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Humanistic and economic burden of cardiovascular disease related comorbidities and hypoglycaemia among patients with type 2 diabetes in Japan

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ABSTRACT

Aim: This study aims to examine the humanistic and economic burden of cardiovascular disease (CVD)-related comorbidities and hypoglycaemia among respondents with type 2 diabetes (T2D) in Japan.

Methods: This study used the Japan National Health and Wellness Survey 2016 database. Respondents who self-reported a physician-diagnosed T2D were included. Respondents with or without the condition of interest (CVD-related comorbidities or hypoglycaemia) were compared via generalized linear models in terms of the outcome variables: (1) health-related quality of life (HRQoL), (2) work productivity and activity impairment, (3) healthcare resource utilization and (4) economic costs.

Results: A total of 1478 survey respondents reported a diagnosis of T2D (mean age 63.6 ± 10.6 years, mean HbA1c 6.91 ± 1.1%). Of whom, 804 subjects (54.4%) had at least one CVD related comorbidities, and 369 subjects (29.3%) reported experiences of hypoglycaemia episodes. Patients with CVD-related comorbidities or hypoglycaemia episodes had worse HRQoL, more work and activity impairment, increased health care visits, and higher costs.

Conclusions: CVD related comorbidities and hypoglycaemia remains a significant humanistic and economic burden in patients with T2D. The findings suggested that appropriate T2D management with proper medication choice are important to control CVD related comorbidities and hypoglycaemia among T2D patients to alleviate the burden.

1. Introduction

Diabetes has become one of the most important public health issues worldwide. It affected 422 million adults in 2014, and the number is estimated to rise to 552 million by 2030 [1]. In Japan, the total number of people with diabetes was estimated to have reached 7.2 million as of 2015, ranked fifth in the world [2], and this number is anticipated to increase to

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approximately 8.9 million in 2030 [3]. Notably, the aging population in Japan may further aggravate the situation given the higher prevalence of diabetes among the elderly [3], and it is projected that 31.2% of the Japanese population will be aged over 65 years by 2030 [4].

In Japan, Type 1 diabetes is rare, and the majority of the cases are first diagnosed in young children aged below 9 years old [5]. Type 2 diabetes (T2D), on the other hand, can develop at any age, and accounts for 90–95% of all diabetes cases [6]. As long-term hyperglycaemia is detrimental to the vascular system, patients with T2D are at increased risk for cardiovascular disease (CVD) related comorbidities, including hypertension, dyslipidaemia, and obesity, placing these patients at greater risk for CVD events. According to World Health Organization (WHO), cardiovascular disease was the most common underlying cause of death, accounting for approximately 50% of death in patients with T2D [7], which emphasizes the importance of good T2D management in place to alleviate the mortality and morbidity burden.

Glycaemic control with oral hypoglycaemic agents and insulin has shown to reduce the risk for CVDs and mortality [8–10]. However, balancing the needs of glycaemic control and lower risk of hypoglycaemia can be challenging. Several commonly used glucose lowering agents may introduce the side-effect of hypoglycaemia. A survey done by the Japan Diabetes Society (JDS) found that the majority of patients with T2D who experienced severe hypoglycaemia were insulin (60.8%) or sulfonylurea (33.1%) users [11], both of which are widely used in Japan. Additionally, epidemiologic evidence from a meta-analysis showed that severe hypoglycaemia is strongly associated with CVD among patients with T2D [12]. Similarly, a large scale Japanese retrospective cohort study (N = 58,223) reported that T2D patients with severe hypoglycaemia had approximately 3-fold increased risk of CVD [13], which highlights the needs for alternative T2D therapy that can reduce the risk of hypoglycaemia and improve patients' CVD outcomes.

Along with the high mortality and morbidity associated with CVD and hypoglycaemia among patients with T2D, previous research studies, mainly European or US studies, also reported that CVD and hypoglycaemia are associated with negative impact on health-related quality of life (HRQoL), work productivity and activity impairment, and often increased healthcare resource utilization among T2D patients [14–18]. Many studies have also reported that CVD and hypoglycaemia would increase the cost of diabetes [19–22]. Particularly, the costs for T2D patients with CVD are approximately three times higher as compared to those without CVD [22]. However, few of studies have quantified the actual cost of CVD and hypoglycaemia in Japan.

This study aims to quantify the burden of the presence of CVD related comorbidities and occurrence of hypoglycaemia among patients with type 2 diabetes patients in Japan in a single analysis from four aspects: (1) health-related quality of life (HRQoL), (2) work productivity and activity impairment, (3) healthcare resource utilization and (4) economic costs. These findings may provide important suggestions for diabetes management in Japan.

2. Subjects, materials and methods

2.1. Data source

Data used for this study were obtained from the 2016 Japan National Health and Wellness Survey (NHWS) (Kantar Health, New York, USA) (N = 39,000). The NHWS is an internet-based, self-reported survey from a representative nationwide sample of adults (aged ≥ 18 years old) using a stratified random sample framework with quotas approximating the gender and age distribution of the Japan general population. The NHWS received Pearl Institutional Review Board (Indianapolis, IN) approval and informed consent was obtained for subjects before joining the study [23].

The inclusion criterion for this analysis was adult respondents who completed the NHWS with self-reported a diagnosis of T2D by a physician. Respondents with Charlson Comorbidity Index (CCI) (as described below) above 30 were identified as outliers and were, therefore, excluded from the analysis.

2.2. Measures

All measures analysed in this study were collected and obtained from the 2016 Japan NHWS.

2.2.1. Demographics and health characteristics

Characteristics analysed in this study included age, sex, education, household income level, health insurance status, employment status, smoking status, exercise behaviour, alcohol consumption, body mass index (BMI), and the Charlson Comorbidity Index. BMI was converted to underweight: BMI < 18.5, normal weight: 18.5 ≤ BMI < 25, overweight or obese: BMI ≥ 25, or decline to answer). The CCI is a weighted summary score that measures one's comorbid burden with higher scores indicating greater comorbid burden [24].

2.2.2. Diabetes related outcomes

Diabetes related outcomes analysed in this study includes the presence of CVD related comorbidities and experiences of hypoglycaemia. The presence of CVD related comorbidities was defined as a self-reported physician diagnosis of the following diseases: angina, congestive heart failure, heart attack, atherosclerosis, hypertension, peripheral artery disease (PAD), high cholesterol, stroke, and transient ischemic attack (TIA). Experiences of hypoglycaemia were defined if the respondent has ever experienced hypoglycaemia as a result of their diabetes.

2.2.3. Health-related quality of life (HRQoL)

HRQoL was measured using the Short Form-36 version 2 (SF-36v2) health survey that included three aspects: physical component summary (PCS), mental component summary (MCS) scores (range 0–100), and health state utility score derived via the SF-6D algorithm (range 0–1) [25,26]. Higher scores indicate better quality of life.

2.2.4. Work productivity and activity impairment

The health burden on work-related activities was measured using the validated work productivity and activity impair-

ment (WPAI) questionnaire with four metrics: (1) absenteeism (percentage of work time missed in the past 7 days), (2) presenteeism (percentage of impairment experienced at work in the past 7 days), (3) overall work productivity loss (a combination of absenteeism and presenteeism) were assessed for employed respondents, and (4) activity impairment (percentage of daily activity impairment in the past 7 days) were assessed for all respondents [27]. These four subscales were generated in the form of percentages ranging from 0% to 100% with higher values indicating greater impairment.

2.2.5. *Healthcare resource utilization*

Healthcare resource utilization was evaluated using self-reported number of visits in the last 6 months to healthcare providers (practitioner/family practitioners, internists, and dentists as well as more specialized physicians), the emergency room (ER), and the number of hospitalizations for the patient's own medical condition. The number of visits were then annualized to show the annual burden.

2.2.6. *Direct and indirect costs*

The indirect costs were calculated using the human capital method by integrating the work productivity and activity measures (absenteeism and presenteeism) and monthly wage rates from the Japan Basic Survey on Wage Structure, 2016 [28]. The direct costs were estimated by multiplying unit costs for physician visits, emergency room visits, and hospitalizations obtained from Ministry of Health, Labour and Welfare, Japan [29,30] by the number of visits. Both indirect and direct costs were annualized. Costs were reported in the local currency (Japanese Yen [¥]).

2.3. *Statistical analysis*

Patient characteristics and patient burdens were summarized using means and standard deviations (SDs) for continuous variables and counts and percentages for categorical variables. Differences between groups were tested using one-way ANOVAs for means and Pearson's Chi-square test for proportions.

Generalized linear models were conducted to examine the association between health and economic outcomes and diabetes related outcomes, i.e. (1) the presence of CVD related comorbidities and (2) experiences of hypoglycaemia. The diabetes related outcome was the primary predictor of health and economic outcomes. Subjects without diabetes related outcomes were used as the reference group. Covariates that were included in the model depend on the significance obtained from the bivariate analysis, as well as an assessment of collinearity (high correlation) between variables. The analysis of CVD related comorbidities adjusted for demographic and health characteristics, experience of hypoglycaemia, and diagnosis of anxiety, depression and insomnia. The analysis of hypoglycaemia adjusted for demographic and health characteristics and diagnosis of CVD related comorbidities, anxiety, depression, and insomnia. Normal distributions with identity link functions were used for predicting continuous dependent variables, i.e. HRQoL variables: MCS, PCS and health state utility scores, and negative binomial distributions with log link functions were used for predicting over-dispersed dependent variables, i.e. work productivity loss, healthcare resource use, and indirect and direct costs variables. Regression coefficients and relative risks of the main predictor, as were appropriate for GLM) function specified, were reported with 95% confidence intervals (CIs) and p-values for all multivariate regression models. Adjusted means with 95% CIs for all outcomes were calculated by groups using a maximum likelihood algorithm and reported on their original metric. Significance was assessed at a 0.05 level, two-sided. All analyses were conducted using IBM SPSS Statistics 23 [28].

3. Results

3.1. *Patient characteristics*

Flow of inclusion for this analysis is shown in Fig. 1. From 39,000 subjects in the Japan 2016 NHWS, we excluded subjects without a self-reported experience of T2D (N = 37,418), with a self-reported experience but without a diagnosis of T2D (N = 102) and with CCI > 30 (N = 2). Of a total of 1478 subjects, all were included in the final analysis for CVD related comorbidities, and 1260 subjects were included in the final analysis for hypoglycaemia, after excluding 218 subjects with missing values.

Of the 1478 subjects, the mean age was 63.6 years (SD 10.6), and the majority of the subjects were male (82.5%), married or living with partner (75.5%). Around half of the subjects completed a university education (49.7%) and currently employed (48%). Around one third of the subjects were overweight or obese (38.1%). 65.6% of the subjects were current smokers (24.3%) or ex-smokers (41.3%), and 69.5% of the subjects were current alcohol drinkers. The average CCI was 1.36 (SD 0.78). The mean HbA1c was 6.91% (SD 1.11), and the mean duration of time since diagnosis of DM was 13.2 years (SD 10.1). In terms of pharmacotherapies, 33.4% of the subjects used DPP-4, 23.7% used metformin, 23.3% used SU, 14.1% used alpha-glucosidase inhibitors (AGI) and 9.4% used thiazolidinedione. A total of 204 (13.8%) subjects reported a use of insulin. Of all respondents with T2D, 804 respondents (54.4%) had at least one CVD related comorbidities (CVD+), with hypertension (41.3%), high cholesterol (25.8%), angina (7.2%), heart attack (1.5%), stroke (1.4%), among the most prevalent comorbidities (Supplemental table 1). A total of 369 subjects (29.3%) reported an experience of hypoglycaemia episodes due to their diabetes (hypo +), and of which 82 were on basal insulin that accounted for 69.5% of the subjects on basal insulin. Those who experienced hypoglycaemia had an average of 2.6 hypoglycaemic events in the past three months (SD 3.2). Among 1260 respondents who had completed hypoglycaemia data, 211 (16.7%) were CVD+/hypo+, 158 (12.5%) were CVD−/hypo+, 476 (37.8%) were CVD+/hypo−, and 415 (32.9%) were CVD−/hypo−.

As shown in Table 1, compared to CVD− subjects, CVD+ subjects were older, less likely to be employed and current smoker, and more likely to be overweight or obese and had higher CCI. Hypo+ and hypo− subjects had similar demographic and life-style characteristics, but hypo+ subjects had higher CCI. Among all, CVD+/hypo+ subjects the highest CCI (1.65) compared to other subjects. (Supplemental table 2).

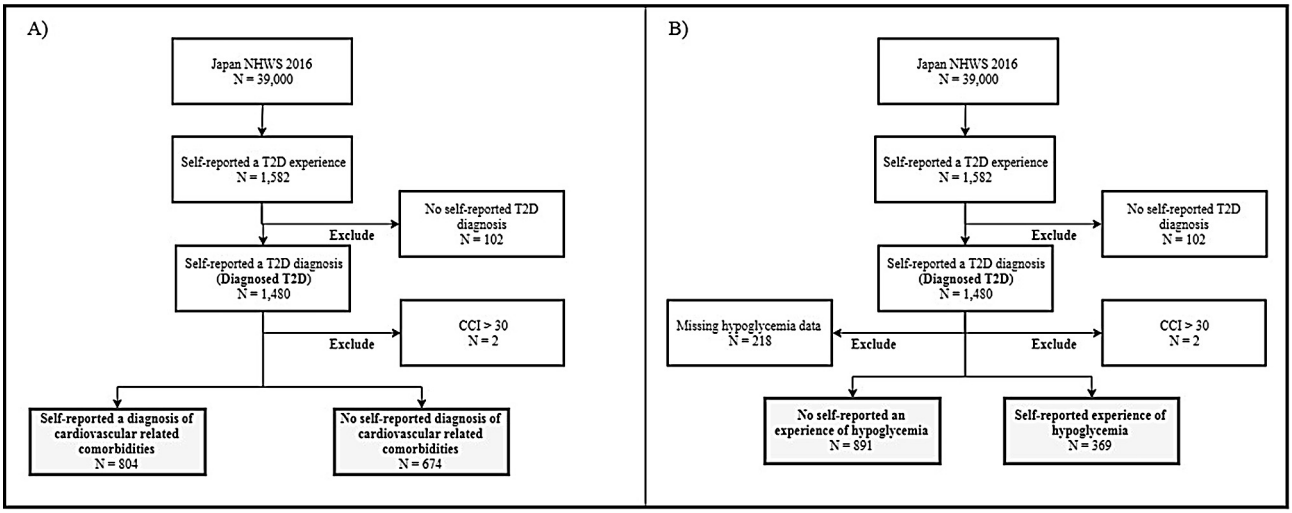

Fig. 1 – Flow chart of sample selection for the analysis of cardiovascular disease related comorbidities (A) and hypoglycaemia (B) among respondents with type 2 diabetes.

The use of pharmacotherapies was similar regardless of CVD status, but Hypo+ subjects were more likely to report the use of basal insulin compared with hypo− counterparts (22.2% vs. 4.0%). Similarly, CVD+/hypo+ were more likely to report the use of basal insulin compared with CVD+/hypo− and CVD−/hypo− subjects (23.2% vs. 3.2% vs. 5.1%; Supplemental table 2).

3.2. *Burden in T2D respondents with/without CVD related comorbidities*

After adjustment for potential confounders, CVD related comorbidities in type 2 diabetes patients were associated with significantly lower HRQoL, manifested as lower PCS, MCS, and health utility scores (all $p < 0.05$) (Table 2). The average percentage of time impairment experienced while at work because of health (presenteeism) and overall work impairment were found to be significantly higher among CVD+ employed subjects CVD− counterpart (all $p < 0.05$). Approximately 56% of working time was affected in CVD+ patients, while 44% was affected in CVD− patients. In addition, CVD+ subjects had significantly higher total number of healthcare provider visits (adjusted means: 10.0 times vs 8.1 times, $p < 0.001$) and higher indirect costs (adjusted means: ¥762,811 vs. ¥575,549, $p < 0.001$) compared to those CVD−.

3.3. *Burden in subjects with/without hypoglycaemia*

After adjustment for potential confounders, hypoglycaemia in type 2 diabetes patients were associated with significant lower HRQoL, manifested as lower PCS, MCS, and health utility scores (all $p < 0.001$) (Table 3). Absenteeism, presenteeism, and overall work impairment were significantly higher among hypo+ working subjects compared to hypo− working subjects (all $p < 0.05$). In hypo+ patients, approximately 12% and 57% of working time were absent and impaired respectively, while only 4% and 43% of working time were absent and impaired in hypo− patients. Hypo+ subjects also had significantly higher number of healthcare provider visits (adjusted means: 10 times vs 8 times), emergency room (ER) visits (adjusted means: 0.13 vs 0.06) and hospitalizations (adjusted means: 13 vs 3.6) compared to hypo− subjects (all $p < 0.001$). They also had significantly higher indirect costs (adjusted means: ¥757,473 vs ¥579,605) and direct costs (adjusted means: ¥26,126,379 vs ¥7,890,439) compared to those without hypoglycaemia (all $p < 0.05$).

3.4. *Burden in subjects with CVD related comorbidities and hypoglycaemia*

After adjustment for potential confounders, having both CVD related comorbidities and hypoglycaemia episodes (CVD+/hypo+) in type 2 diabetes patients were associated with significant lower HRQoL, manifested as lower PCS, MCS, and health utility scores, and significant higher absenteeism, presenteeism, total work productivity loss, activity impairment, number of HCP visits, indirect costs and direct costs (all $p < 0.05$; supplementary table 3) compared with CVD+/hypo− and CVD−/hypo−. CVD+/hypo+ patients also reported more severe burdens in terms of HRQoL (i.e. PCS, MCS, and health utility scores), presenteeism, total work productivity loss, activity impairment, and indirect costs (all $p < 0.05$; supplementary table 3) compared with CVD−/hypo + patients. However, no significant difference was found between CVD+/hypo− and CVD−/hypo+ because their corresponding 95% confidence intervals for the regression coefficients (β)/relative risks overlapped substantially (supplementary table 3).

4. Discussion

All analyses of this study were based on patient-reported outcomes that were collected directly from patients rather than physicians or caregivers. This provides a holistic view of a patient health including both patients' physical functioning,

Table 1 – comparison of characteristics between different study subgroups.

Demographics and clinical characteristics		CVD related comorbidities, N (%)			Hypoglycaemia, N (%)[a]		
		No (N = 674)	Yes (N = 804)	P-value	No (N = 891)	Yes (N = 369)	P-value
Age (Mean ± SD)		62.4 (11.6)	64.5 (9.5)	<0.001	64.0 (10.1)	63.0 (11.1)	0.133
Gender	Male	556 (82.5)	650 (80.8)	0.416	731 (82.0)	291 (78.9)	0.189
Marital status	Married or living with partner	515 (76.4)	601 (74.8)	0.403	682 (76.5)	280 (75.9)	0.294
Education	University degree	340 (50.4)	395 (49.1)	0.533	446 (50.1)	183 (49.6)	0.534
Employment status	Currently employed	343 (50.9)	366 (45.5)	0.040	428 (48.0)	175 (47.4)	0.844
Household income	<¥3,000,000	118 (17.5)	142 (17.7)	0.123	132 (14.8)	77 (20.9)	0.061
	¥3,000,000–<¥5,000,000	196 (29.1)	212 (26.4)		243 (27.3)	101 (27.4)	
	5,000,000–<¥8,000,000	144 (21.4)	205 (25.5)		230 (25.8)	77 (20.9)	
	≥¥8,000,000	139 (20.6)	177 (22)		201 (22.6)	76 (20.6)	
	Decline to answer	77 (11.4)	68 (8.5)		85 (9.5)	38 (10.3)	
Health insurance	National Health Insurance	374 (55.5)	450 (56)	0.385	488 (54.8)	218 (59.1)	0.296
	Social Insurance	224 (33.2)	243 (30.2)		298 (33.4)	106 (28.7)	
	Late Stage Elderly Insurance	53 (7.9)	85 (10.6)		78 (8.8)	37 (10)	
	Other	18 (2.7)	19 (2.4)		22 (2.5)	5 (1.4)	
	No insurance	5 (0.7)	7 (0.9)		5 (0.6)	3 (0.8)	
Body mass index	Overweight or obese	199 (29.5)	364 (45.3)	<0.001	348 (39.1)	138 (37.4)	0.499
	Normal	421 (62.5)	411 (51.1)		501 (56.2)	206 (55.8)	
	Underweight	39 (5.8)	12 (1.5)		25 (2.8)	14 (3.8)	
	Decline to answer	15 (2.2)	17 (2.1)		17 (1.9)	11 (3)	
Smoking status	Current	199 (29.5)	160 (19.9)	<0.001	216 (24.2)	90 (24.4)	0.866
	Former	250 (37.1)	360 (44.8)		366 (41.1)	146 (39.6)	
	Never	225 (33.4)	284 (35.3)		309 (34.7)	133 (36)	
Current alcohol drinker		466 (69.1)	561 (69.8)	0.791	616 (69.1)	249 (67.5)	0.564
Regular exercise		415 (61.6)	453 (56.3)	0.042	517 (58.0)	223 (60.4)	0.429
Charlson comorbidity index (Mean ± SD)		1.26 (0.61)	1.44 (0.89)	<0.001	1.3 (0.69)	1.54 (0.99)	<0.001
Pharmacotherapies used	Not on any prescription medications	192 (28.5)	179 (22.3)	0.057	181 (20.3)	29 (7.9)	<0.001
	Metformin	25 (3.7)	45 (5.6)		52 (5.8)	13 (3.5)	
	DPP-4	68 (10.1)	82 (10.2)		127 (14.3)	19 (5.1)	
	Metformin and SU	25 (3.78)	23 (2.9)		32 (3.6)	13 (3.5)	
	Metformin and DPP-4	36 (5.3)	49 (6.1)		60 (6.7)	21 (5.7)	
	Metformin, DPP-4 and SU	18 (2.7)	36 (4.5)		37 (4.2)	15 (4.1)	
	Basal Insulin	57 (8.5)	65 (8.1)		36 (4.0)	82 (22.2)	
	Other drugs	253 (37.5)	325 (40.4)		366 (41.1)	177 (48.0)	

[a] N total = 1260.

Table 2 – Comparison of health and economic burden among subjects with/ without CVD related comorbidities.

	Multivariate analysis		Adjusted means				
			No CVD related comorbidities		CVD related comorbidities		
	β	95% confidence interval (CI)	Mean	SE	Mean	SE	p-Value
SF-36: Mental component summary	−2.43	−3.52, −1.46	43.7	1.9	41.3	1.9	<0.001
SF-36: Physical component summary	−1.71	−2.89, −0.53	43.1	2.1	41.4	2.1	0.004
Health utility scores	−0.02	−0.03, −0.002	0.7	0.02	0.6	0.02	0.021
	Relative risk (RR)	95% confidence interval (CI)	Mean	SE	Mean	SE	p-Value
ABSENTEEISM[a]	1.81	0.99, 3.29	5.1	5.6	9.2	10.6	0.053
PRESENTEEISM[b]	1.28	1.02, 1.60	43.9	17.8	55.9	23.1	0.035
TOTAL Work Productivity Impairment[c]	1.31	1.05, 1.65	20.3	8.7	26.7	11.6	0.018
TOTAL Activity Impairment	1.04	0.91, 1.20	55.6	13.7	57.9	14.2	0.553
Total # of HCP visits in the past 6 months	1.23	1.11, 1.36	8.1	1.6	10.0	2.0	<0.001
Visited ER in the past 6 months	1.07	0.58, 2.00	0.1	0.1	0.1	0.1	0.820
Hospitalized in the past 6 months	1.46	0.82, 2.61	5.6	5.3	8.2	7.8	0.203
Indirect cost[d]	1.33	1.06, 1.66	¥575,549	¥250,121	¥762,811	¥337,819	0.015
Direct cost	1.44	0.85, 2.45	¥11,952,313	¥10,589,638	¥17,247,591	¥15,361,399	0.176

Multivariate analyses were conducted using generalized linear models using each health and economic burden measure as the outcome variable and CVD related comorbidities as the primary predictor. Subjects without CVD related comorbidities were used as the reference group. All models were adjusted for potential confounders, including age, gender, marital status, education, employment status, household income, health insurance, CCI, BMI, smoking status, alcohol consumption, exercise behaviour, experience of hypoglycaemia, and diagnosis of anxiety, depression and insomnia. Regression coefficient (beta) or relative risk (RR), 95% confidence interval (CI), adjusted mean, standard error, and p-value was reported for each model.

[a] N = 561.

[b] N = 585.

[c] N = 559.

[d] N = 559.

Table 3 – Comparison of health and economic burden among subjects with/without hypoglycemia.

	Multivariate analysis		Adjusted means				
			No hypoglycaemia		Hypoglycaemia		
	β	95% confidence interval (CI)	Mean	SE	Mean	SE	p-value
SF-36: Mental component summary	−2.61	−3.77, 1.78	43.83	1.92	41.21	1.93	<0.001
SF-36: Physical component summary	−3.24	−4.5, −1.99	43.88	2.08	40.64	2.09	<0.001
Health utility scores	−0.04	−0.06, −0.03	0.67	0.02	0.63	0.02	<0.001
	Relative risk (RR)	95% confidence interval (CI)	Mean	SE	Mean	SE	p-value
ABSENTEEISM[a]	3.06	1.53, 6.10	3.90	4.43	11.93	13.53	<0.001
PRESENTEEISM[b]	1.34	1.06, 1.69	42.87	17.43	57.26	23.65	0.016
TOTAL Work Productivity Impairment[c]	1.34	1.05, 1.70	20.11	8.77	26.91	11.57	0.017
TOTAL Activity Impairment	1.45	1.25, 1.68	43.67	10.75	63.42	15.94	<0.001
Total # of HCP visits in the past 6 months	1.23	1.11, 1.38	8.09	1.62	9.99	2.02	<0.001
Visited ER in the past 6 months	1.96	1.06, 3.65	0.06	0.06	0.13	0.11	0.033
Hospitalized in the past 6 months	3.56	2.01, 6.30	3.60	3.39	12.82	12.30	<0.001
Indirect cost[d]	1.31	1.03, 1.66	¥579,605	¥256,161	¥757,473	¥330,622	0.029
Direct cost	3.31	1.95, 5.61	¥7,890,439	¥6,946,464	¥26,126,379	¥23,406,153	<0.001

Multivariate analyses were conducted using generalized linear models using each health and economic burden measure as the outcome variable and hypoglycaemia as the primary predictor. Subjects without hypoglycaemia were used as the reference group. All models were adjusted for potential confounders, including age, gender, marital status, education, employment status, household income, health insurance, CCI, BMI, smoking status, alcohol consumption, exercise behaviour, and diagnosis of CVD related comorbidities, anxiety, depression and insomnia. Regression coefficient (beta) or relative risk (RR), 95% confidence interval (CI), adjusted mean, standard error, and p-value was reported for each model.

[a] N = 561.

[b] N = 585.

[c] N = 559.

[d] N = 559.

patients' thoughts and opinions on the severity of their health conditions, and the impact of the conditions on their daily lives. Such data can only be obtained from patients.

As described in previous studies, diabetes has led to great social and economic burden to both patients and the society, and the cost of diabetes increases with the development of CVD related comorbidities. A published study showed that approximately 36.4% of healthcare expenditure for people with diabetes was attributable to major comorbidities among which 26.4% was for cardiovascular related services [31–33]. In our study, we also found that more than half (54.4%) of the type 2 diabetes patients had CVD related comorbidities and having CVD related comorbidities were associated with worse HRQoL, more work productivity and activity impairment, and increased healthcare resource utilization compared to those without these conditions. In addition, the cost of T2D patients with CVD related comorbidities was 1.4-fold higher after adjustment for confounders. This suggests the need for integrated approaches to prevent and control CVD related comorbidities, including life-style intervention, glycaemic control, and control of hypertension and dyslipidaemia.

To improve patients HRQoL and reduce the disease burden, glycaemic control was the key component of diabetes management which has proven an effective way to reduce the risk of long-term CVD and the associated economic burden [34–36]. Despite that, CVD remains a major cause of mortality and morbidity among T2D patients. Most of the current pharmacotherapies do not adequately modulate the underlying mechanisms that causes accelerated CVD in diabetes. The development and use of diabetes pharmacotherapies that can provide cardiovascular beneficial effects is necessary to alleviate the health and economic burden associated with CVD related comorbidities among T2D patients.

The current analysis also showed that the presence of CVD related comorbidities was more prevalent among older, unemployed and overweight or obese T2D respondents who had more underlying comorbidities, similar to earlier studies [39–41]. Counter to conventional beliefs that smoking is associated with greater risk for CVDs [42,43], T2D respondents who were current smokers were found at lower rate among patients with CVD related comorbidities in this analysis. This could be a result of reverse causation, which is a common concern in cross-sectional studies and it is difficult to determine the temporal order of exposure and outcomes. It is possible that T2D respondents decided to quit smoking after diagnosis and would be consistent with the higher percentage of former smokers observed in T2D respondents with CVD related comorbidities.

We found around one-third (29.3%) of the patients with T2D reported an experience of hypoglycaemia in this study. Hypoglycaemia is the major limiting factor in the lowering glucose treatment of patients with diabetes. Severe hypoglycaemia was associated with increased risk of CVD or CVD events [12], cognitive impairment [44], dementia [45], and even increased mortality [46]. Consistent with previous studies [20,21], we found that hypoglycaemia in patients with type 2 diabetes was associated with worse quality of life, reduced productivity, and increased health care costs. The results also suggested that T2D respondents who experienced hypoglycaemia tended to have higher CCI and be treated with basal insulin.

In this study, we also compared the direct and indirect cost of CVD related comorbidities and hypoglycaemia. We observed that the direct cost of hypoglycaemia was increased around two times compared to those without hypoglycaemia, while the direct cost of CVD related comorbidities increased 40% compare to those without comorbidities. This might be explained by the significantly increased ER visits and hospitalization in the patients with hypoglycaemia episodes. Early detection and treatment of hypoglycaemia would be needed to avoid the ER visits and hospitalization, especially in patients with basal insulin treatment.

As hypoglycaemia was associated with increased humanistic and economic burden, and it was common in patients with basal insulin, patients may consider using the basal insulin analog with a flatter, more stable PKPD profile to reduce the risk of hypoglycaemia and therefore improve outcomes [47]. For example, currently available literature has shown that the basal insulin analog (e.g. glargine, detemir, and degludec) results in lower hypoglycaemia risk and has no additional harmful impact on CVD compared with current basal insulin (e.g. neutral protamine Hagedorn [NPH], or isophane) [48].

Additionally, a substantial proportion (16.7%) of T2D respondents who had completed hypoglycaemia data reported an experience of both hypoglycaemia and CVD related comorbidities in this study, and they had worse HRQoL, more work productivity and activity impairment, more healthcare resource utilization and more costs compared with those with only one of the conditions. This emphasizes the needs for early and immediate disease management, especially for patients who have already had either one of the conditions, to prevent or delay the progression of the disease, and consequently to alleviate the humanistic and economic burden.

This study shows the burden of both CVD and hypoglycaemia in patients with T2D and the patients centered evidence for the need to treat early and safely to prevent either comorbidities. Lately, newer glucose lowering agents, including multiple choices of oral glucose lowering agents and injectable regimens, have been included in diabetes management showing good efficacy with a lower risk of hypoglycaemia and some of them also provides CVD benefit. Relevant potential treatment options available includes sodium–glucose cotransporter 2 (SGLT-2) and Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs). A recent randomized control trial showed that the use of one sodium–glucose cotransporter 2 (SGLT-2) inhibitor was associated with 14% reduction of mortality from cardiovascular causes, myocardial infarction, or stroke (the primary cardiovascular outcomes occurred in 10.5% and 12.1% of the patients in the treatment and placebo group, respectively) in patients with type 2 diabetes at high risk for cardiovascular events [37]. Studies have also reported the effect of GLP-1RAs in reducing the CVD risk among patients with high risk for CVD, though

more solid proof from ongoing clinical tries would be anticipated [38]. Early use of such therapies with additional benefit in addition to glycaemic control may improve not only the clinical outcome but also the patient related outcomes that was examined in this study.

Limitations of this study are in the following aspects. Data from the NHWS are self-reported and cross-sectional and not externally validated using other data sources such as medical records or physician reports. Causal relationships between T2D treatment and health outcomes cannot be assumed. All data are patient reported so no verification of diagnoses or healthcare resource utilization can be conducted. The NHWS is broadly representative of the Japanese adult population but representativeness of each treatment T2D subsample is unknown. For example, although the prevalence of diabetes is higher in male than female in Japan [49], we observed a disproportionate sample size of male subjects in this T2D subsample. Finally, while the most updated data are used to extrapolate costs, the actual costs may be underestimated due to external factors such as, inflation, although relative comparisons (i.e., relative differences in costs between one group and another) should not be affected.

5. Conclusion

In conclusion, CVD related comorbidities and hypoglycaemia is associated with significant humanistic and economic burden in patients with T2D. These findings confirmed the importance of developing better T2D treatment with better CVD and hypoglycaemia outcomes to alleviate the burden.

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Conflict of interests

Yasuo Terauchi has received honoraria for speakers bureaus from Astellas Pharma Inc., AstraZeneca K.K., Bayer Yakuhin, Ltd., Daiichi Sankyo Company Limited, Dainippon Sumitomo Pharma Co., Ltd., Eli Lilly Japan K.K., Kowa Pharmaceutical Company Ltd., Merck Sharp & Dohme K.K., Mitsubishi Tanabe Pharma Corporation, Nippon Boehringer Ingelheim Co., Ltd., Novo Nordisk Pharma Ltd., Ono Pharmaceutical Co., Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Sanofi K.K., Shionogi & Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd. and Takeda Pharmaceutical Company Limited; and has received grants from Astellas Pharma Inc., AstraZeneca K.K., Bayer Yakuhin, Ltd., Daiichi Sankyo Company Limited, Dainippon Sumitomo Pharma Co., Ltd., Eli Lilly Japan K.K., Kowa Pharmaceutical Company Ltd., MSD K.K., Mitsubishi Tanabe Pharma Corporation, Nippon Boehringer Ingelheim Co., Ltd., Novo Nordisk Pharma Ltd., Ono Pharmaceutical Co., Ltd., Pfizer Japan Inc., Sanwa Kagaku Kenkyusho Co., Ltd., Sanofi K.K., Shionogi & Co., Ltd, Taisho Toyama Pharmaceutical Co., Ltd. and Takeda Pharmaceutical Company Limited.

Asuka Ozaki, Yuki Tajima and Yujin Shuto are employees of Sanofi K.K.

Xiahong Zhao, Cheryl Teoh and Dena Jaffe are employees of Kantar Health LLC and received a consulting fee from Sanofi K.K. Japan during the conduct of the study.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.01.019.

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