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Effect of socioeconomic deprivation on outcomes of diabetes complications in patients with type 2 diabetes mellitus: a nationwide population-based cohort study of South Korea

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ABSTRACT

Introduction This study aimed to examine the effect of socioeconomic deprivation on the outcomes of diabetes complications in patients with type 2 diabetes mellitus (T2DM).

Research design and methods We conducted a cohort study using claims data and 2005 national census data. We included of 7510 patients newly diagnosed with T2DM from 2004 to 2012 and aged 40 years or above. We excluded participants who had onset of diabetes complications and hospitalization within 1 year after initial onset T2DM, aged less than 40 years and with missing covariates. We used the regional socioeconomic deprivation index and classified study participants into five categories according to the quintile distribution. We calculated the adjusted HR and 95% CI for hospitalization related to diabetes complications and all-cause mortality by applying Cox proportional hazards model and the adjusted subdistribution hazards model. Results The percentages of participants in the first quintile (least deprived) to fifth quintile (most deprived) were 27.0%, 27.9%, 19.5%, 14.8%, and 10.8% for socioeconomic deprivation; 25.4%, 28.8%, 32.4%, 34.6%, and 37.6% for hospitalization due to diabetes complications; 1.3%, 2.1%, 2.5%, 2.9%, and 3.6% for deaths from diabetes complications; and 5.7%, 7.2%, 9.7%, 9.7%, and 13.1% for deaths from all causes, respectively. Participants with higher socioeconomic deprivation had a higher HR for hospitalization and mortality from all-cause and diabetes complications. These associations were the strongest among men and participants in their 40s in hospitalization related to diabetes complications, 50s in diabetes complicationsspecific mortality and 50s and 60s in all-cause mortality. Conclusions Patients with T2DM with high socioeconomic deprivation had higher hospital admission and mortality rates for diabetes complications than those with low deprivation. We cannot fully explain the effect of socioeconomic deprivation on diabetes outcomes. Therefore, further studies are needed in order to find underlying mechanisms for these associations.

INTRODUCTION

Diabetes is estimated to affect about 415 million adults worldwide; 5.5 million

Significance of this study

What is already known about this subject?

Individuals living in low-income households, as well as those of low socioeconomic status, have a higher risk of diabetes complications than those of other socioeconomic groups.

What are the new findings?

- Participants with higher socioeconomic deprivation have higher HR for hospital admission and mortality from all-cause and diabetes complications compared with those with lower socioeconomic deprivation.
- These associations were the strongest among men and participants in their 40s in hospitalization related to diabetes complications, 50s in diabetes complications-specific mortality and 50s and 60s in all-cause mortality.

How might these results change the focus of research or clinical practice?

The differences in medical and in social and economic factors may play an important role in the outcomes of diabetes complications. Health policy makers and professionals should consider these factors when formulating preventive strategies for adverse diabetes outcomes.

deaths are caused by diabetes in 2015. The prevalence rate of diabetes continues to rise and is expected to reach 10.4% by 2040.¹ Patients with type 2 diabetes mellitus (T2DM) have a high risk of complications such as heart disease, stroke, renal disease, and retinopathy.^{2–5} Although the mortality rate among people with diabetes is decreasing, they remain at a significantly higher risk of developing these complications than people without diabetes.⁶ Individuals living in low-income households, as well as those

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with low socioeconomic status, have a higher risk of diabetes complications than those of other socioeconomic groups.⁷⁻¹⁰ Low socioeconomic status is associated with many factors known to contribute to poor health outcomes, including decreased access to recommended preventive care, low care utilization, poor metabolic control and psychological pain.¹⁰ In addition, previous studies have proven that the results of diabetes complications differ according to an individual's socioeconomic status and from neighborhood to neighborhood.¹¹⁻¹⁶

Socioeconomic deprivation encompasses the current individual socioeconomic status and social relationships, community-level characteristics and gradients of socioeconomic position at the individual and community level.¹⁰¹⁷¹⁸ Socioeconomic position is a complex structure based on socially derived economic factors that determine the relative status of an individual or group within a society. The differences in socioeconomic status between the social strata can lead to inequalities in health.^{13 19 20}

Although many studies have assessed the association of socioeconomic deprivation with the incidence of diabetes complications and mortality due to diabetes, their study populations were mostly Western. This study aimed to examine the effect of socioeconomic deprivation on diabetes complications outcomes among Korean patients with T2DM.

METHODS

Study population

This study used a random sample of claims data from the Korean National Health Insurance Service, which included information about approximately 1 million patients. The data included unique anonymous number for each patient with age, sex, type of insurance, and a list of diagnoses according to the International Classification of Diseases version 10 (ICD-10). The dataset also contained claimed medical costs, prescribed drugs, and medical history.

We conducted a cohort study of patients newly diagnosed with T2DM (ICD-10 code: E11, except for E11.9), using a 2.5% stratified random sample. From 13893 patients diagnosed as having T2DM from 2004 to 2012, we excluded patients with a pre-existing diagnosis of T2DM, diabetes complications, and the use of diabetes medication from 2002 to 2003. Accordingly, we selected 9536 with newly diagnosed T2DM. Then, we excluded 2026 patients who were aged <40 years, died of diabetes complications within 1 year after the onset of T2DM, or had missing covariates. Finally, 7510 patients were enrolled in the study.

Predictor variables

Data from the national census conducted in 2005 were used to assess the socioeconomic deprivation index. The data were a 2% random sample from the nationwide population and publicly accessible through the Microdata Service System provided by Statistics Korea.

We focused mainly on socioeconomic deprivation indices in 250 regions using the 2005 Korean census data. Areas with relatively large and heterogeneous populations, ranging from 12000 to 630000, which are administratively defined in Korea as regions, were used as space units for analysis.²¹ A region is defined as the smallest citystate unit that can implement autonomous policies and the lowest statistical unit with official data. For area-level deprivation measures, the degree of urbanicity, which is designated by the government (metropolitan, urban, and rural), and a socioeconomic deprivation index was assigned to each region. The socioeconomic deprivation index was generated by modifying the Townsend and Carstairs index, which has been used in previous studies²¹⁻²³ and calculated by Kim and colleagues' methodology.²¹ For every region, we calculated the proportion of households: (1) living in an apartment, (2) without a car, (3) congested (>1.5 people/ room), (4) with a woman homeowner, (5) renting a home and (6) under substandard living conditions (without hot water supply, a flush toilet, or modern kitchen). In addition, we calculated the proportion of adults older than 25 years who were: (7) unemployed among high school graduates, (8) unemployed among the economically active, (9) employed manually and (10) who were older than 65 years. All proportions were z-standardized; we did not include home ownership and unemployment rate in further analysis since the factor analysis with varimax rotation showed that these factors differ from the others. Finally, we averaged z-standardized scores of the eight remaining proportions (households living in an apartment, households without cars, crowded conditions, women homeowners, and individuals with educational level lower than high school graduation among adults over 25 years of age) to constitute a regional deprivation index. A positive and high score implied a higher level of deprivation. We classified study participants into five categories according to the quintile distribution of the regional deprivation index (first quintile being least and fifth quintile most deprived).

Age was classified into four groups: 40-49, 50-59, 60-69, and ≥ 70 years. Household income was estimated using the health insurance premium and divided into tertiles. Medical aid was defined as non-payment of health insurance premiums, low income as the bottom 20% of health insurance premiums, middle income as 20%–80% of the premiums, and high income as the top 20% of premiums. The Charlson comorbidity index (CCI) was calculated for 1 year before the onset of T2DM. We included the use of insulin during the follow-up period in the analysis.

Outcome variables

We used ICD-10, fee-for-service, and prescribed drug codes to assess the incidence of T2DM, diabetes complications, hospital admissions, and mortality from diabetes complications including neurovascular disease, cardiovascular disease, end-stage renal disease, proliferative retinopathy, lower extremity arterial disease, diabetic foot, and autonomic neuropathy (online supplementary eTable 1). Mortality due to diabetes complication was defined as the occurrence of death 1 year following the onset of T2DM.

Statistical analysis

The baseline characteristics of the study population were analyzed descriptively using the χ^2 test, *t*-test, and analysis of variance. Thereafter, we calculated the adjusted HR and 95% CI for hospitalization related to diabetes complications and all-cause mortality by applying Cox proportional hazards model, and the adjusted subdistribution HR (sHR) and 95% CI for diabetes complications-specific mortality by applying Cox proportional subdistribution hazards model. In this model, we adjusted for these regional and individual characteristics: sex, age, household income, types of insurance, CCI, disability status, use of insulin treatment, classification of hospital visited, and year of onset of T2DM. The follow-up time was calculated from the onset of T2DM to the time of death due to diabetes complications, loss to follow-up, death from another cause, or to the end of the study on 15 December 2013 for those who did not have complications or did not die. Hence, the follow-up time was equivalent to the duration of diabetes. The number of hospital admissions and mortality rate due to diabetes complications, stratified by socioeconomic deprivation, were measured from the time of diagnosis, using the overall survival after 1 year of T2DM onset as the event variable. Lastly, we conducted subgroup analyses by sex and age. The rates of events were calculated as the number of events per 1000 personyears along with the 95% CI using the standard life table analysis technique. All statistical analyses were performed using SAS V.9.4 and R V.3.6 (The R Development Core Team, Vienna, Austria). Statistical significance was defined as p<0.05.

RESULTS

Figure 1 shows the socioeconomic deprivation scores according to the 250 regions. The deeper color represents a higher socioeconomic deprivation score than the light color. Socioeconomic deprivation scores ranged from -5.16 to 8.72.

Table 1 shows the overall demographic characteristics of the study population. We observed a total of 7510 participants with T2DM. The percentages of participants from the first quintile to the fifth quintile of socioeconomic deprivation were 27.0% (n=2027), 27.9% (n=2096), 19.5% (n=1467), 14.8% (n=1111), and 10.8% (n=809). According to socioeconomic deprivation groups from the first to the fifth quintile, 25.4% (n=514), 28.8% (n=603), 32.4% (n=476), 34.6% (n=384), and 37.6% (n=304) were hospitalized due to diabetes complications; 1.3% (n=26), 2.1% (n=44), 2.5% (n=36), 2.9% (n=32), and 3.6% (n=29) died from diabetes complications; and 5.7% (n=115), 7.2% (n=151), 9.7% (n=142),



Figure 1 The socioeconomic deprivation scores according to the 250 regions.

9.7% (n=108), and 13.1% (n=106) died from all causes, respectively (online supplementary eTable 2).

Figure 2 shows the cumulative incidence function of diabetes complications-specific mortality, other-cause mortality, and hospitalization with diabetes complications assessed using Gray's test according to socioeconomic deprivation with competing risks. The cumulative diabetes complications mortality and hospital admission rates for the fifth quintile group were higher than those for other groups (Gray's test: p=0.0015). The diabetes complications-related mortality rates per 1000 patient-years were 1.83 (95% CI 1.26 to 2.67), 2.91 (95% CI 2.16 to 3.91), 3.47 (95% CI 2.50 to 4.80), 4.04 (95% CI 2.86 to 5.71), and 5.10 (95% CI 3.54 to 7.34) from the first quintile to the fifth quintile, respectively (online supplementary eTable 3).

Table 2 shows the adjusted HRs of outcomes using Cox proportional subdistribution hazards models according to socioeconomic deprivation and covariates. The second (HR 1.15, 95% CI 1.02 to 1.30), third (HR 1.28, 95% CI 1.13 to 1.45), fourth (HR 1.42, 95% CI 1.24 to 1.62) and fifth (HR 1.48, 95% CI 1.28 to 1.71) quintile of socioeconomic deprivation had higher HRs for hospitalization related to diabetes complications compared with the first quintile. For mortality from diabetes complications, the sHRs of the third (sHR 1.72, 95% CI 1.03 to 2.87), fourth (sHR 2.07, 95% CI 1.22 to 3.51) and fifth (sHR 2.38, 95% CI 1.39 to 4.07) quintile were higher than those of the first quintile. The third (HR 1.64, 95% CI 1.28 to 2.11), fourth (HR 1.62, 95% CI 1.24 to 2.11), and

Table 1 The overall characteristics of the study population

			Socioeconomic deprivation										
	Total		First qu (least)	iintile	Secon	d quintile	Third q	juintile	Fourth	quintile	Fifth ((most	quintile :)	
Variables	Ν	%	Ν	%	Ν	%	Ν	%	Ν	%	Ν	%	P value
Sex								·					0.013
Men	4455	59.3	1237	61.0	1271	60.6	837	57.1	663	59.7	447	55.3	
Women	3055	40.7	790	39.0	825	39.4	630	42.9	448	40.3	362	44.7	
Age (years)													<0.001
40–49	2273	30.3	678	33.4	662	31.6	429	29.2	314	28.3	190	23.5	
50–59	2519	33.5	701	34.6	694	33.1	483	32.9	378	34.0	263	32.5	
60–69	1773	23.6	440	21.7	486	23.2	356	24.3	267	24.0	224	27.7	
70+	945	12.6	208	10.3	254	12.1	199	13.6	152	13.7	132	16.3	
Household income													<0.001
First tertile	2898	38.6	686	33.8	750	35.8	622	42.4	453	40.8	387	47.8	
Second tertile	1983	26.4	543	26.8	527	25.1	386	26.3	306	27.5	221	27.3	
Third tertile	2629	35.0	798	39.4	819	39.1	459	31.3	352	31.7	201	24.8	
Types of insurance													<0.001
Self-employed insured or NHI	6767	90.1	1891	93.3	1933	92.2	1287	87.7	970	87.3	686	84.8	
Medical aid	743	9.9	136	6.7	163	7.8	180	12.3	141	12.7	123	15.2	
Charlson Comorbidity Inde	x												0.172
0	3724	49.6	1032	50.9	1070	51.0	702	47.9	518	46.6	402	49.7	
1	2457	32.7	650	32.1	674	32.2	489	33.3	392	35.3	252	31.1	
2+	1329	17.7	345	17.0	352	16.8	276	18.8	201	18.1	155	19.2	
Disability													0.461
Healthy	6892	91.8	1871	92.3	1939	92.5	1331	90.7	1005	90.5	746	92.2	
Severe	158	2.1	43	2.1	39	1.9	35	2.4	25	2.3	16	2.0	
Mild	460	6.1	113	5.6	118	5.6	101	6.9	81	7.3	47	5.8	
Onset of diabetes complication	ations												0.461
No	537	7.2	139	6.9	166	7.9	100	6.8	82	7.4	50	6.2	
Yes	6973	92.8	1888	93.1	1930	92.1	1367	93.2	1029	92.6	759	93.8	
Insulin treatment													0.765
No	7067	94.1	1908	94.1	1967	93.8	1381	94.1	1054	94.9	757	93.6	
Yes	443	5.9	119	5.9	129	6.2	86	5.9	57	5.1	52	6.4	
Hospital classification													<0.001
General hospital	995	13.2	290	14.3	326	15.6	187	12.7	103	9.3	89	11.0	
Hospital	407	5.4	96	4.7	113	5.4	61	4.2	88	7.9	49	6.1	
Clinic	5597	74.5	1546	76.3	1543	73.6	1115	76.0	829	74.6	564	69.7	
Others	511	6.8	95	4.7	114	5.4	104	7.1	91	8.2	107	13.2	
Year of onset type 2 diabet	es												0.070
2004	1967	26.2	528	26.0	529	25.2	391	26.7	289	26.0	230	28.4	
2005	1863	24.8	524	25.9	521	24.9	351	23.9	278	25.0	189	23.4	
2006	1195	15.9	309	15.2	372	17.7	226	15.4	170	15.3	118	14.6	
2007	564	7.5	173	8.5	156	7.4	113	7.7	72	6.5	50	6.2	
2008	801	10.7	188	9.3	197	9.4	184	12.5	126	11.3	106	13.1	
2009	444	5.9	120	5.9	120	5.7	82	5.6	71	6.4	51	6.3	
2010	268	3.6	75	3.7	75	3.6	54	3.7	39	3.5	25	3.1	
2011	280	3.7	75	3.7	88	4.2	41	2.8	51	4.6	25	3.1	
2012	128	1.7	35	1.7	38	1.8	25	1.7	15	1.4	15	1.9	
Total	7510	100.0	2027	27.0	2096	27.9	1467	19.5	1111	14.8	809	10.8	

NHI, National Health Insurance.



Cumulative incidence of hospitalization with diabetes complications according to socioeconomic deprivation

Cumulative incidence of diabetes complications-specific mortality (DCSM) and other-cause mortality (OCM) according to socioeconomic deprivation



Figure 2 Cumulative incidence function of DCSM and OCM and hospitalization with diabetes complications according to socioeconomic deprivation.

fifth (HR 2.05, 95% CI 1.57 to 2.68) quintile had higher HR for all-cause mortality than the first quintile. The HR of the second quintile for all cause and the sHR of the second quintile for diabetes complications-specific mortality were not statistically significant.

Figure 3 shows the results of the subgroup analyses of adjusted sHR for diabetes-specific mortality using Cox proportional subdistribution hazards model and for hospitalization related to diabetes complications and allcause mortality using Cox proportional hazards model. Among men, those in the second, third, fourth, and fifth quintile of socioeconomic deprivation had higher HR for hospitalization compared with those in the first quintile. Among women, however, only those in the fourth and fifth quintile showed significantly higher HR for hospitalization than those in the first quintile. For mortality from

Table 2 The adjusted subdistribution HRs of outcomes using Cox proportional hazards models with competing risks according to socioeconomic deprivation and covariates											
	Socioeconomic deprivation										
	First quintile (least)	Second quintile	Third quintile	Fourth quintile	Fifth quintile (most)						
Variables	Reference	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)						
Hospitalization with diabetes complications	1.00	1.15 (1.02 to 1.30)	1.28 (1.13 to 1.45)	1.42 (1.24 to 1.62)	1.48 (1.28 to 1.71)						
Mortality with diabetes complications	1.00	1.60 (0.98 to 2.60)	1.72 (1.03 to 2.87)	2.07 (1.22 to 3.51)	2.38 (1.39 to 4.07)						
All-cause mortality	1.00	1.22 (0.96 to 1.56)	1.64 (1.28 to 2.11)	1.62 (1.24 to 2.11)	2.05 (1.57 to 2.68)						

Analysis was adjusted for the following covariates: sex, age, household income, types of insurance, Charlson Comorbidity Index, disability, onset of diabetes complications, insulin treatment, hospital classification, and year of onset type 2 diabetes.



Figure 3 Adjusted HR for hospitalization and all-cause mortality and adjusted subdistribution HR for diabetes complications mortality according to subgroups.

diabetes complications in men, the fourth and fifth quintile had higher sHR than the first quintile. There were no statistically significant differences among women. Similar trends were observed for all-cause mortality. Among the participants in their 40s, only the third, fourth, and fifth quintile group had higher HRs for hospitalization than the first quartile group. However, similar trends were observed for the group of participants in only their 50s in diabetes complications-specific and in their 50s and 60s in all-cause mortality.

DISCUSSION

This study examined the effect of socioeconomic deprivation on mortality from diabetes complications among patients with T2DM under the national health insurance system of Korea. Patients with T2DM with high socioeconomic deprivation had a significantly higher rate of diabetes-related outcomes and all-cause mortality than those with low socioeconomic deprivation, after controlling for a variety of covariates. Moreover, these associations were the strongest among men and participants in their 40s in hospitalization related to diabetes complications, 50s in diabetes complications-specific mortality, and 50s and 60s in all-cause mortality.

Neighborhoods or communities can play an important role in the health status of residents through the availability of healthcare and general attitude to health and health behaviors.¹⁰¹⁸ In South Korea, there is a difference in regional characteristics between the metropolitan and rural areas due to the surge in economic growth and modernization, and migration of population from rural to urban areas.²⁴⁻²⁶ Previous studies reported that rural areas had lower income, more unmet medical needs, higher proportion of people aged 65 years or above, poor accessibility to healthcare service, and underutilization of health service manpower compared with metropolitan areas.^{22 27–30} However, the degree of urbanity can neither explain our age subgroup results nor the fact that there were no significant differences in older patients. A study in the UK showed similar inverse association between socioeconomic status and the prevalence of T2DM in the middle years of life.⁷ This factor may not be able to explain the relationship between the prevalence of diabetes and the socioeconomic status, and it may even underestimate this relationship.

Previous studies have shown that deprivation level is associated with prevalence of T2DM, chronic diabetes complications, mortality, and hospitalization due to diabetes complications.^{31–37} The Whitehall study and the WHO multinational study showed that people of lower socioeconomic status had 1.7 times higher all-cause mortality and 2.1 times higher mortality from cardiovas-cular disease than those in higher classes.³⁸ A Swedish study showed that low neighborhood socioeconomic

status is associated with 1.1 times higher OR for coronary heart disease in men and 1.2 times in women.³⁷ In patients with diabetes, factors such as low income, low education, and living in poor areas are related to higher smoking rates, less frequent blood sugar monitoring, less exercise, and poor access to primary and professional care.^{39–42} Therefore, patients with diabetes living in economically disadvantaged areas are likely to have a high risk of hospitalization and mortality from all causes and diabetes complications. It is a reasonable hypothesis that these factors may partly or substantially explain our findings. However, this is an ecological study based on aggregated data at area level, and our results cannot distinguish between contextual and compositional effects.

The observed associations are stronger in men than in women. The differences in biology, culture, lifestyle, environment, and socioeconomic status between men and women may lead to differences in predisposition, development, and clinical presentation of cardiovascular diseases.⁴³ Previous studies have reported that genetic effects, epigenetic mechanisms, nutritional factors, and sedentary lifestyle affect the risk and complications of diabetes differently in both sexes.⁴⁴ We believe that men are likely to engage in unhealthy behavior such as binge drinking, heavy smoking, and consumption of non-nutritious foods. Together with high socioeconomic deprivation, these factors have a synergistic effect on hospital admission and mortality due to diabetes complications.

In the subgroup analysis according to age groups, participants in their 50s showed a strong relationship between socioeconomic deprivation and mortality from diabetes complications and all-cause mortality. A previous study demonstrated that a high proportion of working-age people are still dying from diabetes.¹ One possible explanation is that young patients are likely to be obese, have higher insulin resistance, and more aggressive treatment may be needed to control blood sugar levels.⁴⁵ Another possibility may be the increased attention paid to medications prescribed to older people to control their blood sugar, suggesting the need to improve blood sugar management in young patients.^{46 47} Moreover, this could be the result of a survival effect, as people with diabetes in lower socioeconomic groups die prematurely due to complications such as cardiovascular disease.³⁸

Some limitations of this study are worth mentioning. First, other important covariates may have been omitted, such as clinical data regarding body mass index, blood pressure, fasting glucose level, and hemoglobin A1c level; education level; health behaviors such as alcohol consumption, smoking, and physical activity; and other individual social factors. Although such factors are strongly associated with diabetes complications outcomes, they were not included because of the limited information available in the claims data. Moreover, we could not consider long-standing diabetes that went undiagnosed. Second, we could not consider the consistency of individual socioeconomic deprivation within any region because of the lack of information. We could not differentiate between contextual and compositional effects because our findings are based on aggregated data at area level. This might have caused the inconsistent results between men and women, age groups, and household income levels. Therefore, caution is needed when interpreting these results. Further studies need to consider both area-level and individual-level socioeconomic deprivation as factors that influence diabetes outcomes. Third, we could not measure diabetes severity. However, we tried to account for diabetes severity by including the use of insulin and CCI in our analysis. Fourth, although regional characteristics were adjusted using some regional information, we could not fully control regional factors because of the limitation of the data. Finally, we could not validate our study modeling approach and diagnosis of outcomes. To overcome this, we defined the diagnosis of outcomes using both ICD-10 and medicine codes.

The present findings are valuable because of the following strengths of our study. First, we used a stratified random sample of a large and comprehensive nationallevel dataset, which included patients with diabetes with a long follow-up period, thus securing the external validity of the study. Second, as this study was an observational longitudinal cohort study, the association between the independent variables and survival is more confirmative than it would have been if obtained using a crosssectional study. Finally, we considered a subdistribution hazard model because the naive Kaplan-Meier analysis with competing events as censored observations may be biased.⁴⁸ This model yields a measure of association that reflects both the association of diabetes with a causespecific death and the contribution of competing events by actively maintaining individuals with and without diabetes in the risk set.⁴⁹

In conclusion, patients with T2DM with high socioeconomic deprivation had higher hospitalization and mortality rates due to diabetes complications than those with low deprivation. This effect was strongest among men and participants in their 50s. Although we cannot fully explain the effect of socioeconomic deprivation on diabetes outcomes, we believe that the difference in social and economic factors, as well as in medical factors, may play a key role. Health policy makers and professionals should consider these factors when formulating preventive strategies for adverse diabetes outcomes.

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Contributors D-WC conducted the design of the study, interpretation of data, and writing of the initial manuscript. D-WC, SAL and DWL conducted analysis of the data. JHJ, K-TH and SK reviewed the manuscript. E-CP is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed, contributed to, and approved the manuscript.

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