Cardiovascular Diseases and Life Expectancy in Adults With Type 2 Diabetes: A Korean National Sample Cohort Study

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Objective: Although type 2 diabetes is a strong risk factor for cardiovascular disease and mortality, information on its association with mortality and life expectancy according to cardiovascular comorbidities is limited, especially in Asia. Thus, this study assessed mortality and reductions in life expectancy associated with cardiometabolic multimorbidity.

Design and Methods: A total of 569,831 participants older than 30 years from Korean National Health Insurance Service–National Sample Cohort were enrolled between 2002 and 2006 and followed for a median of 12.0 years. They were categorized into five mutually exclusive groups according to baseline disease status, as follows: none (reference group); diabetes only; diabetes and stroke; diabetes and myocardial infarction (MI); and diabetes, stroke, and MI. Mortality rates and hazard ratios (HRs), reductions of life expectancy, and age-specific contributions to life expectancy were calculated by constructing life tables.

Results: The mortality rates per 1000 person-years were 6.85, 19.86, 67.17, 66.34, and 115.52 in the reference, diabetes only; diabetes and stroke; diabetes and MI; and diabetes, stroke, and MI groups, respectively. The corresponding HRs for all-cause mortality were 1.70 [95% confidence interval (CI), 1.66 to 1.75], 3.66 (95% CI, 3.32 to 4.03), 3.56 (95% CI, 3.06 to 4.14), and 4.79 (95% CI, 3.05 to 7.50) compared with the reference group. The estimated reductions in life expectancy were greater at younger ages and markedly increased with more cardiometabolic comorbidities.

Conclusion: Young Asians with type 2 diabetes, especially those with cardiovascular comorbidity, did not live as long than their nondiabetic equivalents. Thus, these individuals require special attention to prevent further reductions in life expectancy. (***J Clin Endocrinol Metab*** **102: 3443–3451, 2017)**

The prevalence of type 2 diabetes is increasing worldwide (1), and evidence suggests it is associated with increased cardiovascular morbidity and mortality (2, 3). Although people with type 2 diabetes mostly die of causes other than cardiovascular disease (CVD), CVD is still an important contributor to this excess mortality (2). Likewise, the proportions of people with type 2 diabetes (4) and CVD, especially stroke (5), have increased rapidly in Asia. Factors such as aging, urbanization, and associated lifestyle changes, as well as an adverse intrauterine environment and the resulting epigenetic changes, may contribute to the unique diabetes epidemic in Asian countries (6).

Evidence exists on the mortality risk among diabetic populations (7–9); however, most of these studies were conducted in Western populations. Moreover, evidence

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Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; ICD, International Classification of Diseases; MI, myocardial infarction; NHIS-NSC, Korean National Health Insurance Service–National Sample Cohort.

on the association of diabetes and cardiovascular comorbidity with life expectancy is sparse, even in Western countries (5, 6), and to our knowledge, none exists in Asia. For instance, a recent Korean study reported increased excess mortality in people with type 2 diabetes (10). However, besides mortality and excess mortality risks, the potential association of diabetes and cardiovascular comorbidity such as myocardial infarction (MI) and stroke with total life expectancy has not been investigated. Thus, despite the rapid increase in the prevalence of diabetes, currently, there are no Asian-specific estimates of life expectancy, to our knowledge, in people with diabetes and/or CVD.

Therefore, we aimed to estimate the life-years lost to type 2 diabetes according to the presence and type of cardiovascular comorbidity by using data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC).

Research Design and Methods

Study population

This study used data from the NHIS-NSC 2002–2013, details of which were described in previous studies (10). The data are from a nationally representative random sample of 1,025,340 individuals, who account for ~2.2% of the entire population in 2002 (10). The data were compiled by using probabilistic sampling to represent an individual's total annual medical expenses within each of 1,476 strata defined by age, sex, eligibility status (employed or self-employed), and income level (20 quantiles for each eligibility status and medical-aid beneficiary) combinations via proportional allocation from the 46,605,433 Korean residents in 2002 (10, 11). The information included contains all inpatient and outpatient medical claims data, including personal information, prescription drugs, diagnostic and treatment codes, and primary and additional diagnosis codes. In addition, each unique de-identified number is linked to mortality information from the Korean National Statistical Office. Importantly, this cohort contains the general health examination data of subjects who participated in biannual examinations. From this cohort, retrospective data of individuals older than 30 years were extracted between January 2002 and December 2013 (N = 575,696). This study was approved by the NHIS inquiry commission. The personal privacy of each participant was protected by de-identification of the national insurance claim data for analysis. This study was also approved by the institutional review board of the Asan Medical Center (IRB-No 2016-0149).

Definition of type 2 diabetes

From the NHIS-NSC, we selected subjects with records of having type 2 diabetes between January 2002 and December 2006. Type 2 diabetes was defined if antidiabetic drugs were prescribed and the 10th revision of the International Classification of Diseases (ICD)-10 codes E11 (noninsulin-dependent diabetes mellitus), E12 (malnutrition-related diabetes mellitus), E13 (other specified diabetes mellitus), or E14 (unspecified diabetes mellitus) were assigned as either principal or additional diagnosis. Antidiabetic drugs dispensed in the pharmacy during the study period in Korea consisted of six classes (*i.e.*, sulfonylureas, biguanide, α-glucosidase inhibitor, thiazolidinediones, meglitinide, and insulin) (12). In addition, incretin-based therapies (*i.e.*, glucagonlike peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors) were not introduced within the study period.

Definition of cardiovascular comorbidity

MI and stroke (ischemic or hemorrhagic) were included as cardiovascular comorbidities in this study. Cases of MI and stroke that occurred between January 2002 and December 2006 were identified using hospital discharge records with the following ICD-10 codes as a principal or subsidiary diagnosis: codes for MI were I21 (ST elevation and non-ST elevation MI), I22 (subsequent ST elevation and non-ST elevation MI), I23 (certain current complications following ST elevation and non-ST elevation MI), whereas those of stroke included I63 (cerebral infarction), I64 (stroke, not specified as hemorrhage or infarction), I693 (sequelae of cerebral infarction), I694 (sequelae of stroke, not specified as hemorrhage or infarction), and G45 (transient cerebral ischemic attacks and related syndromes); I60 (subarachnoid hemorrhage), I61 (intracerebral hemorrhage), I62 (other nontraumatic intracranial hemorrhage), I690 (sequelae of subarachnoid hemorrhage), I691 (sequelae of intracerebral hemorrhage), and I692 (sequelae of nontraumatic intracranial hemorrhage) (13).

This cohort was followed up from the index date until the end of the study period (*i.e.*, December 31, 2013), until the last year of qualification for those who were alive, or until the date of death for those who died. We attempted to minimize the effect of existing medical conditions other than type 2 diabetes, stroke, and MI by excluding all deaths that occurred within the first year of the index date. In addition, we excluded those subjects with any history of admission due to malignancy based on ICD-10 code (C00 to C97) between January 2002 and December 2006, to avoid confounding the association between cardiovascular comorbidity and the risk of death due to preexisting malignancy (14). Finally, subjects with a history of stroke and/or MI without diabetes were also excluded. The flow used to select study participants is summarized in Fig. 1.

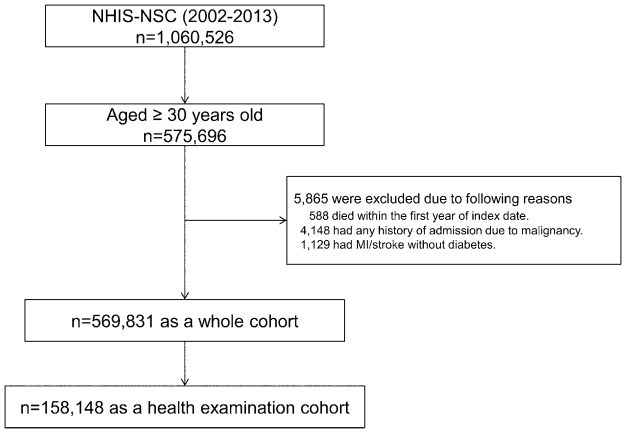

Figure 1. Selection of study participants. NHIS-NSC, National Health Insurance Service-National Sample Cohort.

Covariates

We included the following covariates based on ICD-10 code, which could have influence on mortality: hypertension (I10, essential hypertension), dyslipidemia (E78, disorders of lipoprotein metabolism and other lipidemias), and chronic kidney disease (N18-9, chronic kidney disease and unspecified kidney failure). As a separate analysis, we selected subjects who had undergone a health examinations between January 2002 and December 2006 (n =158,148; health examination cohort) among our whole cohort (Fig. 1). In this subgroup, we considered the following additional covariates: body mass index (BMI; kg/m^2), smoking habits (current smoker vs noncurrent smoker), drinking habits (heavy drinking vs nonheavy drinking), and physical activity (moderate vs nonmoderate), defined as a frequency per week. Heavy drinking was defined as consuming seven or more drinks on the same occasion and more than 3 days per week, and moderate physical activity was defined as exercising at least five times per week.

Statistical analysis

We categorized participants into the following five mutually exclusive groups according to the presence and type of cardiometabolic morbidity at baseline: (1) none (reference group), (2) diabetes only, (3) diabetes and stroke, (4) diabetes and MI, and (5) diabetes, stroke, and MI. In addition, the latter three groups were described as having cardiometabolic multimorbidity, defined as a history of diabetes with at least one cardiovascular comorbidity. We assessed the associations of these baseline groups with the risk of death from any cause.

We calculated the mortality rate per 1000 person-years according to the disease status at baseline. Time to death was estimated by the Kaplan-Meier method and statistical differences among groups according to cardiometabolic morbidity were compared by the log-rank test. Next, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models. The HRs were obtained in our whole cohort and health examination cohort, in which other covariates including BMI, smoking and drinking habits, and physical activity could be obtained.

In addition, we estimated the life expectancies according to the age groups (5-year intervals from 30 years of age) and baseline cardiometabolic morbidities in our whole cohort. The detailed statistical methods used to estimate the life expectancies are described in the Supplemental Methods. After these estimations, we calculated the reductions in life expectancy according to the age groups and baseline cardiometabolic multimorbidity by adopting two different references: participants with none of the cardiometabolic conditions assessed in our cohort and general population data from the 2002 National Life Tables for Korea (15). Finally, the age-specific contributions to differences in life expectancy due to cardiometabolic multimorbidity were estimated using Arriaga's decomposition methods (16). The total contribution of an age group to the life expectancy gap (in years) is the sum of the direct, indirect, and interaction effects.

All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC).

Results

Baseline characteristics of the study subjects

Of the 569,831 participants, 40,026 (7.01%) had a history of diabetes at enrollment, 784 (0.14%) had a history of both diabetes and stroke, 326 (0.06%) had both diabetes and MI, and 25 (0.01%) had diabetes, stroke, and MI (Table 1). The NHIS database does not provide the exact age of each subject but instead indicates the ages ranges according to 18 age groups (infants younger than 1 year, ages 1 to 4 years, age groups with 5-year-intervals between 5 and 79 years, and ≥80 years) (9). Although the number of enrolled subjects without cardiometabolic comorbidities declined with increasing age, it consistently peaked at 60 to 69 years of age among those with diabetes (29.19%), those with diabetes and stroke (38.01%), those with diabetes and MI (41.72%), and those with diabetes, MI, and stroke (36.00%; Table 1).

The most common comorbidity other than diabetes, MI, and stroke throughout all disease status categories was hypertension, followed by dyslipidemia and chronic kidney disease (Table 1). In participants with diabetes and those with diabetes and at least one of the cardiovascular comorbidities (*i.e.,* MI and stroke), the prevalence of hypertension, dyslipidemia, and chronic kidney disease was significantly higher than that among those free of diabetes, MI, and stroke (Table 1).

When other covariates were compared within the health examination cohort, participants with diabetes and/or cardiovascular comorbidities had higher systolic blood pressure, total cholesterol levels, and BMI, and a greater proportion of individuals with a moderate level of physical activity compared with participants free of diabetes, MI, and stroke (Table 1).

Mortality among people with diabetes and without diabetes

In the reference group among our whole cohort, the all-cause mortality rate was 6.85 per 1000 person-years at risk (Table 2). By contrast, the mortality rates were 19.86 per 1000 person-years in participants with a history of diabetes, 67.17 per 1000 person-years in those with diabetes and stroke, 66.34 per 1000 person-years in those with diabetes and MI, and 115.52 in those with diabetes, stroke, and MI (Table 2). When the mortality rate was calculated within the health examination cohort, a similar pattern was observed across these five groups (*i.e.,* 4.02, 13.20, 41.06, 46.53, and 142.95, respectively, per 1000 person-years from the reference group to those with diabetes, stroke, and MI; Table 1).

Figure 2 shows the survival curve according to the presence of cardiometabolic comorbidities in our whole cohort [Fig. 2(a)] and the heath examination cohort [Fig. 2(b)], respectively. Compared with reference group, the subjects of the other four groups (*i.e.,* diabetes only, diabetes with stroke, diabetes with MI, and diabetes with MI and stroke) had higher probabilities of death (log-rank test, $P < 0.001$ for all comparisons). There

Table 1. Baseline Characteristics of the Study Participants According to Cardiometabolic Morbidity at Baseline

	Disease Status at Baseline					
	None	Diabetes	Diabetes and Stroke	Diabetes and MI	Diabetes, Stroke, and MI	*P* Value[a]
Participants	528,670 (92.59)	40,026 (7.01)	784 (0.14)	326 (0.06)	25 (0.01)	
Male sex[b]	273,651 (51.76)	18,689 (46.69)	393 (50.13)	143 (43.87)	11 (44.00)	<0.0001
Age group (y) at index date[b]						
30–39	184,219 (34.85)	3209 (8.02)	7 (0.89)	8 (2.45)	0 (0.00)	<0.0001[c]
40–49	158,837 (30.04)	8474 (21.17)	58 (7.40)	28 (8.59)	2 (8.00)	
50–59	84,773 (16.04)	10,801 (26.98)	163 (20.79)	64 (19.63)	5 (20.00)	
60–69	61,427 (11.62)	11,685 (29.19)	298 (38.01)	136 (41.72)	9 (36.00)	
70–79	28,499 (5.39)	4977 (12.43)	228 (29.08)	70 (21.47)	7 (28.00)	
80+	10,915 (2.06)	880 (2.20)	30 (3.83)	20 (6.13)	2 (8.00)	
Comorbidities (based on ICD-10)[d]						
Hypertension[b]	115,766 (21.90)	27,449 (68.58)	728 (92.86)	295 (90.49)	24 (96.00)	<0.0001
Dyslipidemia[b]	96,886 (18.33)	24,439 (61.06)	545 (69.52)	250 (76.69)	14 (56.00)	<0.0001
Chronic kidney disease[b]	3350 (0.63)	1601 (4.00)	96 (12.24)	45 (13.80)	5 (20.00)	<0.0001
Health examination record	145,620 (27.54)	12,305 (30.74)	158 (20.15)	63 (19.33)	2 (8.00)	
Current smoker[e]	41,524 (28.52)	2879 (23.40)	25 (15.82)	13 (20.63)	0 (0.00)	<0.0001
Heavy drinker[e,f]	11,604 (7.97)	1116 (9.07)	9 (5.70)	6 (9.52)	0 (0.00)	<0.0001
Moderate physical activity[e,g]	10,995 (7.55)	1732 (1.19)	22 (13.92)	10 (15.87)	0 (0.00)	<0.0001
SBP, mean (SD) mm Hg	124.84 (17.26)	132.07 (18.54)	136.44 (20.18)	134.87 (22.95)	143.00 (24.04)	<0.0001[h]
≥140 mm Hg, No. (%)[e]	31,168 (21.40)	4352 (35.37)	71 (44.94)	27 (42.86)	1 (50.00)	<0.0001
TC, mean (SD), mg/dL	196.99 (37.81)	203.02 (42.26)	202.91 (46.61)	204.27 (43.40)	185.50 (50.20)	<0.0001[i]
≥240 mg/dL, No. (%)[e]	18,127 (12.45)	2,140 (17.39)	28 (17.72)	16 (25.40)	0 (0.00)	<0.0001
BMI, mean (SD), kg/m^2[j]	23.71 (2.81)	24.74 (2.81)	24.18 (2.92)	25.19 (3.14)	25.04 (1.39)	<0.0001[k]
≥25 kg/m^2, no. (%)[e]	47,054 (32.31)	5,755 (46.77)	60 (37.97)	32 (50.79)	1 (50.00)	<0.0001

Data given as No. (%) unless otherwise indicated.

Abbreviations: SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol.

[a] *P*-value was estimated using χ^2 tests for categorical variables and one-way analysis of variance for continuous variables.

[b] The denominators used to calculate the percentages are in row 2 of this table.

[c] *P*-value was estimated using Mantel-Haenszel tests for linear associations.

[d] ICD-10 codes used to define hypertension, dyslipidemia, and chronic kidney disease were I10, E78, and N18-9, respectively.

[e] Missing data were excluded from the health examination analysis. The denominators used to calculate the percentages are [none (N = 145,620); diabetes (N = 12,305), diabetes and stroke (N = 158); diabetes and MI (N = 63); and diabetes, stroke, and MI (N = 2)].

[f] Heavy drinker was defined as consuming seven or more drinks on the same occasion more than 3 d/wk.

[g] Moderate physical activity was defined as more than five times per week.

[h] Tukey honest significant difference (HSD) test for posthoc pairwise comparison revealed significant differences between groups (none vs. diabetes, *P*-value < 0.0001; none vs. diabetes and stroke, *P*-value < 0.0001; none vs. diabetes and MI, *P*-value < 0.0001; diabetes vs. diabetes and stroke *P*-value = 0.015).

[i] Tukey HSD test for posthoc pairwise comparison revealed significant differences between groups (none vs. diabetes, *P*-value < 0.0001).

[j] Calculated as weight in kilograms divided by height in meters squared. Outliers were excluded from the analysis.

[k] Tukey HSD test for *post hoc* pairwise comparison revealed significant differences between groups (none vs diabetes, $P < 0.0001$; none vs diabetes and MI, $P = 0.040$).

was no statistical difference in the probabilities of death between subjects with diabetes and stroke vs those with diabetes and MI in both cohorts, and subjects with diabetes, stroke, and MI vs those with diabetes and MI in the health examination cohort.

Table 2 also presents the adjusted HRs for mortality in our whole cohort and the health examination cohort. Compared with the reference group, the adjusted HRs for mortality in the whole cohort were 1.70 (95% CI, 1.66 to 1.75) for participants with a history of diabetes, 3.66 (95% CI, 3.32 to 4.03) in those with a history of both diabetes and stroke, 3.56 (95% CI, 3.06 to 4.14) in those with diabetes and MI, and 4.79 (95% CI, 3.05 to 7.50) in those with diabetes, stroke, and MI (Table 2). In the health examination cohort, the fully adjusted HRs for mortality were 1.93 (95% CI, 1.82 to 2.05), 3.60 (95% CI, 2.78 to 4.66), 4.66 (95% CI, 2.96 to 6.41), and 6.71 (95% CI, 1.68 to 26.85), respectively.

The trend of increasing HRs for all-cause mortality according to disease status was similarly observed in both male (Supplemental Table 1) and female (Supplemental Table 2) participants.

Table 2. All-Cause Mortality Among Study Participants According to Disease Status at Baseline

Disease Status at Baseline	No. of Participants	No. of Deaths	Person-Years	Mortality Rate[a]	Adjusted HR (95% CI)[b]	Fully Adjusted HR (95% CI)[c]
Whole cohort						
Diabetes, stroke, and MI	25	19	164.5	115.52	4.79 (3.05–7.50)	
Diabetes and MI	326	169	2547.5	66.34	3.56 (3.56–4.14)	
Diabetes and stroke	784	418	6223.4	67.17	3.66 (3.32–4.03)	
Diabetes	40,026	7765	391,031.6	19.86	1.70 (1.66–1.75)	
None	528,670	41,878	6,114,552.2	6.85	1.00	
Health examination cohort						
Diabetes, stroke, and MI	2	2	14.0	142.95	5.28 (1.32–21.11)	6.71 (1.68–26.85)
Diabetes and MI	63	26	558.8	46.53	4.82 (3.28–7.10)	4.36 (2.96–6.41)
Diabetes and stroke	158	59	1436.8	41.06	3.53 (2.73–4.57)	3.60 (2.78–4.66)
Diabetes	12,305	1614	122,317.6	13.20	1.81 (1.71–1.91)	1.93 (1.82–2.05)
None	145,620	6893	1,714,800.8	4.02	1.00	1.00

[a]Mortality rates were calculated assuming an exact Poisson distribution and expressed as 1000 person-years.

[b]HRs were calculated using Cox proportional hazards regression models adjusted for age (per 5-year interval), sex, hypertension, dyslipidemia, and chronic kidney disease at baseline in whole cohort.

[c]HRs were calculated using Cox proportional hazards regression models adjusted for age (per 5-year interval), sex, hypertension, dyslipidemia, chronic kidney disease, BMI, smoking and drinking habits, and physical activity at baseline in health examination cohort. There were missing values in BMI (0.08%). We applied a multiple imputation procedure using a Markov Chain Monte Carlo method to impute missing values of BMI. The multiply imputed data sets were analyzed by the same analytical procedures, and the results from these analyses were combined to obtain an overall estimate.

Estimates of life-years lost associated with diabetes

A life table was constructed using calculations to estimate the life expectancy of our whole cohort (Supplemental Table 3). Using these results, the age-specific absolute differences in life expectancies of our cohort population according to cardiometabolic comorbidities were obtained (Supplemental Tables 4 and 5). The years of life lost by disease status of the cohort participants at baseline, compared with the reference group, are illustrated in Fig. 3(a). Generally, the difference in life expectancy in each age group increased with an increasing number of cardiometabolic comorbidities accompanied, compared with those in the reference group [Fig. 3(a)]. In addition, the difference in life expectancy was the highest in the youngest age group and declined with increasing age across all cardiometabolic categories [Fig. 3(a); Supplemental Table 4). For example, the difference in life expectancy was 23.79 in participants with diabetes, stroke, and MI and continually decreased to 8.71 in those between 75 and 79 years of age [Fig. 3(a); Supplemental Table 4).

When we used the 2002 National Life Table data as the reference group, similar patterns in life expectancy of each age group according to the increasing number of cardiometabolic comorbidities and associated estimates of life-years lost across age groups were observed [Fig. 3(b); Supplemental Table 5).

Contribution of age to the loss of life expectancy associated with diabetes

As shown in Table 3, the overall life-years lost to diabetes in our whole cohort were 6.10 compared with those without diabetes. Compared with the reference group, the estimated life-years lost were 16.68 in those with a history of both diabetes and stroke, 21.10 in those with diabetes and MI, and 23.80 in those with all three conditions (Table 3). The maximum contribution of age to the reduction of life expectancy was observed in younger age groups, which peaked at 45 to 49 years of age (12.04%) in participants with a history of diabetes; 40 to 44 years (33.17%) in those with a history of both diabetes and stroke, 35 to 39 years (33.65%) in those with diabetes and MI, and 45 to 49 years (36.79%) in those with all three conditions (Table 3). The years and contributions of age to life expectancy were significantly reduced in subjects older than 60 years of age (Table 3).

Discussion

This large, population-based, retrospective cohort study revealed the risk of mortality and estimates of age-specific reductions in life expectancy associated with different combinations of cardiometabolic morbidity (*i.e.,* a history of diabetes, stroke, and MI). As expected, individuals with diabetes showed an approximate 70% increased relative risk of mortality compared with those without diabetes (Table 2). The mortality rates and the age, sex, and other covariates adjusted HRs for mortality further increased significantly with an additional history of MI or stroke, or both. For instance, participants with only one of the studied conditions had an HR for mortality of about 1.7; for the combination of diabetes and one cardiovascular comorbidity (*i.e.,* stroke or MI), the HR was about 3.5; and for a combination of all three conditions, the risk of death reaches approximately five-fold

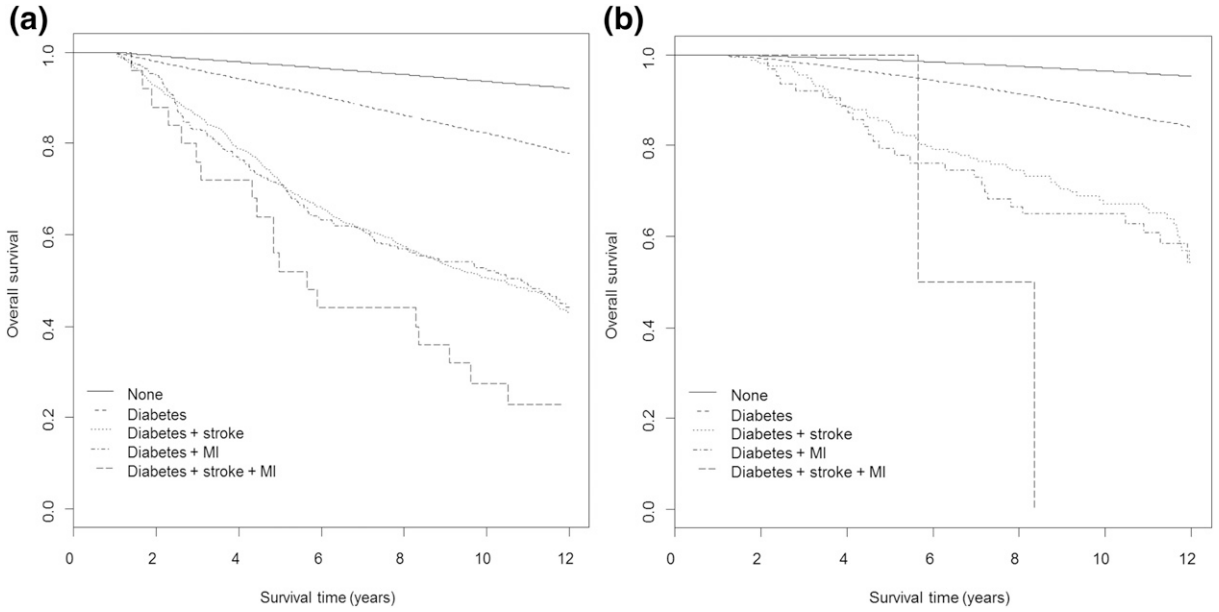

Figure 2. Survival curves (a) in the whole cohort and (b) in the health examination cohort. Log-rank tests revealed $P < 0.001$ for all comparisons except the comparisons between subjects with diabetes and stroke vs those with diabetes and MI in both cohorts ($P = 0.887$ and 0.587, respectively) and between subjects with diabetes, stroke, and MI vs those with diabetes and MI in the health examination cohort ($P = 0.074$).

(Table 2). This trend remained consistent in both the health examination cohort analysis (Table 2) and sex-specific analysis (Supplemental Tables 1 and 2).

The increasing pattern of mortality risk with increasing cardiometabolic multimorbidity was also reported in a previous study that used data from the Emerging Risk Factors Collaboration and the UK Biobank (17). In this study, the HRs of all-cause mortality were ~2, 4, and 8 in those patients who had combinations of one, two, or three cardiometabolic morbidities, respectively (17). Similarly, another study using data from the Framingham Heart Study showed that people with diabetes and CVD had a significantly higher HR for mortality compared with those with diabetes but without CVD (18), thereby highlighting the negative, additive, and nonoverlapping effects exerted by the combination of diabetes and CVD.

Multiple studies have reported higher excess mortality attributable to type 2 diabetes in those younger than age 55 years compared with older people (2, 10, 19). Also, a recent study estimating the cumulative survival of people according to their cardiometabolic multimorbidity observed the maximum years of life lost to diabetes in their youngest age group (*i.e.*, age 40 through 49 years) and its gradually attenuating tendency with increasing age (17). Likewise, in our study, the age-specific contributions to life expectancy were generally highest in the younger age groups (except a few outliers due to a small number of subjects) and attenuated with increasing age, regardless of disease status (Table 3). In line with previous findings

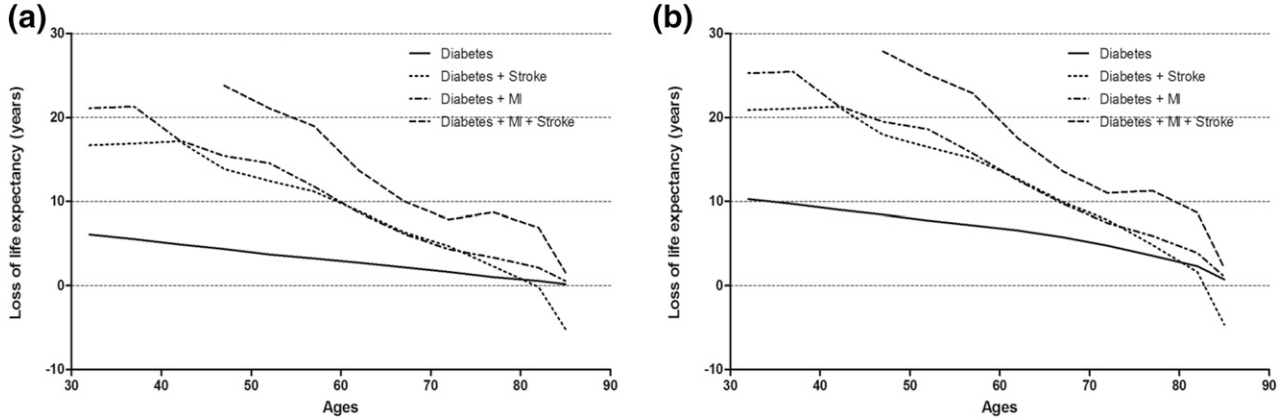

Figure 3. Modeling of the years of life lost according to disease status of the participants at baseline compared with (a) those participants free of diabetes, stroke, and MI; and (b) in reference to the 2002 National Life Tables for Korea.

Table 3. Contribution of Age (Absolute Year and Percent Contributions) to Life Expectancy According to Cardiometabolic Morbidity[a]

Age Group, Year Range	Diabetes		Diabetes and Stroke		Diabetes and MI		Diabetes, Stroke, and MI	
	Total Effect of Age, y	Contribution of Age, %	Total Effect of Age, y	Contribution of Age, %	Total Effect of Age, y	Contribution of Age, %	Total Effect of Age, y	Contribution of Age, %
30–34	0.65	10.58	−0.19	−1.12	−0.19	−0.89	NA	NA
35–39	0.76	12.38	−0.28	−1.67	7.10	33.65	NA	NA
40–44	0.64	10.53	5.53	33.17	2.86	13.56	NA	NA
45–49	0.73	12.04	2.17	13.03	1.41	6.68	8.75	36.79
50–54	0.55	9.09	1.90	11.39	3.59	17.02	5.73	24.07
55–59	0.56	9.22	2.81	16.85	2.87	13.60	6.73	28.28
60–64	0.60	9.79	2.23	13.39	1.65	7.83	1.64	6.89
65–69	0.57	9.38	1.17	7.04	0.90	4.27	0.54	2.26
70–74	0.55	8.96	0.95	5.67	0.42	2.00	0.08	0.33
75–79	0.30	4.94	0.39	2.33	0.32	1.50	0.40	1.70
80–84	0.15	2.50	0.16	0.96	0.15	0.70	−0.08	−0.32
85+	0.04	0.60	−0.17	−1.04	0.02	0.08	0.00	0.01
Total	6.10	100.00	16.68	100.00	21.10	100.00	23.80	100.00

Abbreviation: NA, not available.

[a]Reference: diabetes, stroke, MI-free group.

(2, 10, 17, 19), our study results strongly suggest that young diabetic individuals, especially those with cardiovascular comorbidities, are much more likely to have their lifespan shortened compared with their counterparts who do not have diabetes and are older.

In general, the overall and age-specific reductions in life expectancy observed in our study are slightly less than those reported in previous studies of other ethnic populations. For instance, the overall life-years lost to diabetes were 6.10 in our cohort (Table 3), whereas it was ~7.8 to 8.4 in a study that used the Framingham Heart study data (18). Also, a large study of the noninstitutionalized US population showed a median reduced life expectancy of 8 years in the diabetic population 55 to 64 years old, and a 4-year reduction in the diabetic population 65 to 74 years old (19). Another study using US NHIS data found diabetes decreased life years by 3.30 to 18.74 years depending on age, sex, and race (20). In contrast, the lost years of life expectancy in our cohort were ~3 years for those 55 to 64 years of age and ~2 years for those 65 to 74 years of age [Fig. 3(a); Supplemental Table 4), which were much less than those reported in the aforementioned studies of Western populations (19, 20). These differences in life expectancy could be caused by multiple factors. First, some of these studies (18, 19) were conducted in the time during which treatment with statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and antiplatelet agents was much less common practice (21). Therefore, our study, with a more recent dataset, could have led to more favorable results. Second, many of these studies did not subcategorize diabetic subjects according to the presence of cardiovascular comorbidity and its types (18–20). Thus, the additive and malicious effects caused by the combination of diabetes and cardiovascular complications could have been mixed into the single category of "having diabetes." However, a few recent studies that considered cardiovascular comorbidity in their analyses also observed greater losses of life-years to cardiometabolic multimorbidity in a stepwise manner (17, 18), implying that subject categorization is not a major contributor to this difference.

Last, it is plausible that ethnic differences could have resulted in the more favorable life expectancy in our study, as suggested by previous studies (20, 22). It is well known that the pathophysiology and epidemiology of Asian type 2 diabetes differs from those in Western populations (4, 5, 23, 24). For instance, the high proportion of body fat and prominent abdominal obesity in Asian people compared with those of European origin with similar BMI levels reflect a higher predisposition to insulin resistance at a lesser degree of obesity compared with people of European descent (25, 26). Moreover, Asian people exhibit an earlier onset of impaired insulin secretion (25, 26). These ethnic differences in the pathophysiology of diabetes may be responsible for the development of type 2 diabetes in Asian populations in a much shorter time, in a younger age group, and in people with much lower BMI (4). Therefore, it is possible that treatment with lifestyle modification and medication at younger ages before the development of macrovascular disease may have slowed the progression of atherosclerosis and lowered the risk of cardiovascular death in Asian people with type 2 diabetes (22).

Our study has several strengths that make it different from previous studies. First, to our knowledge, this was

the first study to evaluate and observe the reduced life expectancy among Asians with diabetes compared with people without such conditions. In a few previous studies that investigated the ethnic differences within a single country, white and black races were the majority of the study populations; people with Korean or East Asian backgrounds were categorized as "Others," along with people from other various Asian backgrounds. However, because the characteristics of type 2 diabetes may vary even within Asian countries (4), the ethnic differences found in the aforementioned studies (20, 22) could not have been generalized to East Asian populations. Second, detailed categorization of our cohort population using different combinations of CVD enabled us to delineate the additive effect of cardiovascular multimorbidity on mortality and life expectancy. Third, we have calculated and shown the age-specific contribution to the shortening of life expectancy in our cohort (Table 3), suggesting that not only the age at diagnosis but also the current age of an individual with diabetes can be a risk determinant in predicting the loss of life expectancy. Last, this study used a large and national sample of patients with diabetes that allowed for a comprehensive understanding and ascertainment of information on mortality and life expectancy.

Despite these strengths, our study has several limitations. First, our study only included people with type 2 diabetes and, hence, did not reflect information on mortality and life expectancy in people with type 1 diabetes in Korea. However, a much greater proportion of the diabetic population is diagnosed with type 2 diabetes in Korea (27); thus, we believe that our results are applicable to the majority of the Korean diabetic population. Second, because we defined type 2 diabetes, stroke, MI, and other covariates based on the presence of ICD-10 codes (and the prescription records of antidiabetic drugs when defining type 2 diabetes), it might have under- or overestimated the actual number of aforementioned conditions. Last, we did not have a sufficient number of participants younger than 45 years. Hence, the absolute differences in life expectancy in the category of participants with diabetes, stroke, and MI could not be calculated (Table 3). Similarly, because information on other covariates, such as lifestyle habits and BMI, could not be obtained in the whole cohort, the mortality risk according to the cardiovascular multimorbidity might not represent the actual risk, as is the case with all epidemiological studies.

In conclusion, for the first time in Asia, to our knowledge, we observed the additive mortality risk and significantly shorter age-specific life expectancy in people with type 2 diabetes, depending on the number of cardiometabolic morbidities. Younger people, especially those with multimorbidity, lost a substantial amount of their life-years to diabetes compared with those without diabetes, stroke, and MI, despite being of the same age. Although the extent of the mortality risk and loss of life expectancy was less than that in Western studies, our results suggest that young Asians with diabetes should be followed and managed more stringently according to their cardiovascular comorbidities.

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References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004;**27**(5):1047–1053.
2. Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjörnsdottir S, Wedel H, Clements M, Dahlqvist S, Lind M. Excess mortality among persons with type 2 diabetes. *N Engl J Med*. 2015;**373**(18):1720–1732.
3. Sharma MD, Farmer JA, Garber A. Type 2 diabetes and cardiovascular risk factors. *Curr Med Res Opin*. 2011;**27**(Suppl 3):1–5.
4. Yoon KH, Lee JH, Kim JW, Cho JH, Choi YH, Ko SH, Zimmet P, Son HY. Epidemic obesity and type 2 diabetes in Asia. *Lancet*. 2006;**368**(9548):1681–1688.
5. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. *Ann N Y Acad Sci*. 2013;**1281**:64–91.
6. Nanditha A, Ma RC, Ramachandran A, Snehalatha C, Chan JC, Chia KS, Shaw JE, Zimmet PZ. Diabetes in Asia and the Pacific: implications for the global epidemic. *Diabetes Care*. 2016;**39**(3):472–485.
7. Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet*. 2006;**368**(9529):29–36.
8. Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, Holme I, Njølstad I, Fletcher A, Nilsson P, Lewington S, Collins R, Gudnason V, Thompson SG, Sattar N, Selvin E, Hu FB, Danesh J; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting

glucose, and risk of cause-specific death. *N Engl J Med*. 2011; **364**(9):829–841.
9. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, Deanfield J, Smeeth L, Timmis A, Hemingway H. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people. *Lancet Diabetes Endocrinol*. 2015;**3**(2):105–113.
10. Kang YM, Kim YJ, Park JY, Lee WJ, Jung CH. Mortality and causes of death in a national sample of type 2 diabetic patients in Korea from 2002 to 2013. *Cardiovasc Diabetol*. 2016;**15**(1):131.
11. Kim NH, Lee J, Kim TJ, Kim NH, Choi KM, Baik SH, Choi DS, Pop-Busui R, Park Y, Kim SG. Body mass index and mortality in the general population and in subjects with chronic disease in Korea: a nationwide cohort study (2002-2010). *PLoS One*. 2015;**10**(10): e0139924.
12. Ko SH, Kim DJ, Park JH, Park CY, Jung CH, Kwon HS, Park JY, Song KH, Han K, Lee KU, Ko KS; Task Force Team for Diabetes Fact Sheet of the Korean Diabetes Association. Trends of antidiabetic drug use in adult type 2 diabetes in Korea in 2002-2013: nationwide population-based cohort study. *Medicine (Baltimore)*. 2016;**95**(27):e4018.
13. Statistics Korea. Korean standard classification of diseases and causes of death (KCD-7). 2016. https://kssc.kostat.go.kr:8443/ksscNew_web/ekssc/main/main.do#. Accessed April 1, 2016.
14. Jee SH, Sull JW, Park J, Lee SY, Ohrr H, Guallar E, Samet JM. Body-mass index and mortality in Korean men and women. *N Engl J Med*. 2006;**355**(8):779–787.
15. Service KSI. National Life Table 2002. [In Korean] http://kosis.kr/statisticsList/statisticsList_01List.jsp?vwcd=MT_ZTITLE&parentId=A#SubCont. Accessed December 1, 2016.
16. Arriaga EE. Measuring and explaining the change in life expectancies. *Demography*. 1984;**21**(1):83–96.
17. Di Angelantonio E, Kaptoge S, Wormser D, Willeit P, Butterworth AS, Bansal N, O'Keeffe LM, Gao P, Wood AM, Burgess S, Freitag DF, Pennells L, Peters SA, Hart CL, Håheim LL, Gillum RF, Nordestgaard BG, Psaty BM, Yeap BB, Knuiman MW, Nietert PJ, Kauhanen J, Salonen JT, Kuller LH, Simons LA, van der Schouw YT, Barrett-Connor E, Selmer R, Crespo CJ, Rodriguez B, Verschuren WM, Salomaa V, Svärdsudd K, van der Harst P, Björkelund C, Wilhelmsen L, Wallace RB, Brenner H, Amouyel P, Barr EL, Iso H, Onat A, Trevisan M, D'Agostino RB, Sr, Cooper C, Kavousi M, Welin L, Roussel R, Hu FB, Sato S, Davidson KW, Howard BV, Leening MJ, Rosengren A, Dörr M, Deeg DJ, Kiechl S, Stehouwer CD, Nissinen A, Giampaoli S, Donfrancesco C, Kromhout D, Price JF, Peters A, Meade TW, Casiglia E, Lawlor DA, Gallacher J, Nagel D, Franco OH, Assmann G, Dagenais GR, Jukema JW, Sundström J, Woodward M, Brunner EJ, Khaw KT, Wareham NJ, Whitsel EA, Njølstad I, Hedblad B, Wassertheil-Smoller S, Engström G, Rosamond WD, Selvin E, Sattar N, Thompson SG, Danesh J; Emerging Risk Factors Collaboration. Association of cardiometabolic multimorbidity with mortality [published correction appears in JAMA. 2015;314(11):1179]. *JAMA*. 2015;**314**(1): 52–60.
18. Franco OH, Steyerberg EW, Hu FB, Mackenbach J, Nusselder W. Associations of diabetes mellitus with total life expectancy and life expectancy with and without cardiovascular disease. *Arch Intern Med*. 2007;**167**(11):1145–1151.
19. Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971-1993. *Diabetes Care*. 1998;**21**(7):1138–1145.
20. Leung MY, Pollack LM, Colditz GA, Chang SH. Life years lost and lifetime health care expenditures associated with diabetes in the U.S., National Health Interview Survey, 1997-2000. *Diabetes Care*. 2015;**38**(3):460–468.
21. Lutgers HL, Gerrits EG, Sluiter WJ, Ubink-Veltmaat LJ, Landman GW, Links TP, Gans RO, Smit AJ, Bilo HJ. Life expectancy in a large cohort of type 2 diabetes patients treated in primary care (ZODIAC-10). *PLoS One*. 2009;**4**(8):e6817.
22. Wright AK, Kontopantelis E, Emsley R, Buchan I, Sattar N, Rutter MK, Ashcroft DM. Life expectancy and cause-specific mortality in type 2 diabetes: a population-based cohort study quantifying relationships in ethnic subgroups. *Diabetes Care*. 2017;**40**(3): 338–345.
23. Ohn JH, Kwak SH, Cho YM, Lim S, Jang HC, Park KS, Cho NH. 10-year trajectory of β-cell function and insulin sensitivity in the development of type 2 diabetes: a community-based prospective cohort study. *Lancet Diabetes Endocrinol*. 2016;**4**(1):27–34.
24. Ramachandran A, Snehalatha C, Shetty AS, Nanditha A. Trends in prevalence of diabetes in Asian countries. *World J Diabetes*. 2012; **3**(6):110–117.
25. He Q, Horlick M, Thornton J, Wang J, Pierson RN, Jr, Heshka S, Gallagher D. Sex and race differences in fat distribution among Asian, African-American, and Caucasian prepubertal children. *J Clin Endocrinol Metab*. 2002;**87**(5):2164–2170.
26. Park YW, Allison DB, Heymsfield SB, Gallagher D. Larger amounts of visceral adipose tissue in Asian Americans. *Obes Res*. 2001;**9**(7): 381–387.
27. Kim DJ. The epidemiology of diabetes in Korea. *Diabetes Metab J*. 2011;**35**(4):303–308.