the claims case data contained the date of birth, region of residence, sex, and date of hospital visit. From this cohort, deceased members of the insured population from January 1, 2006 to December 31, 2018 were selected. To obtain information on age at death, we followed a cohort of 3,394,502 deceased insured, and requested the NSIS to link their records and causes of death. The study was reviewed and approved by the Institutional Review Board (IRB) of the National Health Insurance Service Ilsan Hospital (NHIS-2021-1-218). All participants originally provided written informed consent to participate in the NHIS.

Definition of diabetes and death certificates

From the NHIS database, we utilized each subject's medical records for 2 years prior to their date of death and applied operational definitions for diabetes and comorbidities. Diabetes was defined as being present if the following three criteria were met: having a diabetes diagnosis code; having at least one service claim with a diagnosis of diabetes (in outpatient or inpatient care); and receiving at least one prescription for a hypoglycemic agent. The principal and additional diagnoses were determined by the International Classification of Diseases, 10th Revision (ICD-10) code for diabetes (E11–E14). Hypertension was defined as the corresponding ICD-10 codes (I10–13, I15) and treatment with anti-hypertensive agents; and dyslipidemia was defined as the ICD-10 code of E78 and treatment with lipid-lowering agents. Cancer was considered to have been diagnosed when the patient had a cancer code (ICD-19 code of C00–C97) and had been registered for the Exempted Calculation of Health Insurance (ECHI) with V codes in the NHIS to confirm the diagnostic codes. In South Korea, when a patient is newly diagnosed with cancer, the treating physician is required to apply for registration in the ECHI with the ICD-10 code under the relieved Co-Payment Policy. Cancer patients who are registered with the NHIS have been issued a V code and are reimbursed for 95% of their medical costs by the Korean government for 5 years [12]. The control population was defined as individuals without a prior history of diabetes, hypertension, dyslipidemia, or cancer. For a detailed analysis of the Korean population with diabetes, stratification by sex and comorbidities (dyslipidemia and hypertension) was performed (Fig. 1). To obtain the age at death and cause of death, we merged death records collected by the NSIS with disease-specific codes, and extracted the five most common causes of death in South Korea: cancer (C00–C97), cerebrovascular disease (I60–I69), cardiovascular disease

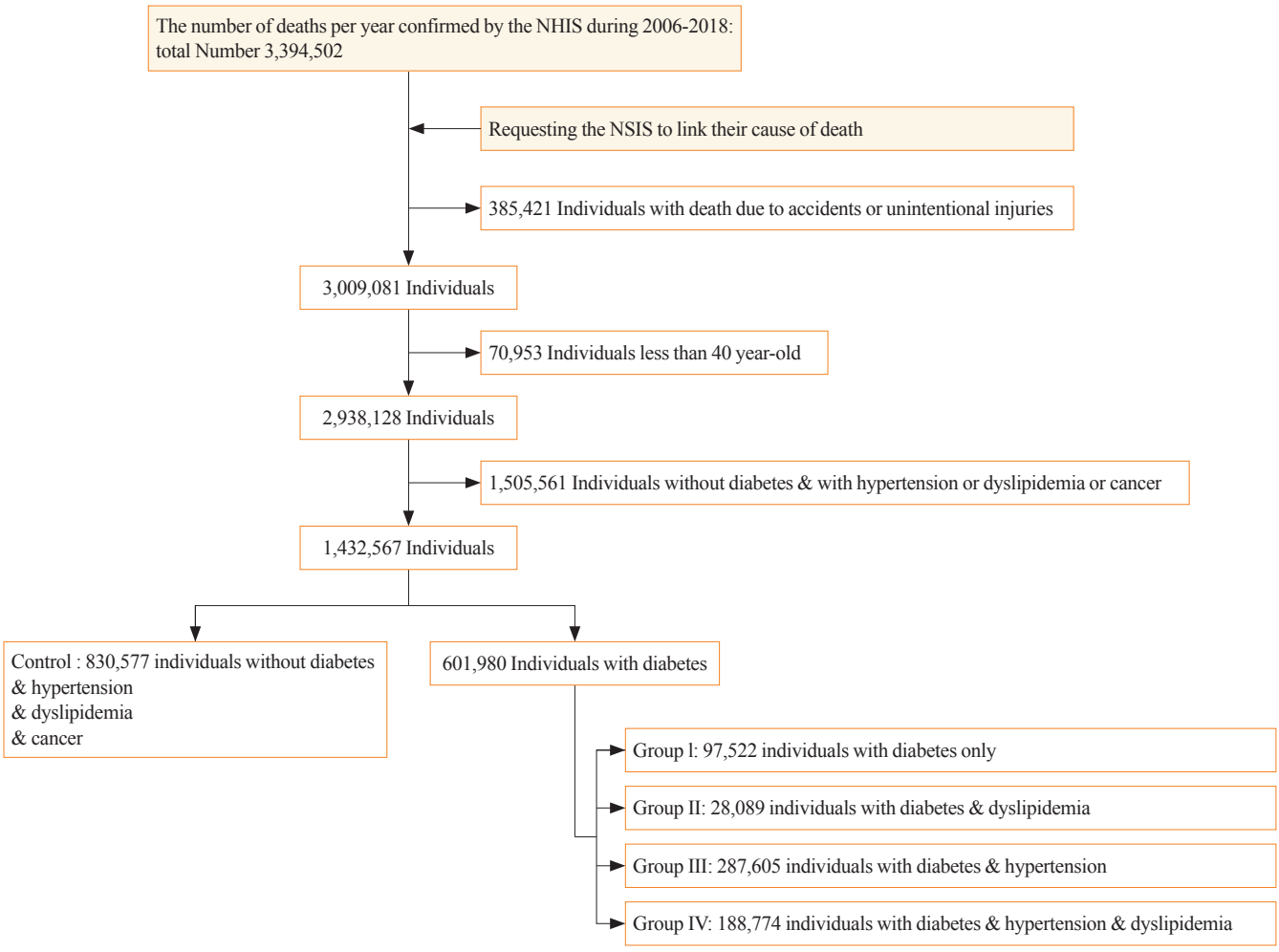

Fig. 1. Flow diagram of subject inclusion and exclusion in the Korean National Health Insurance Service (NHIS) claims database and National Statistical Information Service (NSIS).

(I20–I25), diabetes (E11–E14), and pneumonia (C00–C97). Deceased individuals under 40 years of age who died from accidental or unintentional injuries were excluded.

Statistical analysis

Descriptive statistics were used to investigate the data, expressed as number and frequency (percentage). The chi-square test was used to analyze numerical and frequency data. Continuous variables were expressed as mean±standard deviation, and categorical variables as numbers and percentages. Subjects were classified into groups with or without diabetes, and further subdivided according to the presence of hypertension or dyslipidemia as comorbidities. Multivariable linear regression analysis was used to adjust for covariates, including sex, year, and verified interactions. Subgroup analysis was conducted to investigate the age and cause of death in individuals with diabetes by sex and comorbidities (hypertension and dyslipidemia). Two-way analysis of variance with type III sum of squares was applied to consider the statistical significance of differences by groups. Annual age-standardized mortality was also estimated by applying the direct standardization method using the standard population data from the controls and people with diabetes in 2012. Multivariable linear regression analysis was performed to confirm changes in trends, with the year as the explanatory variable and the age-standardized mortality rate as the dependent variable. A $P<0.05$ was considered to indicate statistical significance. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Availability of data and materials

Data can be accessed through the NHIS' National Health Insurance Data Sharing Service website (http://nhiss.nhis.or.kr/bd/ab/

bdaba021eng.do). To gain access to the NHIS data, a completed application form, a research proposal, and the applicant's IRB approval document should be submitted to and reviewed by the Review Committee of Research Support in NHIS. After the approval is granted, data will be provided to the applicant for a fee. Upon request, the causes of death prepared by Statistics Korea and information regarding the participant's district of residence can be provided by the NHIS after review by the committee.

RESULTS

During the period from 2006 to 2018, the total population of the South Korea increased by 3,196,964, with mortality remaining constant at an approximate range of 242,266/year to 298,820/year [13]. A total of 3,394,502 people died during this period. We excluded 456,224 subjects who died from accidents or unintentional injuries and were under 40 years of age. Of the 2,938,128 deceased subjects, 20.5% (601,990) had diabetes. Finally, the current study assessed a total of 1,432,567 deaths, including 830,577 control deaths with no evidence of diabetes, hypertension, dyslipidemia, or cancer, and 601,990 diabetes deaths from 2006 to 2018. The population with diabetes was classified into four groups according to ICD-10 codes and medication claim data: diabetes only (group I, n=97,522) without dyslipidemia or hypertension, diabetes with dyslipidemia (group II, n=28,089), diabetes with hypertension (group III, n=287,605), and diabetes with both hypertension and dyslipidemia (group IV, n=188,774) (Fig. 1, Supplemental Table S1). The mortality numbers per year were variable during the period and ranged from 58,532 to 79,224 in the control population, but steadily increased from 29,642 in 2006 to 63,073 in 2018 among the diabetes population.

From 2006 to 2018, the mean age at death significantly increased in both the diabetes and control populations (P<0.001) (Fig. 2A). In 2006, the mean age at death in the diabetes population was 5.2 years younger than that of the control population (70.8 years for diabetes vs. 76.0 years for control). However, the overall age at death increased by 0.44 and 0.26 year/year during the 12-year study period in the diabetes and control populations, respectively. The mean age at death among those with diabetes increased much more sharply than that of the control population, by 0.18 year/year, resulting in a narrowed disparity in the mean age at death between the two populations (P<0.001). In 2018, the disparity in mean age at death between the control and diabetes populations was 3.0 years. This trend was more prominent in men. In 2006, the mean ages at death in the diabetes populations in men and women were 2.2 and 7.5 years younger than those of the control population, respectively. The overall increase in age at death (0.44 year/year for men, 0.46 year/year for women) was similar in both sexes. The disparity in age at death in men decreased, became even in 2015, and then reversed (Fig. 2B). For women, the disparity in age at death was 7.5 years in 2006 and narrowed to 4.9 years in 2018 (Fig. 2C).

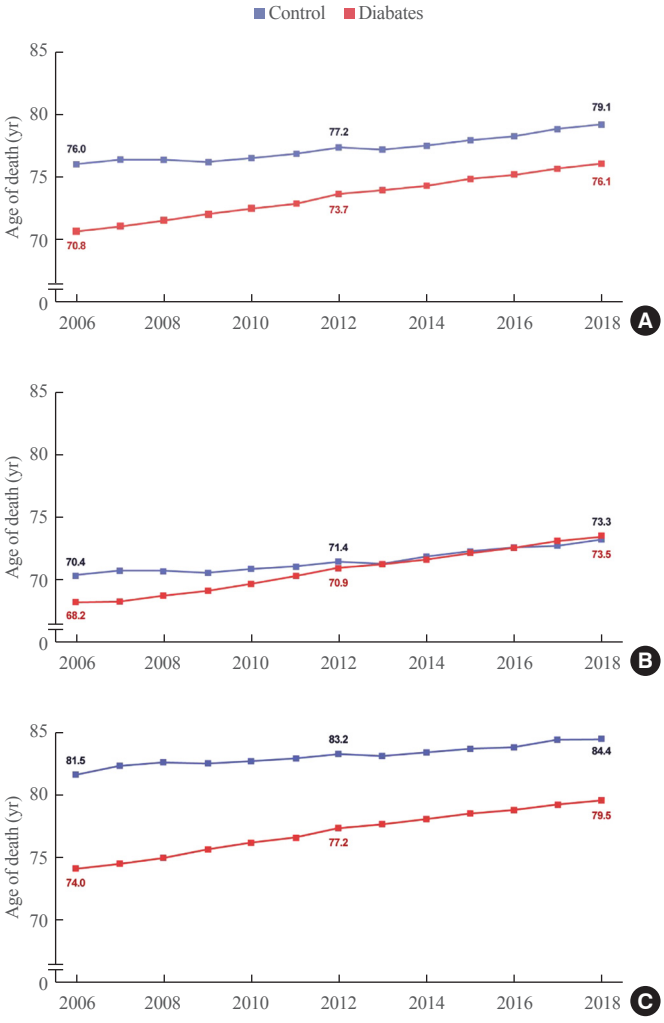

Fig. 2. Changes in age of death among individuals with diabetes and controls. (A) Overall, (B) men, (C) women.

In an analysis by group, according to comorbid diseases, the mean age at death steadily increased in all groups (Fig. 3A). In addition, the number and proportion of deaths steadily increased in group II with dyslipidemia and group IV with hypertension and dyslipidemia, whereas those in group I, with diabetes only, were sustained (Supplemental Table S1). Deaths among individuals in group III with hypertension increased and remained

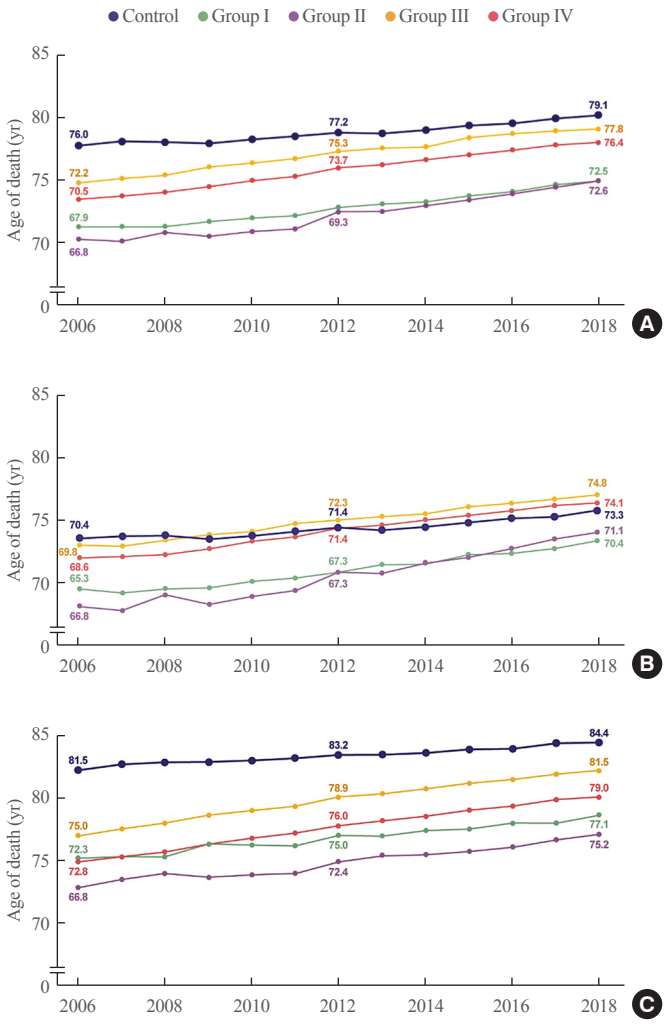

Fig. 3. Changes in age of death among controls and individuals with diabetes according to the presence of comorbidities. (A) Overall, (B) men, (C) women. Group I, diabetes only; Group II, diabetes with dyslipidemia; Group III, diabetes with hypertension; Group IV, diabetes with both hypertension and dyslipidemia. Compared to the control population, the increases in the mean death age were higher by 0.16, 0.33, 0.23, and 0.26 year/year for Groups I, II, III, and IV, respectively (all $P<0.001$).

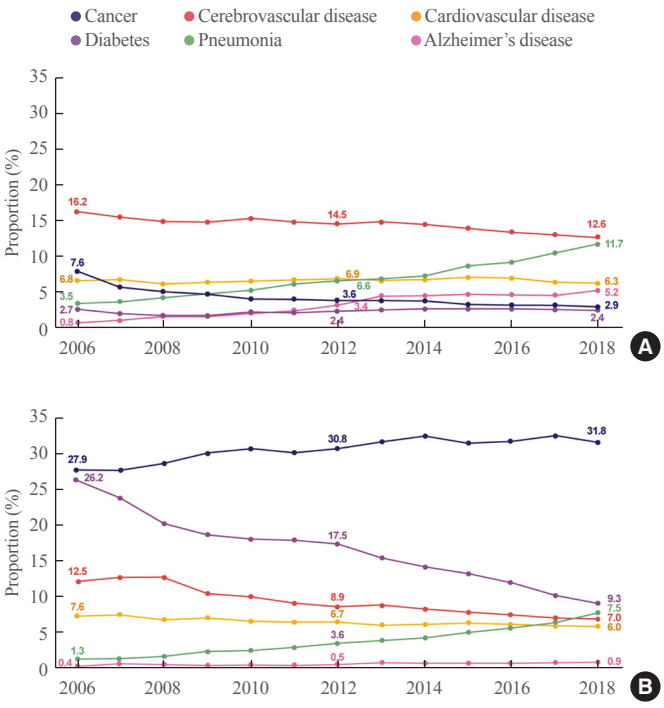

Fig. 4. Age-standardized mortality rate in individuals with diabetes and controls. (A) Control, (B) diabetes.

at a plateau since 2013 (Supplemental Fig. S1). In 2006, the mean age at death was 67.9, 66.6, 72.2, and 70.5 years in groups I, II, III, and IV, respectively. Regression analysis showed that compared to the control population, the increases in the mean death age were higher by 0.16, 0.33, 0.23, and 0.26 year/year in groups I, II, III, and IV, respectively (all $P<0.001$) (Supplemental Table S2). In men, the mean age at death in group III (69.8±10.2 years in 2006 to 74.8±10.7 years in 2018) and group IV (68.6±9.4 years in 2006 to 74.1±9.9 years in 2018) increased and surpassed that of the control population (Fig. 3B). The mean annual changes in age at death were higher in the diabetes groups than in the control group (0.22, 0.48, 0.22, and 0.29 year/year for groups I, II, III, and IV, respectively). Among women in all diabetes groups, a similar trend was observed, but without their age at death overtaking that of the control population (Fig. 3C). The mean annual changes in age at death were higher in diabetes groups than in the control group (0.14, 0.33, 0.22, and 0.34 year/year for groups I, II, III, and IV, respectively).

In the control population, deaths from cerebrovascular disease decreased, but deaths due to pneumonia increased, and both were comparable in 2018 (12.6% vs. 11.7%) (Fig. 4A). In the population with diabetes, cancer was the most common cause of death, accounting for approximately 30% of total deaths, and the death rate from cancer remained constant for 12 years (27.9% in 2006 and 31.8% in 2018) (Fig. 4B). However, other causes of death changed; deaths from cardiovascular disease, cerebrovascular disease, and diabetes decreased, while deaths from pneumonia and Alzheimer's disease increased. The decline in deaths from cerebrovascular disease and cardiovascular disease was more rapid in the diabetes population than in the control population (from 23.0% to 18.9% in the control group and from 20.1% to 13.0% in the diabetes group). Comparable findings were observed in both men and women with diabetes (data not shown). In a subgroup analysis divided according to

comorbid diseases, a similar trend in results was observed. The proportion of deaths from vascular disease (cerebrovascular and cardiovascular disease) decreased more in group III with hypertension (21.7% in 2006 to 12.2% in 2018) and group IV with hypertension and dyslipidemia (28.9% in 2006 to 15.5% in 2018) than in the other groups (Supplemental Fig. S2).

When further analyses were performed with standardized age adjustment, the age-adjusted death rate for cancer remained steady, with values of 6.4/1,000 in both 2006 and 2018, respectively. The declines in the age-adjusted death rate for vascular disease were more prominent; 2.8 to 1.5/1,000 for cerebrovascular disease, and 1.7 to 1.2/1,000 for cardiovascular disease (all $P<0.001$). Additionally, the age-adjusted death rate for the population with diabetes also decreased from 5.9 to 1.9/1,000, with statistical significance ($P<0.001$). The age-adjusted death rates for pneumonia and Alzheimer's disease increased from 0.3 to 1.6/1,000 and from 0.1 to 0.2/1,000, respectively (all $P<0.001$) (Supplemental Table S3).

DISCUSSION

Diabetes has been considered a risk factor for premature mortality, and individuals with diabetes are expected to have a relatively short life expectancy [5,7,13,14]. Using nationwide, population-based, consecutive NHIS and NSIS data, the current study demonstrated a statistically significant increase in age of death in populations with diabetes and a decrease in the disparity in death age between populations with and without diabetes. The disparity in age of death in men became numerically even in 2015 and then reversed. In individuals with diabetes, deaths from vascular diseases (cerebrovascular and cardiovascular disease) and diabetes decreased, while deaths from pneumonia and Alzheimer's disease increased. The number and proportion of subjects with diabetes with hypertension and/or dyslipidemia also sharply increased from 2006 to 2018. Furthermore, when the population with diabetes was analyzed according to sex and comorbidities, the decrease in deaths from vascular disease was more prominent in individuals with diabetes accompanied by hypertension and/or dyslipidemia as comorbidities.

The current study has several strengths. The key strength is that the study's findings reported longitudinal trends in the age of death among individuals with diabetes over a 12-year period, and demonstrated a much sharper increase in age of death in the population with diabetes compared to those without. The study also found that age at death in all populations with diabetes was markedly lower than that of the control population. However, the disparity in age at death between the diabetes and control populations shortened from 5.2 years in 2006 to 3.0 years in 2018. According to previous diabetes cohort reports, the decreasing trend in diabetes-related deaths has been observed since the 1990s [15]. Recently, an Asian study also reported decreases in mortality rates for diabetes [16]. Considering the exploding incidence of diabetes, it is plausible to expect that the lifespan of individuals with diabetes could be closer to or longer than that of the general population. In terms of sex differences, there was no statistical significance regarding increases in age at death between men and women in the population with diabetes. However, the mean age at death was comparable in men with or without diabetes. The age of death between diabetes and non-diabetes populations in men had a gap of 2.2 years, which was narrower than the gap of 6.5 years in women in 2006. With a 0.24 year/year increase in age at death for the diabetes population, men with diabetes have reached a higher numeric death age compared to the men without diabetes since 2017. Similar to the results of the current study, men with and without diabetes had the same life expectancy in a previous study published in Bulgaria [17], and a United States national health survey showed that the all-cause mortality decline was greater in men than in women among the population with diabetes [18]. Individuals with diabetes showed a remarkable improvement in terms of the decrease in deaths from vascular disease [18]. Another Canadian study demonstrated an improvement in mortality in men compared to that of women in the general population [19]. The absolute decline in deaths among men was greater for circulatory disease, thus narrowing the mortality gap between men and women [19]. A possible explanation for the increase in age of death in men and decreased number of deaths from vascular disease in the population with diabetes is that men with diabetes receive more benefits from curative and preventive interventions for vascular disease.

Second, the current study showed an increase in the number and proportion of individuals with diabetes who also had hypertension and dyslipidemia over the 12-year study period. A United States nationwide data analysis also showed that the overall prevalence of concurrent hypertension, dyslipidemia, and diabetes, as well as diabetes with concurrent hypertension or dyslipidemia, increased significantly and nearly doubled during 1999 to 2012 [20]. Indeed, guidelines from the American Diabetes Association and the Korean Diabetes Association have emphasized the importance of controlling these comorbidities [21,22]. However, as far as we know, this is the first study to demonstrate prominent improvements in age at death among

people with diabetes who also had hypertension and/or dyslipidemia. Interestingly, sharp increases in age of death in individuals with diabetes and hypertension/dyslipidemia were identified compared to their counterparts with diabetes who did not have either hypertension or dyslipidemia. For example, the number of deaths increased approximately 5.8-fold from 4,666 in 2006 to 26,874 in 2018 among those with diabetes accompanied by hypertension and dyslipidemia, while their proportion increased from 15.7% in 2006 to 42.6% in 2018 among the total diabetes population. The age of death of these subjects increased by 0.26 year/year more than controls, and the rate of increase exceeded that of the diabetes-only group. Among the male diabetes population in the study cohort, the gap in age at death between the control population and the diabetes with hypertension and dyslipidemia group gradually narrowed, and eventually became even and then reversed. A recent study demonstrated that patients with diabetes had little or no excess risk of death if hyperglycemia, dyslipidemia, and hypertension were controlled within target levels [23]. Indeed, a study in Hong Kong showed that improvements in metabolic risk factor control, along with increased use of antihypertensive drugs and statins, were associated with a decline in death [16]. Interestingly, compared to other concurrent diabetes groups, the number and proportion of the diabetes-only group slightly increased, but generally remained stable in our study (Supplemental Fig. S1). Meanwhile, the number and proportion of diabetes patients with dyslipidemia and/or hypertension increased (Supplemental Fig. S1), and the proportion of deaths from cerebrovascular and cardiovascular diseases in those populations declined (Supplemental Fig. S2). As we categorized the subgroups according to ICD codes and medication prescriptions, we postulate that the diabetes population with dyslipidemia and/or hypertension, taking any type of metabolism-related medications, might have benefited more than those with diabetes only who took anti-diabetes medications. Even considering the absence of data on lipid panels and blood pressure values in our study population, the early diagnosis and stricter medication treatment of hypertension and dyslipidemia in patients with diabetes would be emphasized as a way to obtain better outcomes in vascular mortality.

Third, the causes of death in the population with diabetes have changed. Deaths from cancer have steadily increased, whereas deaths from diabetes, cerebrovascular disease, and cardiovascular disease have decreased among those with diabetes. This trend is slightly different from what has been observed in United States data, which demonstrated a decline in cancer-related deaths in individuals with diabetes [18]. Diabetes is closely related to an increased risk for malignant neoplasms in the breast, liver, pancreas, endometrium, colon, rectum, and bladder [24], and deaths from breast and colorectal cancer have decreased in the United States population with diabetes [25]. Although a decline in deaths from cardiovascular disease in the control group was observed, a more substantial reduction in cerebrovascular and cardiovascular diseases was observed with respect to deaths in individuals with diabetes in the current study. This finding is in line with previous studies that compared populations with and without diabetes [18,26-28]. Taken together, we postulate that the increasing number of diabetes patients with dyslipidemia and hypertension, as well as the reductions in deaths from diabetes, cerebrovascular disease, and cardiovascular disease, might have increased the age at death in the population with diabetes. This phenomenon also likely reflects the impact of medical advances in drug development and the management of dyslipidemia and hypertension in patients with diabetes.

Lastly, we used two official Korean population-based databases from the NHIS and NSIS. The NHIS, the single compulsory insurer in the Korean public health insurance sector, provides health insurance, while managing the enrollment of the insured and their dependents, collecting contributions, and setting medical fee payment schedules for all Korean citizens. Furthermore, to remove data on the non-medical causes of death, deceased individuals aged under 40 years who died from congenital anomalies, accidents, or unintentional injuries including suicide, which was one of the most common causes of death in Korea [29], were excluded using the NSIS data. These findings, derived from reliable official databases, were consistent with previously reported trends in cause-specific mortality among individuals with diabetes. The average proportion of deaths from vascular diseases in the population with diabetes was similar to those in previous studies [30,31]. In addition, the overall proportion of other causes of death, including cancer and diabetes, was also comparable to other results. Statistical reliability was ensured due to the overall size of the nationwide cohort and the credibility of data configuration.

Several issues remained unresolved in the current study. First, as both diagnosis codes and drug prescription claims were applied to define diseases, information on medication adherence was not available. Due to the lack of information in our data, we could not utilize laboratory parameters (blood glucose, glycated hemoglobin, and cholesterol levels) and physical examination results (blood pressure and body mass index) in defining the disease diagnosis. It is possible that the diabetes only group may

have actually had uncontrolled blood pressure and dyslipidemia due to refusal to take the corresponding medications or physicians' mismanagement. Additionally, physicians might have recommended stricter targets for diabetes patients with comorbidities than for those with diabetes alone. Due to the application of diagnosis codes and prescription claims for disease definition, the current study may have excluded patients who were actually diagnosed with diabetes, hypertension, and/or dyslipidemia, but did not take medications, which would have led to selection bias. Second, due to the study cohort characteristics (in particular, due to the use of claims data), we could not assess the quality of life after the diagnosis of diabetes or other comorbidities. Additionally, this study did not consider individuals' family history of vascular disease, social history, and health behaviors including exercise and diet, which contribute to the control of chronic diseases. Lastly, although subjects with a prior history of cancer and diabetes were excluded from the control population, a significant proportion of deaths from cancer and diabetes was detected in the controls. The limitations of claims data and the possibilities for definitional disparities in the inclusion criteria from NHIS and the endpoint records from NSIS in this study design could have been a source of bias.

In conclusion, this nationwide study of a representative sample of the total Korean population demonstrated increased longevity in individuals with diabetes, as well as a decrease in deaths due to cerebrovascular and cardiovascular diseases in individuals with diabetes. More strikingly, a sharp increase in age at death was observed in diabetes accompanied by hypertension and/or dyslipidemia, while those populations rapidly expanded. Based on these findings, we suggest that proper care and treatment for diabetes may help prevent the disease from poorly affecting the patient's lifespan, and individuals with diabetes could expect a comparable life expectancy to those without diabetes. Prospective, well-designed, longitudinal studies are warranted to elucidate the complexity of the lifespan and the impact of risk reduction in patients with diabetes.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: E.H., S.O.S., B.W.L. Acquisition, analysis, or interpretation of data: E.H., S.O.S., H.S.K., K.J.S., S.H.J., B.S.C. Drafting the work or revising: E.H., S.O.S. Final approval of the manuscript: E.H., S.O.S., B.W.L.

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