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The impact of sex on risk of cardiovascular disease and all-cause mortality in adults with or without diabetes mellitus: A comparison between the U.S. and Japan

Longjian Liu [a,*], Katsuyuki Miura [b,c], Aya Kadota [b,c], Akira Fujiyoshi [b,d], Edward J. Gracely [a,e], Fuzhong Xue [f], Zuolu Liu [g], Naoyuki Takashima [b], Naoko Miyagawa [b,h], Takayoshi Ohkubo [i], Hisatomi Arima [j], Akira Okayama [k], Tomonori Okamura [l], Hirotsugu Ueshima [b,c]

[a] Department of Epidemiology and Biostatistics, Drexel University Dornsife School of Public Health, Philadelphia, PA, USA
[b] Department of Public Health, Shiga University of Medical Science, Otsu, Shiga, Japan
[c] Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Otsu, Shiga, Japan
[d] Department of Hygiene, Wakayama Medical School, Wakayama, Japan
[e] Department of Family, Community, & Prevention Medicine, Drexel University College of Medicine, Philadelphia, PA, USA
[f] Department of Biostatistics, Shandong University School of Public Health, Jinan, Shandong, China
[g] Department of Neurology, University of California at Los Angeles, Los Angeles, CA, USA
[h] International Center for Nutrition and Information, National Institute of Biomedical Innovation, Health and Nutrition, Tokyo, Japan
[i] Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan
[j] Department of Preventive Medicine and Public Health, Fukuoka University, Fukuoka, Japan
[k] Research Institute of Strategy for Prevention, Tokyo, Japan
[l] Department of Preventive Medicine and Public Health, Keio University, Tokyo, Japan

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ABSTRACT

Aims: To test a hypothesis that women with diabetes mellitus (DM) versus those without DM had a significantly higher risk of heart disease (HD), stroke and all-cause mortality than their male counterparts in the U.S. as well as in Japan.
Methods: We analyzed two nationally representative datasets, one from the U.S. NHANES III cohort ($n = 13{,}169$), and the other from the Japan NIPPON DATA90 cohort ($n = 7445$). Hazard ratios (HRs) of DM for risk of mortality and sex-DM interaction effect on mortality were analyzed prospectively using Cox's proportional hazards regression models.
Results: Patients with DM had significantly higher mortality from HD, stroke and all-cause mortality in the U.S. and in Japan. However, the HRs of DM versus non-DM for HD and all-cause mortality were significantly higher in women compared to men in the U.S. (sex-DM interaction: HR = 1.59, p = 0.01, and 1.24, p = 0.045 for HD and all-cause mortality), but the sex-DM interaction effect was not statistically significant in the Japanese cohort.
Discussion: Patients with DM had a significantly higher risk of mortality than those without DM in the U.S. and Japan. However, women with DM versus those without DM had a higher relative risk of HD and all-cause mortality than their counterparts in men in the U.S, but this sex difference by DM status was not observed in the Japanese cohort. Whether the sex-difference effect of DM on HD and all-cause mortality is due to a difference in metabolic disorders between the two populations warrants consideration and further studies.

1. Introduction

The global burden of diabetes mellitus (DM) has risen dramatically over the past two decades and is expected to affect >500 million adults by 2030.[1] In the United States (U.S), >29 million Americans live with DM, and DM was the top 5th cause of death. Furthermore, >50% of patients with DM died of cardiovascular disease (heart disease and stroke).[2,3] Similar to the U.S, the burden of DM has rapidly increased in Japan.[4,5] Several studies have demonstrated a significant effect of DM on an increased risk of cardiovascular disease (CVD) and all-causes mortality using data in the U.S. and Japan.[4,6–11] However, studies of sex differences in the magnitudes of DM on the risk of mortality were limited although sex has been recognized as one of the important biological variables that are related to the etiology of disease and outcomes.[4,12]

* Corresponding author at: Department of Epidemiology and Biostatistics, Drexel University Dornsife School of Public Health, 3215 market ST, Philadelphia 19104, USA.
E-mail address: LL85@Drexel.edu (L. Liu).

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For example, an early report from the U.S. Framingham Study indicated that female patients with DM versus those without DM were at a significantly higher risk of recurrent myocardial infarction and risk of death from CVD and all-cause mortality than their counterparts in males[13] We recently also reported a significant sex-difference in mortality among patients with DM using data from the U.S. national health interview surveys.[14] However, these previous studies were predominately conducted in the U.S., and in which data that participants had self-reported diabetes status instead of using integrated clinical diagnosis (i.e., assessed by serum hemoglobin A1c and/or fasting glucose levels). Furthermore, whether the same sex-difference in health outcomes by DM status occurs in different populations is largely unknown. In the present study, we aimed to conduct a cross-country comparison using data from the third U.S. **N**ational **H**ealth and **N**utritional **E**xamination **S**urvey (NHANES III),[15] and Japan **N**ational **I**ntegrated **P**roject for **P**rospective **O**bservation of **N**on-communicable **D**isease **A**nd its **T**rends in **A**ged (NIPPON DATA).[16–18] We aimed to test a central hypothesis that women with DM versus those without DM had a significantly higher risk of heart disease, stroke and all-cause mortality than their counterparts in men in the U.S. and in Japan.

2. Research design and methods

2.1. Study populations

NHANES III is a nationwide survey conducted by the Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) in the U.S. between October 1988 and October 1994, gathering information representing the health and nutritional status of the noninstitutionalized civilian U.S. population aged two months and older.[15] The study consists of interviews, physical examinations, and data from blood sample analysis. All measurements are processed per standard protocols. Household interviews are conducted before physical examinations. Physical examinations and fasting blood samples are carried out and obtained in mobile examination centers. A detailed description of the survey and its sampling procedures are available at the NHANES III website.[15] The mortality follow-up was conducted by the NCHS in collaboration with the Offices of Vital Statistics based on the link with national death index (NDI). This Linked File provides mortality follow-up from the date of subjects who participated in NHANES III (1988–1994) and their vital status through December 31, 2011[19] The mean (SD) and median follow-up periods were 15.69 (6.42) and 18.25 years. The NHANES III was approved by the CDC Institutional Review Board (IRB). Data obtained from the NCHS are de-identified for the purpose of public use.[15] In the present study, we included participants aged ≥30 years older because CVD mortality is substantially lower in those aged <30 years. Of 15,042 participants aged ≥30, we excluded 22 who had ineligible match on their survival status in the Mortality Linked File, and 1851 who had data gaps that led us to be unable to classify their diabetes status (missing information on physician diagnosis of DM, or missing measures of fasting glucose or serum glycated hemoglobin A1c status). There remained 13,169 (87.5% of 15,042) for the study sample (M: 6159, W: 7010), Fig. 1.

NIPPON DATA, supported by the Ministry of Health and Welfare of Japan, included two independent cohorts of Japanese aged ≥30 at baseline who were enrolled in 1980 and 1990 separately, called NIPPON DATA80 ($n = 10,897$) and NIPPON DATA90 ($n = 8926$). Participants in both NIPPON DATA80 and NIPPON DATA90 were randomly selected from 300 districts across Japan. The two cohorts consisted of physical examinations, blood tests, and a self-administered questionnaire on lifestyle. Mortality follow-ups were conducted for all participants of NIPPON DATA80 and NIPPON DATA90.[18,20,21] Participants in NIPPON DATA90 were followed until November 2010. The mean (SD) and median follow-up periods were 17.84 (4.62) and 20 years. We used NIPPON DATA90 in the present study because it was conducted approximately in the same period (1990–2010) and had the same measures of biomarkers as the U.S. NHANES III (1988–2011). Furthermore, Lipid measurements in NIPPON DATA90 were standardized by the U.S. CDC/NHLBI (Centers for Disease Control and Prevention/National Heart, Lung, and Blood Institute) Lipids Standardization Program,[22] which ensured the comparability between the two datasets. In NIPPON DATA90, of 8383 baseline participants aged ≥30, we excluded 284 subjects who had invalid follow-up data and excluded 654 subjects who had missing values on DM status. There remained 7445 (88.8% of 8383) for the analysis (M: 3128, W: 4317), Fig. 1. The present analysis and dataset obtained from the NIPPON DATA Steering Committee have been approved by the IRB of the Shiga University of Medical Science.[4,18,23,24]

2.2. Definition of diabetes and hyperglycemia

Diabetes was defined for the participants as having serum glycated hemoglobin A1c (HbA1c) ≥6.5%, or fasting glucose ≥126 mg/dL, or a self-report of physician-diagnosis of diabetes, or taking medication for diabetes. We used either HbA1c or fasting glucose measures in the definition, because HbA1c level has been shown a highly reliable and correlated marker of fasting glucose and applied in studies when fasting sample is not available.[4,5] The same definition was applied to both samples from the NHANES III and the NIPPON DATA90. However, there was a slight difference in the measurement of serum HbA1c level using high-performance liquid chromatography (HPLC) technique between the two datasets. In the U.S. NHANES III, HbA1c levels were measured by a boronate affinity HPLC system, certified by the U.S.

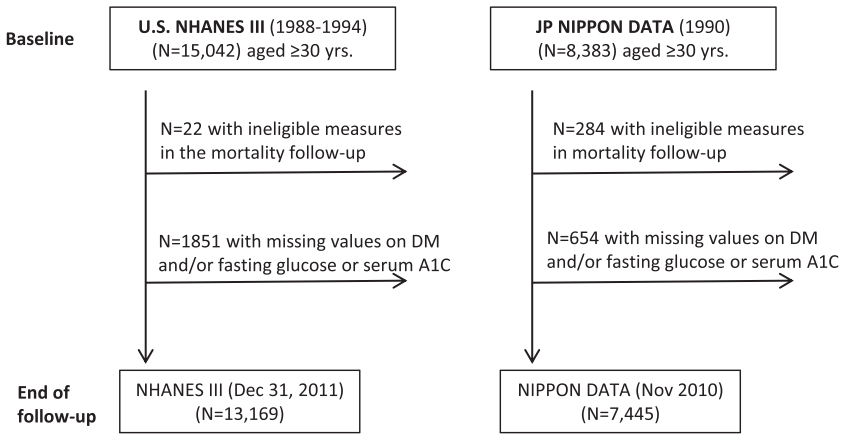

Fig. 1. Study populations: Data from the U.S. NHANES III and the JP NIPPON DATA90.

CDC. In Japan, HbA1c levels were measured by a high-resolution type ion-exchange HPLC, certified by the Japan Society of Clinical Chemistry and the Japan Diabetes Society (JDS). To have an internationally comparable value between the U.S. and Japan, the values of HbA1c measured in Japan are adjusted using the formula, HbA1c (%) = 1.02 × HbA1c (%, JDS) + 0.25(%). This adjustment approach is standardized, validated and recommended by the Japan National Glycohemoglobin Standardization Program (NGSP) and JDS.[4,5] In the study, participants who had HbA1c ≥5.7% or fasting glucose ≥100 mg/dL were classified as having elevated glucose (hyperglycemia) in both the U.S. and Japan samples.

2.3. Covariates

A set of baseline measures were included as covariates in data analysis: age (years), sex (men, women), smoking status (current smokers, former smokers or never smokers). Body mass index (BMI) was calculated by weight (kg) divided by height squared. Obesity was defined using the WHO criteria of BMI ≥30 kg/m^2 [weight(kg) / height (m^2)]. We used BMI as a measure of abnormal body weight in the U.S. and Japan datasets, instead of using waist circumference (WC) because WC was not available in the NIPPON DATA. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg or diastolic BP (DBP) ≥90 mm Hg or current use of anti-hypertensive medication or a self-reported physician-diagnosis of hypertension. Hypercholesterolemia was defined as total cholesterol ≥240 mg/dL or subjects' self-reported physician diagnosis of hypercholesterolemia. Baseline coronary heart disease (CHD) and stroke were defined by subjects' self-reported physician-diagnosis of the disease. This approach using self-reported physician-diagnosis of chronic conditions has been examined as a valid method in population-based surveys in the U.S. and Japan.[25–28]

2.4. Outcomes and time of follow-up

Causes of death from cardiovascular disease (CVD) were evaluated from national death index (NDI), a standard death record system in the U.S., and death certificate confirmed from annual follow-up surveys in the NIPPON DATA90. Disease specific causes of CVD were recorded using the 10th revisions of the International Classification of Diseases (ICD-10: I00-I99). Coronary heart disease (CHD) was coded as ICD-10: I21-I25, heart failure as ICD-10: I50, and stroke as ICD-10: I60-I69. Death from heart disease included CHD and heart failure (ICD-10: I21-I25 and I50). Time (year) of follow-up was calculated from the baseline interview to the end of follow-up, or until the date of death if a participant died before the end of follow-up, whichever occurred first.

2.5. Statistical analysis

A serial analysis was conducted. First, we examined sex differences in baseline characteristics of participants by countries. Differences in continuous variables were tested using ANOVA, and in categorical variables using Chi-square analysis. Second, to compare disease-specific (heart disease and stroke) and all-cause mortality rates, we estimated age-adjusted mortality using a direct age-standardized method and using the world standard population.[29,30] This analysis was done by sex and country in subjects with or without DM. Third, we used Cox proportional hazards regression (Cox) models to estimate hazard ratios (HRs) and their confidence intervals (95%CI) of DM and elevated glucose (hyperglycemia) for risk of mortality from heart disease, stroke, and all-cause by sex and countries. Cox models were conducted separately to estimate the impacts of DM and hyperglycemia on the study outcomes. We examined the effect of hyperglycemia to address the impact by including pre-diabetes. In the analysis, follow-up time (years) and death from heart disease and stroke, and all-cause mortality (yes or no) were the dependent variables, and DM and hyperglycemia were the independent variables, respectively. Two sets of Cox models were performed separately with adjustment for age (years) (Model 1), and adjustment for age (years), hypertension (yes vs. no), hypercholesterolemia (yes vs. no), obesity (yes vs. no), and ever smoking status (yes vs. no), (Model 2). Finally, the excess HRs of diabetes and hyperglycemia in women versus men for risks of heart disease, stroke, and all-cause mortality were estimated by testing a two -way interaction effect of sex (women vs. men) with DM (yes vs. no), and sex with hyperglycemia (yes vs. no) on the risk of mortality by country.[13,30,31] The basic formula to test the interaction is: $h(t) = h_0(t) \times \exp.(\beta_1{*}DM + \beta_2{*}Sex + \beta_3{*}Sex{*}DM + \ldots + \beta_n{*}X_n)$, where t represents the survival time, h(t) is the hazard function determined by a set of covariates (i.e., here, DM, Sex, Sex*DM, … X_n). The coefficients ($\beta 1, \beta 2, \beta_3, \ldots \beta_n$) measures the impact (i.e., the effect size) of covariates. The term h_0 is called the baseline hazard, it corresponds to the value of the hazard if all the covariates (Xi) are equal to zero (the quantity exp. (0) equals 1). The quantities exp. (β_1……n) are called hazard ratios (HRs). A HR above 1 indicates a covariate that is positively associated with the event probability (i.e., increase in hazard), and a HR <1 indicates a covariate that is negatively associated with the event probability (i.e., reduction in the hazard). β_3 indicates a two-way interaction effect of sex (women vs. men) and DM (yes vs. no) on the hazard of the event. If a two-way interaction effect is significant by country, we further test whether there is a three-way interaction effect (i.e., Sex*DM*Country) on the risk of mortality using a combined sample of the two countries datasets. In the three-way interaction test, variable country was added to the model as a covariate, i.e., to test whether the interaction of Sex*DM on the risk of mortality differs significantly between countries.

All data analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC). We used sampling weights and accounted for the complex sampling design using SAS Procedures for Analysis of Sample Survey Data.[32] A two-sided *p*-value ≤0.05 was considered as having statistical significance.

3. Results

3.1. Baseline characteristics

Table 1 shows that the mean (SE) ages were 49.5 (SE: 0.28) in men and 51.4 (0.26) in women in the U.S. participants, and 53.4 (0.24) in men and 52.5 (0.21) in women in the Japanese participants. Overall, men had significantly higher means of SBP, DBP, and cigarette smoking rates, but lower mean total cholesterol level and obesity rates than in women in both countries' participants, except for glucose level that was higher in men versus women in the U.S. and for HbA1c level that was higher in men versus women in Japan. In the Japanese participants, men had significantly higher prevalence of hypertension, DM, hypercholesterolemia, and stroke than women. In the U.S. participants, men had a significantly higher heart disease rate than women.

3.2. Mortality by diabetes status

During an average cumulative follow-up of (18.2 years in the U.S. cohort, and 20.0 years in the Japan cohort), Table 2 shows that patients with DM versus those without DM had significantly higher all-cause mortality in U.S. men (64.1 vs. 26.2 per 1000 person-years, $p < 0.0001$) and in Japan (35.3 vs. 16.9 per 1000 person-years, $p < 0.0001$). Similar results were observed for mortalities from all-cause, heart disease and stroke in women in both countries, except for a non-significant difference in stroke mortality in Japanese women.

3.3. Hazard ratio of DM for mortality

Table 3 shows that subjects with DM versus those without DM had a significantly higher age-adjusted hazard ratios (HR, 95%CI) of mortality from all-cause and heart disease in the U.S. participants (Model 1). These associations remained significant after adjustment for age, hypertension, hypercholesterolemia, obesity, and smoking status (Model 2).

Table 1
Baseline characteristics of the participants in U.S. NHANES III (1988–1994) and in NIPPON DATA90 (1990).

	U.S.					Japan				
	Men (n = 6159)		Women (7010)			Men (n = 3182)		Women (4317)		
	Mean, %	(SE/SP)	Mean, %	(SE/SP)	p-value	Mean, %	(SE/SP)	Mean, %	(SE/SP)	p-value
Continuous variables										
Age, years	49.47	(0.28)	51.43	(0.26)	<0.0001	53.39	(0.24)	52.51	(0.21)	0.006
BMI, kg/m^2	27.02	(0.10)	27.02	(0.12)	0.974	22.97	(0.05)	22.85	(0.05)	0.111
Systolic BP, mmHg	126.79	(0.31)	123.91	(0.34)	<0.0001	138.01	(0.36)	133.66	(0.32)	<0.0001
Diastolic BP, mmHg	77.99	(0.19)	73.25	(0.16)	<0.0001	83.73	(0.21)	79.59	(0.18)	<0.0001
TC, mg/dL	208.82	(0.84)	212.62	(0.79)	0.001	198.61	(0.66)	206.98	(0.59)	<0.0001
Glucose, mg/dL	100.86	(0.66)	98.58	(0.60)	0.011	103.45	(0.62)	102.77	(0.46)	0.377
HbA1c, %	5.49	(0.02)	5.45	(0.02)	0.128	5.37	(0.01)	5.25	(0.01)	<0.0001
Categorical variables, %										
Smoking status					<0.0001					<0.0001
Never	53.73	(1.07)	71.86	(0.83)		20.43	(0.72)	88.39	(0.49)	
Former	8.85	(0.55)	4.76	(0.37)		24.36	(0.77)	2.55	(0.24)	
Current	37.43	(1.04)	23.38	(0.78)		55.21	(0.89)	9.06	(0.44)	
Obesity (BMI ≥30 kg/m2)	21.54	(0.87)	27.48	(0.79)	<0.0001	1.79	(0.24)	2.80	(0.25)	0.003
Chronic diseases										
Hypertension	37.32	(1.00)	37.29	(0.84)	0.985	53.55	(0.89)	46.03	(0.76)	<0.0001
Hypercholesterolemia	35.80	(1.04)	37.52	(0.86)	0.201	17.14	(0.67)	22.98	(0.64)	<0.0001
Diabetes mellitus	9.14	(0.54)	9.57	(0.46)	0.548	8.86	(0.51)	5.10	(0.33)	<0.0001
Hyperglycemia	27.12	(0.88)	25.15	(0.70)	0.081	21.58	(0.74)	13.60	(0.52)	<0.0001
Coronary heart disease	6.11	(0.42)	3.22	(0.26)	<0.0001	3.10	(0.31)	2.62	(0.24)	0.220
Stroke	2.48	(0.27)	2.47	(0.22)	0.988	2.53	(0.28)	1.37	(0.18)	0.001

SE/SP: Standard error of Mean, or standard error of Proportion; BMI: Body mass index; BP: blood pressure; TC: Total cholesterol; Convert TC from mg/dl to mmol/L, divided by 38.61. HbA1c: Glycated hemoglobin A1c.
Hypertension was defined as self-report of physician-diagnosis of hypertension, or SBP ≥ 140 or DBP ≥ 90 or under anti-hypertensive medication.
Hypercholesterolemia was defined as self-report of physician-diagnosis of hyperdislipidemia or total cholesterol ≥240 mg/dL (6.2 mmol/L).
Diabetes mellitus (DM) was defined as self-report of physician-diagnosis of DM or serum HbA1c ≥ 6.5% or under medication for DM.
Hyperglycemia was defined for those with serum glucose ≥100 mg/dL, or HbA1C ≥5.7%, or diagnosed DM.
Coronary heart disease and stroke were defined as self-report of physician-diagnosis of each disease.

The HRs (95%CI) of DM for all-cause mortality were 1.57 (1.34–1.83, p < 0.0001) in men and 1.95 (1.69–2.26, p < 0.0001) in women, and the corresponding HRs (95%CI) for mortality from heart disease were 1.42 (1.09–1.85, p = 0.01) in men and 2.32 (1.79–3.00, p < 0.0001) in women. Fig. 2 shows that there were significant interaction effects of sex (women vs. men) and DM (yes vs.no) on the risks of all-cause mortality (HR = 1.24, 95%CI: 1.01–1.54, p = 0.045), and heart disease mortality (HR = 1.59, 95%CI: 1.11–2.27, p = 0.013). In other words, female patients with DM had a 24% relatively higher risk of death from all-cause, and 59% from heart disease mortality than their counterparts in males. However, the interaction effect of sex and DM on stroke mortality was not significant (HR = 0.78, 95%CI: 0.33–1.85, p = 0.566) in the U.S. participants (Fig. 2).

Table 3 shows that subjects with hyperglycemia versus those without hyperglycemia had significantly higher risks of mortality from all-cause, heart disease and stroke in U.S. men and women, except a non-significant association between hyperglycemia and heart disease in men (Model 2). Furthermore, there was a significant interaction effect of sex (female vs. male) with hyperglycemia on the risk of heart disease mortality (HR = 1.55, 95%CI: 1.15–2.10, p = 0.004, Fig. 2) in the U.S. cohort.

Similar to the U.S., Japanese participants with DM versus those without DM had significantly higher risks of mortality from all-causes, heart disease and stroke in men and in women (p < 0.05), except for non-significant associations between DM and heart disease (HR = 1.66, (95%CI: 0.92–3.00, p = 0.094) and stroke mortality (HR = 0.88, 9%%C: 0.40–1.94) in women (Table 3). Japanese men and women with hyperglycemia versus those without hyperglycemia had significantly higher risks of death from all-cause and heart disease, but no significance from stroke mortality (Table 3). Fig. 2 shows that there were no significant interaction effects of sex and DM on the risks of all-cause (HR = 0.98, 95%CI: 0.73–1.31), heart disease (HR = 0.71, 95%CI: 0.34–1.47) and stroke mortality (HR = 0.48, 95%CI: 0.19–1.22) among the Japanese participants. Similarly, no significant interaction effects of sex and hyperglycemia on the risk of mortality were observed in the Japan sample.

Table 2
Mortality (per 1000 person year) from all-cause, heart disease and stroke In men and women.

Mortality	Men					Women				
	Nondiabetic		Diabetic			Nondiabetic		Diabetic		
	Event	Rate	Events	Rate	p-value	Events	Rate	Events	Rate	p-value
USA (n = 13,169)										
All-cause	2168	26.2	687	64.1	<0.0001	1932	19.6	728	49.3	<0.0001
Heart Disease	616	7.5	220	20.5	<0.0001	496	5.0	232	15.7	<0.0001
Stroke	104	1.3	42	3.9	<0.0001	143	1.5	44	3.0	<0.0001
Japan (n = 7445)										
All-cause	839	16.9	145	35.5	<0.0001	764	10.1	88	24.2	<0.0001
Heart Disease	87	1.8	25	6.1	<0.0001	99	1.3	14	3.9	<0.001
Stroke	95	1.9	20	4.9	<0.0001	98	1.3	7	1.9	0.313

Event: Number of death.
Rate = event / (number of individuals at risk * follow-up year) * 1000.

Table 3
Hazard ratio (HR) of diabetes and hyperglycemia for mortality from all-cause, heart disease and stroke.

	Men						Women					
	M1: Age-adjusted			M2: Multi-adjusted			M1: Age-adjusted			M2: Multi-adjusted		
	HR	(95%CI)	p-value	HR	(95%CI)	p-value	HR	(95%CI)	p-value	HR	(95%CI)	p-value
U.S. Diagnosed DM vs. None												
All-cause	1.69	(1.46–1.96)	<0.0001	1.57	(1.34–1.83)	<0.0001	2.16	(1.89–2.47)	<0.0001	1.95	(1.69–2.26)	<0.0001
Heart Dis	1.56	(1.22–2.01)	0.001	1.42	(1.09–1.85)	0.01	2.56	(2.00–3.27)	<0.0001	2.32	(1.79–3.00)	<0.0001
Stroke	1.89	(0.94–3.79)	0.073	1.75	(0.84–3.65)	0.13	1.50	(0.91–2.48)	0.111	1.50	(0.92–2.45)	0.105
Hyperglycemia vs. None												
All-cause	1.39	(1.23–1.56)	<0.0001	1.28	(1.14–1.44)	<0.0001	1.61	(1.44–1.80)	<0.0001	1.45	(1.29–1.64)	<0.0001
Heart Dis	1.21	(0.98–1.49)	0.071	1.08	(0.87–1.33)	0.482	1.88	(1.52–2.33)	<0.0001	1.71	(1.37–2.14)	<0.0001
Stroke	1.89	(0.94–3.79)	0.073	2.13	(1.21–3.74)	0.009	1.50	(0.91–2.48)	0.111	1.53	(1.01–2.30)	0.043
Japan Diagnosed DM vs. None												
All-cause	1.50	(1.25–1.80)	<0.0001	1.48	(1.23–1.78)	<0.0001	1.48	(1.18–1.87)	0.001	1.45	(1.15–1.83)	0.002
Heart Dis	2.42	(1.56–3.77)	<0.0001	2.34	(1.49–3.68)	<0.001	1.78	(0.99–3.22)	0.056	1.66	(0.92–3.00)	0.094
Stroke	1.83	(1.12–3.00)	0.017	1.78	(1.09–2.89)	0.021	0.89	(0.41–1.94)	0.773	0.88	(0.40–1.94)	0.752
Hyperglycemia vs. None												
All-cause	1.38	(1.20–1.58)	<0.0001	1.35	(1.17–1.55)	<0.0001	1.45	(1.25–1.67)	<0.0001	1.44	(1.24–1.68)	<0.0001
Heart Dis	1.86	(1.27–2.74)	0.0015	1.84	(1.25–2.71)	0.002	2.15	(1.45–3.19)	0.0002	2.07	(1.39–3.09)	0.0003
Stroke	1.83	(1.12–3.00)	0.017	1.27	(0.85–1.88)	0.247	0.89	(0.41–1.94)	0.773	1.49	(0.96–2.32)	0.075

DM: Diabetes mellitus.
Multi-adjusted: age (year), hypertension (y vs. n), hypercholesterolemia (y vs. n), obesity (y vs. n), and ever smoked (y vs. n).
Hyperglycemia is classified for those had pre-diabetes or had diagnosed diabetes.

In the combined sample of both countries, although the tests for three-way interactions of sex*DM*country on the risk of mortality are not significant, there is a tendency of an increased interaction effect of sex and DM on the risk of heart disease mortality in the U.S. versus Japan (HR = 2.13, 95%CI: 0.96–4.70, p = 0.063), Fig. 2.

4. Discussion

The present study, using nationally representative data sets from the U.S., and Japan highlights a significantly risk of mortality from heart disease and all-cause in patients with DM versus those without DM.

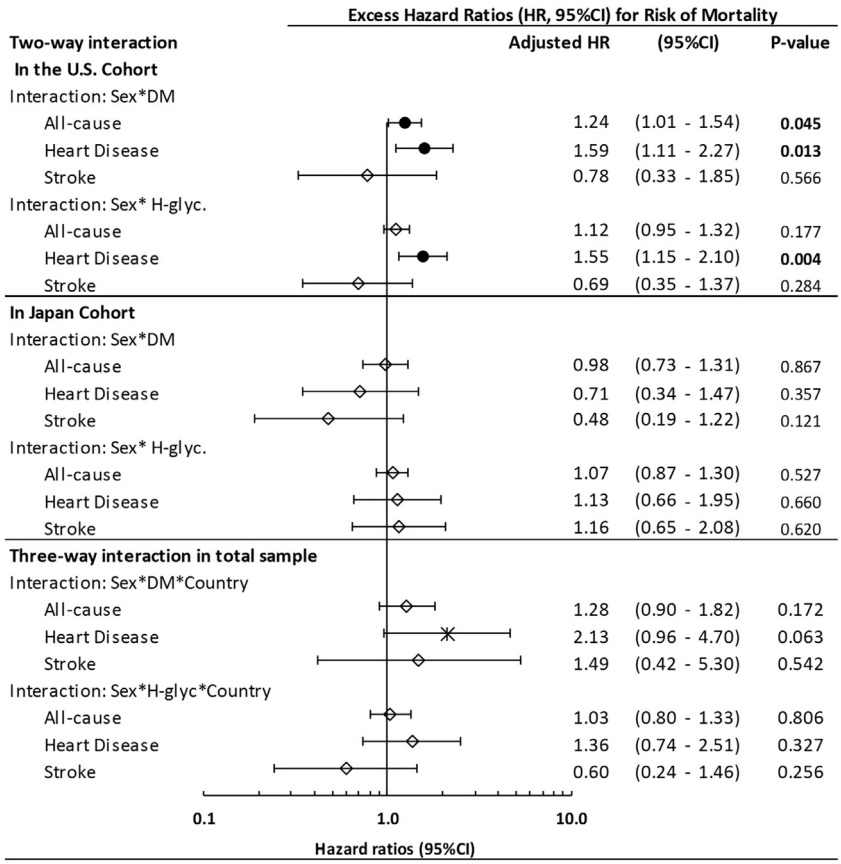

Fig. 2. Excess HR (assessed by interaction effects) for risk of mortality from all-cause, heart disease, and stroke in U.S. and Japan.

The study provides new evidence that women with DM had a significantly higher hazard ratio for mortality from heart disease and all-causes than their counterparts in men in the US cohort, but this excess risk by sex (female vs. male) with DM was not statistically significant in the Japan cohort.

Results from a three-way interaction effect test further suggest that there is a tendency that the excess risk in women with DM for heart disease mortality in the U.S. was 2 times higher than that in Japan (HR = 2.13, 95%CI: 0.96–4.70, p = 0.063). This observed borderline significance may be attributable to a small sample size of death from heart disease in the sample of Japan cohort.

Similar to our findings, most previous studies demonstrated an increased risk of DM associated with mortality. However, the previous studies often did not test the impact of sex difference on health outcomes. In 2001, the U.S. Institute of Medicine (IOM) addressed that examining sex difference in clinical and research studies is critical because there is increasing evidence of fundamental sex differences in the biology of disease.[33] In 2015, the American Heart Association (AHA) called for studies of sex differences in CVD consequence of patients with DM, because "cardiovascular disease may be more deadly for women with diabetes than it is for men".[12] The mechanisms by which women with DM may have a relatively higher risk of death are not clear. Findings from few studies suggest that women with DM: (1) may have heart attack at earlier ages than men; (2) are less likely undergo procedures to open clogged arteries, such as angioplasty or coronary artery bypass grafting than men; (3) are less likely to be on cholesterol lowering medications than men; and (4) are less likely to have their blood sugar or blood pressure under control than men.[12] It is clear more studies are needed.[34]

In the present study, using two nationally representative samples, findings of the study add new evidence to the body of the literature that the impact of sex on the risk of mortality in patients with DM appears different between the U.S. and Japan. Although we remain unable to fully explain the cross-country sex different effects, the severity of comorbidities in patients with DM is likely one of critical factors. For example, in the U.S. sample, women with DM versus those without DM have a higher hazard ratio for mortality from heart disease and all-causes than men with DM, which may be attributable to a relatively higher comorbidity of obesity and hypercholesterolemia in women than in men.[14] However, these comorbid conditions were less severe in Japanese women than that in men. This finding suggests that vigorous strategies of prevention and treatments for women with DM and comorbidities may play a stronger role in reducing sex differences in all-cause and heart disease mortality in the U.S. than that in Japan. In addition, the U.S. – Japan CVD risk differences in women may also be attributable to several other risk factors. For example, Japanese women have a significantly lower prevalence of obesity, hypercholesterolemia and cigarette smoking rate than the U.S. women (Table 1). Furthermore, a significantly difference in dietary patterns may contribute to the differences in the two societies. For example, several studies have observed a strong protective dietary pattern (i.e., lower total fat and saturated fatty acid intake, and higher omega-3 fatty acid intake) against atherosclerosis in the Japanese versus the Americans, and Japanese living in Japan versus Japanese-Americans living in Hawaii (i.e., 3rd and 4th generation Japanese emigrants) in men and in women.[35–38] These findings support that control of the preventable risk factors would have a significantly impact on the reduction of CVD risk between the two societies.

This study has several strengths. First, to the best of our knowledge, it is one of the first cross-country comparisons that observe an excess risk of women with DM for all-cause and CVD mortality using two nationally representative datasets from the U.S. and Japan. Second, the comparison study benefited from the rigorous measurements of risk factors and comparable analysis approaches for data between the two countries. Third, the analysis was conducted using a longitudinal prospective approach that provides an opportunity to interpret potentially temporal associations between exposures and outcomes. Meanwhile, the study is subject to several limitations as well that should be kept in mind when interpreting the results. First, we are unable to examine risk of incident CVD because of lack of the incident measurements. Second, all study variables of interest had a single measure at baseline. We are unable to evaluate possible time-varying effects of DM and covariates on all-cause and CVD mortalities. Third, we cannot answer in detail what factors may contribute to the sex difference between the two countries due to lack of details, such as dietary patterns, which is also beyond the scope of the current analysis and report.

Despite the limitations as mentioned above, two clear and important conclusions follow from our present study. First, DM has a significant impact on all-cause and CVD mortality in both countries. Second, women with DM versus those without DM have a higher hazard ratio for all-cause and heart disease mortality than men in the U.S. However, the excess risk by sex is not observed in the Japan cohort. Whether the different sex effect of DM on all-cause and heart disease mortality is due to a difference in metabolic disorders between the two populations warrants consideration and further studies.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2019.03.008.

Contributions

L Liu, KM, AK, AF and HU participated in the analysis design. L Liu conducted the data analysis and drafted the manuscript. MK, AK, AF, EJG, FX, ZL, NT, NM, TO, HA, AO, TO and HU reviewed and gave invaluable comments on the analysis, edits and revision of the manuscript.

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None reported.

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