


ORIGINAL ARTICLE

Association of hypoglycaemia severity with clinical, patient-reported and economic outcomes in US patients with type 2 diabetes using basal insulin

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Funding information

Sanofi, Bridgewater, New Jersey.

Aims: To evaluate the clinical and patient-reported outcomes and healthcare utilization and costs associated with patient-reported hypoglycaemia in US adults with type 2 diabetes (T2D) treated with basal insulin.

Materials and methods: This was an observational, cross-sectional, survey-based study of adults with T2D on basal insulin \pm oral antidiabetes drugs (OADs) or rapid-acting/premixed insulin, who had in the past ever experienced hypoglycaemia, using US data from the National Health and Wellness Survey. Eligible patients were categorized as having no hypoglycaemia (38.7%), non-severe hypoglycaemia (55.1%), or severe hypoglycaemia (6.2%) in the preceding 3 months. Outcomes included health-related quality of life (HRQoL), work productivity and activity impairment, healthcare resource utilization, and estimated direct and indirect costs. Multivariable regression models were performed to control for patient characteristics.

Results: Patients who experienced severe hypoglycaemia had significantly ($P < .05$) lower HRQoL scores, greater overall impairment of work productivity and activity, greater healthcare resource utilization, and higher costs compared with those who experienced non-severe or no hypoglycaemia. Patients with non-severe hypoglycaemia also reported an impact on the number of provider visits, indirect costs, and HRQoL.

Conclusions: Patients with T2D using basal insulin \pm OADs or rapid-acting/premixed insulin in the United States who experienced severe hypoglycaemia had greater impairment of activity and work productivity, utilized more healthcare resources, and incurred higher associated costs than those with non-severe or no hypoglycaemia. The study also demonstrated the impact that non-severe hypoglycaemic events have on economic and HRQoL outcomes. Reducing the incidence and severity of hypoglycaemia could lead to clinically meaningful improvements in HRQoL and may result in lower healthcare utilization and associated costs.

KEYWORDS

hypoglycaemia, health-related quality of life, work productivity, activity impairment, type 2 diabetes, basal insulin

1 | INTRODUCTION

Diabetes is a chronic, progressive disease with an increasing prevalence worldwide¹ and in the United States.² The economic impact of diabetes is substantial,³ with indirect costs of diabetes accounting for an estimated 36% of the total economic burden in North America.⁴

Type 2 diabetes (T2D) is generally initially managed with lifestyle interventions and oral antidiabetes drugs (OADs), but many patients will eventually require insulin therapy to maintain good glycaemic control.^{5,6}

Some anti-hyperglycaemic agents, such as sulphonylureas and exogenous insulin, can cause hypoglycaemia.⁷ The psychological

impact of hypoglycaemia can affect adherence to treatment, leading to missed or incorrect dosage,⁸ with fear of hypoglycaemia and changes in self-care behaviour possibly compromising glycaemic control.⁹ Research has also shown that, among patients with T2D in the United States, those who experienced hypoglycaemia were more likely to report having lower health-related quality of life (HRQoL) and higher rates of diabetes-related emergency room (ER) and physician visits.¹⁰ For example, the Centers for Disease Control and Prevention report a total of 245 000 ER visits by adults with diabetes in the United States attributed to hypoglycaemia in 2014.² Hypoglycaemia-related medical expenditure and hospitalizations are associated with considerable costs and represent a major contribution to healthcare expenditures in the United States¹¹ and worldwide.¹ US patients who experience hypoglycaemia within 6 months of initiating basal insulin are also at an increased risk of basal insulin therapy discontinuation (68.1% of patients with hypoglycaemia within 6 months vs 53.9% of those without hypoglycaemia within 6 months)¹² and have significantly higher healthcare resource utilization and costs than those without hypoglycaemia (\$13 662 vs \$7506).¹³

Hypoglycaemic symptoms and symptom severity also have an adverse effect on patients' ratings of their HRQoL.¹⁴ It is therefore important to understand the burdens of hypoglycaemia from the patient perspective, including those of non-severe hypoglycaemic episodes that do not require assistance from a healthcare provider. Studies of the burden of hypoglycaemia in T2D often use data captured from administrative claims via International Classification of Diseases Ninth Revision Clinical Modification (ICD-9-CM) codes.^{11,15} In such studies, the setting of the event is often used as a proxy for the severity of the event (ie, events requiring assistance from a healthcare professional, ER visits, or hospitalizations are considered the more severe events),¹⁶ which may result in an underestimation of the true incidence and burden of hypoglycaemia, especially mild-to-moderate hypoglycaemia.^{17,18} Additionally, while a number of real-world database studies have reported costs associated with severe hypoglycaemia,^{19,20} few studies have investigated the direct or indirect burden of self-reported, non-severe hypoglycaemia that is managed by the patient themselves. This study was conducted to evaluate, from the patient's perspective, the clinical and patient-reported outcomes, as well as healthcare utilization and costs, associated with patient-reported severe and non-severe hypoglycaemia in US patients with T2D using basal insulin \pm OADs or rapid-acting/premixed insulin.

2 | MATERIALS AND METHODS

2.1 | Study design

This was an observational, cross-sectional, survey-based study of adults (age \geq 18 years) with T2D living in the United States and using basal insulin \pm OADs or rapid-acting/premixed insulin, who reported having ever experienced hypoglycaemia. Data were obtained from the National Health and Wellness Survey (NHWS), an annual, patient-reported, online survey of demographically representative

cross-sections of the adult populations of 10 countries, including the United States.^{21,22} All data are self-reported directly by participants. For the present study, data for the years 2011, 2012 and 2013 were combined to ensure a sufficiently large sample size for statistical analyses. In the US NHWS, age, gender and race/ethnicity are matched to the demographic profile of the US population (aged \geq 18 years) according to the US Bureau of the Census.

The NHWS is reviewed and approved each year by the Essex Institutional Review Board (Lebanon, New Jersey), and informed consent was obtained from participants before its administration. Deduplication was used if a person participated in >1 year of the survey, and only their most recent record was used. In principle, no data are missing from the NHWS results; however, variables that do not apply to a specific respondent are not included. For example, no data on work productivity are included for respondents who report that they are unemployed. Additionally, respondents are permitted to decline to answer some questions concerning demographic variables (eg, income, weight, height). When no data are recorded for a question, the value is recorded as "missing."

2.2 | Respondents

Potential respondents were identified through the general panel of Lightspeed Research, a partner organization of the NHWS that collects digital data from an online consumer panel.²³ Specific criteria for inclusion in the study were: age \geq 18 years, self-reported diagnosis of T2D, use of a basal insulin with or without the concomitant use of OADs and/or rapid-acting/premixed insulin, and experience of at least 1 hypoglycaemic event in the past. Included patients were surveyed regarding their experience with hypoglycaemia in the preceding 3 months; non-severe hypoglycaemia refers to self-managed events, while severe hypoglycaemia events required third-party assistance.²⁴ It was possible for a respondent to complete >1 survey over the 3-year study period; in these instances, only the most recent data for a given respondent were kept.

2.3 | Study measures

2.3.1 | Demographics and comorbidities

To understand the disease burden associated with hypoglycaemia and evaluate differences between respondents reporting no hypoglycaemia, non-severe hypoglycaemia or severe hypoglycaemia in the preceding 3 months, respondents were compared based on demographics and health history using the variables listed in Appendix S1 in File S1.

2.3.2 | Health-related quality of life

The HRQoL of respondents was assessed using the Medical Outcomes 12-item Short-Form Survey Instrument version 2 (SF-12v2) for the year 2011²⁵; and the Medical Outcomes 36-item Short-Form Survey Instrument version 2 (SF-36v2) for 2012 and 2013.²⁶ The SF-36v2 reports on health status in 8 domains (Physical functioning, Physical role limitations, Bodily pain, General health, Vitality, Social functioning, Emotional role limitations and Mental health), from which 2 summary scores are calculated: the Physical Component Summary

(PCS) and the Mental Component Summary (MCS). These are normed to a mean of 50 for the general US population; a higher score indicates better health status. As the SF12-v2 provides the same metrics as the SF-36v2, data for all 3 years in the study can be pooled for subsequent analyses.²⁵ In addition to generating summary PCS and MCS scores, the SF-36v2 can also be used to generate health state utilities by applying the Short-Form 6 Dimensions (SF-6D) algorithm, which takes items from the domains of the SF-36v2.²⁷ Health utility scores from the SF-6D were derived from the SF-12v2 or SF-36v2 for the respective survey years. The SF-6D health utilities index has interval scoring properties and yields summary scores on a theoretical scale of 0 to 1. Higher scores indicate better health status.

2.3.3 | Work productivity

The work productivity of respondents was evaluated using the Work Productivity and Activity Impairment (WPAI) questionnaire (Table 1).^{28,29} This is a 6-item validated instrument that consists of 4 metrics: absenteeism; presenteeism; overall work productivity loss; and activity impairment. Unemployed respondents were not included in evaluations of absenteeism, presenteeism or work productivity loss.

2.3.4 | Healthcare resource utilization

Healthcare resource utilization over the previous 6 months was assessed by patient recall of the number of overall provider visits, ER visits and hospitalizations (not necessarily diabetes-specific; Table 2).

2.3.5 | Healthcare costs

Both direct and indirect healthcare costs were calculated to give annualized estimates. Direct costs were based on the costs for an average physician visit, ER visit and hospitalization, determined using the 2012 Medical Expenditure Panel Survey.³⁰ For each respondent, the number of each type of visit was multiplied by 2, to project the annual number of visits, and then multiplied by its average cost.

TABLE 1 Work Productivity and Activity Impairment questionnaire^{28,29}

WPAI questionnaire domain	Description
Absenteeism	Percentage of work time missed because of one's health in the past 7 days
Presenteeism	Percentage of impairment experienced while at work in the past 7 days because of one's health; reduced on-the-job effectiveness
Work productivity loss	Overall work impairment estimated as a combination of absenteeism and presenteeism
Activity impairment	Percentage of impairment of regular daily activities because of one's health in the past 7 days, other than work at a job

Abbreviation: WPAI, Work Productivity and Activity Impairment. The WPAI is a validated, 6-item, self-administered questionnaire that quantifies the influence of respondents' general health and disease symptom severity on their work productivity and regular activities during the previous 7 days. Scores from 4 domains are produced. Unemployed respondents were not included in evaluations of absenteeism, presenteeism, or work productivity loss; all respondents provided data for activity impairment; respondents in full- or part-time employment provided data for all 4 domains.

TABLE 2 Assessment of healthcare-resource use visits over the previous 6 months

Healthcare resource utilization	Survey question
Number of provider visits	How many visits did you make to the following traditional healthcare provider(s) in the past 6 months? If you are unsure, please provide your best estimate
Number of ER visits	How many times have you been to the emergency room for your own medical condition ^a in the past 6 months?
Number of hospitalizations	How many times have you been hospitalized for your own medical condition ^a in the past 6 months?

Abbreviation: ER, emergency room.

^a The term "your own medical condition" was used in the survey questions to ensure that all medical conditions were included, not only type 2 diabetes, and to exclude visits to accompany a friend or relative.

Indirect costs were calculated by estimating wages/salaries for each respondent using 2012 data from the Bureau of Labor Statistics.³¹ The number of hours missed because of health impairment (absenteeism), and the number of hours being unproductive while at work (presenteeism) because of health impairment during the previous week were each multiplied by the hourly wage rates to provide the total lost wages; these figures were then multiplied by the average number of work weeks in a year (ie, 50 weeks) to obtain annual indirect cost estimates.

2.4 | Statistical analyses

Bivariate differences were evaluated between respondents experiencing no, non-severe or severe hypoglycaemia for respondent demographics and characteristics, health status, healthcare resource use, and healthcare costs. For categorical variables, χ^2 tests were used to determine significant differences; one-way ANOVAs were used for continuous variables.

To analyse whether hypoglycaemia groups (ie, non-severe vs severe hypoglycaemia with no hypoglycaemia as the reference group for all comparisons) differ on health outcomes, a series of generalized linear models were used to test whether the adjusted means (accounting for covariates) of the outcomes differed between groups. Generalized linear models with identity link functions were used for health status variables as they were normally distributed. Because of a pronounced skew, generalized linear models specifying a negative binomial distribution were used for work productivity and activity impairment, healthcare resource use and cost variables.

Covariates included all variables identified as significantly different between groups in the bivariate analyses, and those identified a priori as clinically important. Specifically, covariates included age, gender, ethnicity, Charlson comorbidity index (CCI; excluding diabetes and diabetes-related complications), income, body mass index, insurance, exercise, years diagnosed with diabetes, glycated haemoglobin (HbA1c), presence of any diabetes complications, and total number of OADs used. Adjusted means and *P* values were reported for each model.

3 | RESULTS

3.1 | Study population

A total of 17 676 unique respondents with T2D were identified from the US NHWS, of whom 2423 met the criteria for inclusion in the study and completed the survey (Figure 1).

3.2 | Patient characteristics according to hypoglycaemia category

The demographics, health characteristics and diabetes characteristics of respondents are shown in Table 3. Patients ($N = 2423$) were categorized into the categories “no hypoglycaemia in the past 3 months” ($n = 938$; 38.7%), “non-severe hypoglycaemia in the past 3 months” ($n = 1335$; 55.1%), and “severe hypoglycaemia in the past 3 months” ($n = 150$; 6.2%). For both non-severe and severe hypoglycaemia, 33.3% of episodes were reported as being nocturnal. Glycaemic control was sub-optimal across the 3 categories, with 47.2%, 48.8% and 44.0% of patients reporting $HbA1c \geq 7.0\%$ in the no, non-severe and severe hypoglycaemia categories, respectively.

In general, the patients with severe hypoglycaemia were significantly younger than those with no hypoglycaemia and those with non-severe hypoglycaemia (mean age 55.32 vs 60.79 and 61.03 years; $P < .001$ for both comparisons); had significantly higher CCI scores than patients with no hypoglycaemia or

non-severe hypoglycaemia (mean 1.51 vs 0.88 and 1.05; $P < .001$ for both comparisons); and were more likely than patients with no hypoglycaemia to have had any microvascular disease, complications from diabetes including macular oedema or diabetic retinopathy, kidney disease, foot or leg ulcer, neuropathic pain, or diabetes with end-organ damage. Concomitant use of rapid-acting/premixed insulin was highest among patients with non-severe hypoglycaemia and lowest among those with no hypoglycaemia.

3.3 | Association of hypoglycaemia with outcomes (unadjusted)

Bivariate analyses were used to compare patients who experienced severe hypoglycaemia with those who experienced non-severe or no hypoglycaemia (Table S1 in File S1). Unadjusted comparisons showed that, compared with patients with non-severe or no hypoglycaemia, those with severe hypoglycaemia had significantly poorer HRQoL (ie, significantly lower SF-36v2 MCS and PCS scores, and significantly lower SF-6D health utility scores); had significantly greater work impairment (absenteeism, presenteeism and overall work impairment) scores and greater activity impairment scores; significantly greater utilization of healthcare resources (numbers of traditional provider visits, ER visits and hospitalizations); and incurred significantly higher associated indirect, direct and total costs.

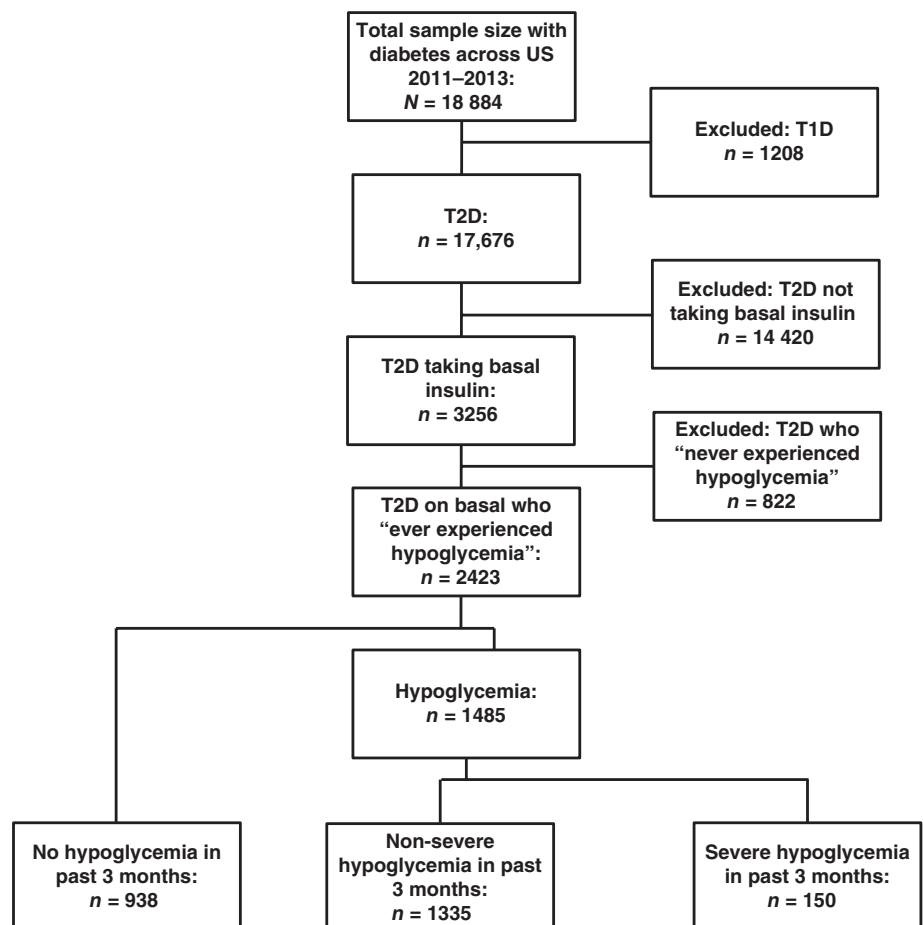


FIGURE 1 Patient attrition. T2D, type 2 diabetes

TABLE 3 Demographics, health characteristics and diabetes characteristics of respondents using basal insulin \pm OADs and/or rapid-acting/premixed insulin with no hypoglycaemia, non-severe hypoglycaemia or severe hypoglycaemia

	Patients with T2D using basal insulin									
	No hypoglycaemia in the past 3 months, N = 938		Non-severe hypoglycaemia in the past 3 months, N = 1335		Severe hypoglycaemia in the past 3 months, N = 150					
	Mean/%	SD/N	Mean/%	SD/N	Mean/%	SD/N				
Demographic characteristics										
Age, years	60.8 _a	11.0	61.0 _a	10.5	55.3 _b	13.0	11.0	<.001		
Gender		Male	61.2%	817 _a	61.3%	92 _a	62.5%	1495	.824	
Race/ethnicity		Non-Hispanic white	73.7%	691 _a	77.4%	1033 _a	72.7%	109 _a	1833	.301
		Non-Hispanic black	11.2%	105 _a	10.3%	137 _a	14.0%	21 _a	263	
		Hispanic	8.6%	81 _a	6.4%	86 _a	8.0%	12 _a	179	
		Other ethnicity	6.5%	61 _a	5.9%	79 _a	5.3%	8 _a	148	
Labour force participation		Yes	30.4%	285 _a	30.0%	400 _a	26.7%	40 _a	725	.652
Currently has insurance		Yes	89.4%	839 _a	91.7%	1224 _a	92.7%	139 _a	2202	.139
Health characteristics										
BMI category		BMI: underweight	0.1%	1 _a	0.1%	2 _a	0.7%	1 _a	4	.058
		BMI: normal weight	4.8%	45 _a	5.7%	76 _a	6.7%	10 _a	131	
		BMI: overweight	19.1%	179 _a	22.7%	303 _a	25.3%	38 _a	520	
		BMI: obese	72.8%	683 _a	69.5%	928 _a	66.7%	100 _a	1711	
		BMI: unknown	3.2%	30 _a	1.9%	26 _a	0.7%	1 _a	57	
Alcohol consumption		Yes	45.0%	422 _a	48.2%	643 _a	52.7%	79 _a	1144	.126
CCI		Yes	0.88 _a	1.38	1.05 _b	1.56	1.51 _c	1.80	1.52	<.001
Presence of any macrovascular disease (congestive heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease)		Yes	24.5% _a	230	26.7% _a	356	32.7% _a	49	635	.092
Presence of any microvascular disease (retinopathy, kidney disease)		Yes	16.2% _a	152	20.7% _b	277	27.3% _b	41	470	.001
Diabetes characteristics										
Years diagnosed with diabetes		Do not know/NA	16.3 _a	9.4	17.1 _a	8.9	15.6 _a	9.4	9.1	.024
HbA1c mean		Controlled <7	7.51 _a	1.46	7.31 _b	1.29	7.78 _a	1.84	1.39	<.001
HbA1c		Uncontrolled ≥ 7	29.5%	277	20.7%	276	37.3%	56	609	.032
		Daytime	33.0% _a	218	38.4% ^a	407	29.8% ^a	28	653	
		Night-time (nocturnal)	67.0% ^a	443	61.6% ^a	652	70.2% ^a	66	1161	
Time of day at which hypoglycaemia occurred among those who experienced hypoglycaemia in the past 3 months		Daytime	0.0% [*]	0	66.7% _a	890	66.7% _a	100	990	1
		Night-time (nocturnal)	0.0% [*]	0	33.3% _a	445	33.3% _a	50	495	
Presence of any complications from diabetes		Yes	43.8% _a	411	49.9% _b	666	62.0% _c	93	1170	<.001
Years using insulin		Yes	8.2 _a	7.4	9.3 _b	7.5	9.1 _{a,b}	9.7	7.7	.003

(Continues)

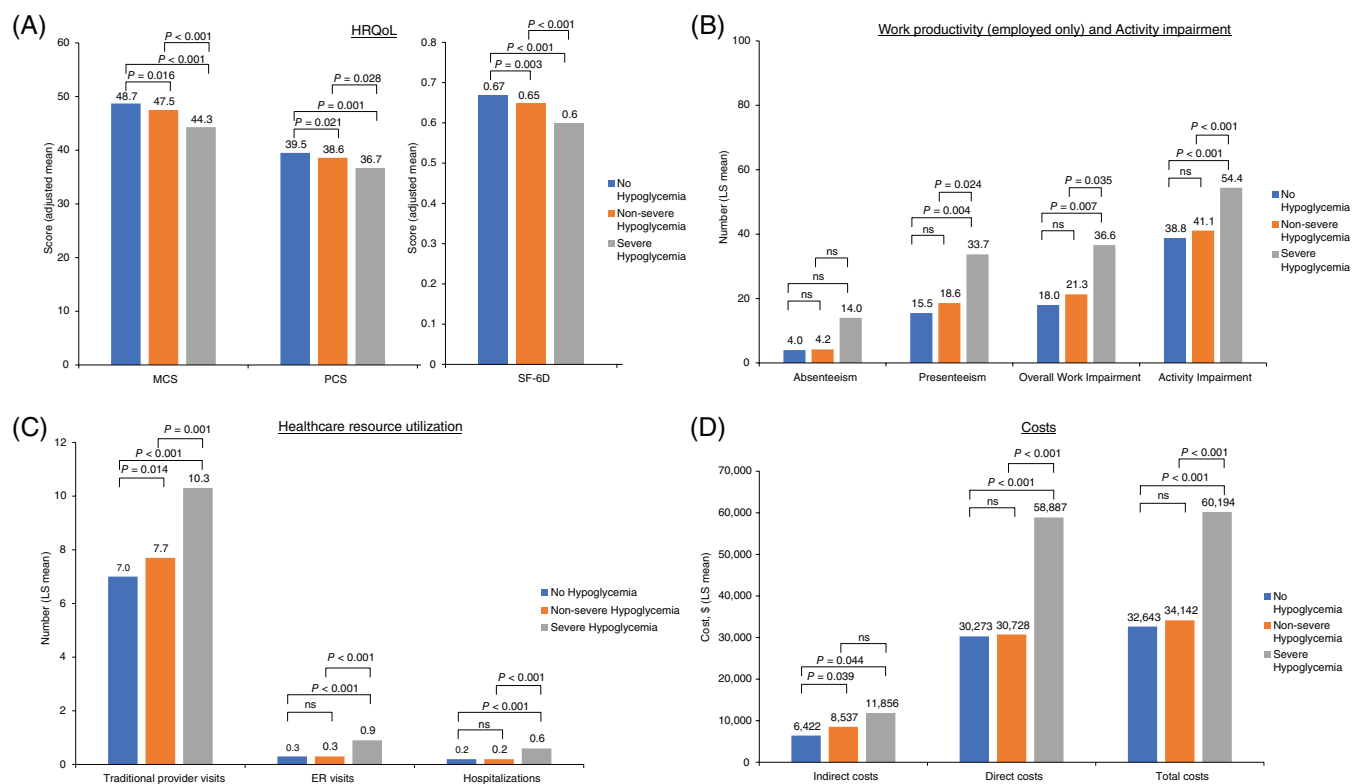


FIGURE 2 A, Health-related quality of life (HRQoL), B, work productivity and activity impairment, C, healthcare resource utilization and D, costs by hypoglycaemia severity among patients with type 2 diabetes using basal insulin \pm OADs or rapid-acting/premixed insulin (adjusted for covariates). All generalized linear models adjusted for the following covariates: age, gender (female vs male), ethnicity (non-Hispanic black, Hispanic, other vs non-Hispanic white), income ($<$ \$50 000, declined to answer vs $>$ \$50 000), insurance (do not have vs have), presence of diabetes complications (have any vs none), glycated haemoglobin (HbA1c; do not know, uncontrolled vs controlled), years diagnosed with diabetes, number of oral antidiabetes drugs, Charlson comorbidity index (excluding diabetes and diabetes-related complications), body mass index (overweight, obese, unknown vs underweight/normal weight), and exercise (≥ 1 times vs 0 times in past month). Non-severe hypoglycaemia refers to self-managed events; severe hypoglycaemia refers to events that required third-party assistance. Costs are in 2012 USD. Absenteeism, presenteeism, overall work impairment and indirect costs calculated only for employed respondents. Total costs for unemployed respondents do not include indirect costs. Physical and mental component summary scores are normed to a mean of 50 and an SD of 10 for the US population. Higher scores indicate better health status. The SF-6D health utilities index has interval scoring properties and yields summary scores on a theoretical 0 to 1 scale. Higher scores indicate better health status. Abbreviations: ns, not significant; LS, least squares

Patients with non-severe hypoglycaemia had greater annual indirect costs compared with those without hypoglycaemia ($P = .039$; Figure 2D).

4 | DISCUSSION

In the present study, we aimed to evaluate the clinical and patient-reported outcomes, as well as healthcare utilization and costs, associated with patient-reported severe and non-severe hypoglycaemia in patients with T2D using basal insulin \pm OADs or rapid-acting/premixed insulin. Outcomes were compared according to self-reported hypoglycaemia severity (no hypoglycaemia, non-severe or severe) experienced during the preceding 3 months. Both in unadjusted comparisons and after adjusting for covariates, patients with severe hypoglycaemia had significantly worse HRQoL; greater impairment in work productivity and activity; greater healthcare resource utilization; and higher associated indirect, direct and total costs compared with those with non-severe or no hypoglycaemia. The prevalence of

hypoglycaemia reported by the patients in this study was high, probably reflecting the use of premixed and rapid/fast-acting preparations along with the basal insulin. Higher rates of hypoglycaemia in real-world practice, compared with clinical trial settings, have been previously reported; for example in the Hypoglycaemia Assessment Tool (HAT) study.³⁷ These observations have been attributed to the inherent constraints of randomized controlled trials (eg, excluding subjects highly vulnerable to hypoglycaemia), which are likely to have resulted in an underestimation of the burden of hypoglycaemia in clinical practice.^{37,38} Additionally, patients with non-severe hypoglycaemia had significantly greater impairment in HRQoL, a higher number of traditional physician's visits and higher indirect costs than patients with no hypoglycaemia. The data from the present analysis support those from previous studies, which report significantly lower HRQoL,¹⁸ and significantly higher economic burden^{11,18} in patients with T2D experiencing hypoglycaemia compared with those without.

Data on NHWS participants with self-reported T2D have been collected in previous studies to assess the severity and frequency of hypoglycaemia episodes among patients treated with OADs only

(no insulin). Among a cohort of US adults re-contacted in 2007, using the EuroQol-5 Dimension (EQ-5D) questionnaire, hypoglycaemia was independently associated with lower HRQoL, as demonstrated by a significantly lower utility score among patients with hypoglycaemia compared with those not reporting hypoglycaemia (0.78 vs 0.86, respectively) as well as a significantly higher score on the 'worry' subscale of the Hypoglycemia Fear Survey, which was administered as an additional questionnaire during the re-contacted survey (17.5 vs 6.2, respectively). The magnitude of worsening in HRQoL increased with the frequency and severity of hypoglycaemic episodes. Symptoms of hypoglycaemia in the preceding 6 months were common in this cohort of patients with T2D using OADs and were reported by up to 63% of patients. Approximately 50% of those with hypoglycaemia symptoms reported mild hypoglycaemia, 33% reported moderate hypoglycaemia, and 17% reported severe (needing assistance of others) or very severe (needing medical attention) hypoglycaemia.³⁹ Williams et al.¹⁰ also reported on adult NHWS participants (data collected 2006-2008) with self-reported T2D who were on at least 1 OAD (no insulin), but focused on recent hypoglycaemia events that occurred in the 2 weeks preceding the survey. Overall, 13.8% of patients in that short-term study reported experiencing hypoglycaemia symptoms. Those with hypoglycaemia in the past 2 weeks were significantly more likely to have lower HRQoL scores, lower treatment satisfaction scores, and higher levels of healthcare resource utilization.

A survey of insulin-treated Japanese patients with either type 1 diabetes or T2D showed that experiencing a non-severe hypoglycaemic event can have a negative impact on diabetes management: 16% of patients with a daytime event and 19% of patients with a nocturnal event changed their insulin dose after the event. After a daytime event, 25% of patients reported a negative impact on their daily activities or work. After a nocturnal event, 34% reported a negative impact on sleep and 23% reported a negative impact on their functioning and well-being the following day.⁴⁰ Non-severe nocturnal hypoglycaemic events not only have serious consequences for patients, but also carry a considerable economic burden as a result of lost work productivity, doctor visits and medical care required because of falls or injuries.⁴¹

The present study adds to the current knowledge base by describing clinical and patient-reported outcomes, healthcare utilization, and direct and indirect costs from a US population of patients with self-reported diabetes, but now focusing on those patients using basal insulin \pm OADs or rapid-acting/premixed insulin. In line with previous real-world studies, the present study highlights the burden of hypoglycaemia on healthcare resource utilization, costs, and HRQoL and shows that this burden increases with severity of hypoglycaemia, but already significantly impacts patients at lower severity levels.

The present study has several strengths. Unlike most real-world studies that capture only the most severe events that result in a healthcare encounter, this study also captured patient reports of non-severe hypoglycaemia. The patients' perspectives may highlight higher rates of hypoglycaemia than would be assumed by healthcare providers or than those which can be extracted from administrative claims or electronic medical record databases. Real-world data

capturing the patient perspective are important to better understand the true burden of hypoglycaemia in the patient's life. Using data from surveys such as the NHWS provides a unique way of capturing the personal and social context of patients, including quality of life, work impairment, healthcare utilization and costs.

Some limitations of the present study should also be mentioned. Because of the self-reported nature of this study, diabetes diagnosis and other variables could not be verified from patients' medical charts or other objective data. The validity of the study may be reduced because self-reported data are subject to recall bias, such as recalling the number of doctor visits, ER visits and hospitalizations. However, the timeframe of the healthcare resource use variables in the study required recall for the past 6 months, which is within the timeframes of other large-scale cross-sectional surveys. For example, the National Health Interview Survey of the Centers for Disease Control and Prevention, a cross-sectional household interview survey, asks about healthcare resource use in the past 12 months.⁴² In addition, patients may have experienced >1 hypoglycaemic event in the past 3 months of the survey, and it cannot be known which event they reported; however, only 1 hypoglycaemic category could be reported for the analysis and the overall rate of hypoglycaemia may have been underestimated in this study. Patient-reported hypoglycaemic events may have been estimated more accurately in this study than would have been possible with other types of real-world studies, such as electronic medical records or claims data analyses. The observational HAT study used self-assessment questionnaires and patient diaries and found that 46.5% of patients with T2D receiving insulin treatment reported hypoglycaemia over a 4-week period, a higher rate of patient-reported hypoglycaemia than previously reported.³⁷ The NHWS data are cross-sectional in nature, self-reported without direct means of validating the responses, and do not allow causal explanations to be made; a randomized controlled study would be needed to identify any causal relationships among the variables under consideration. Although a number of respondent characteristics were adjusted for, there may be additional variables that were not adjusted for or that have not been measured or assessed, which may have biased the results. Further, because claims specifically linking resource use with diabetes and/or hypoglycaemia are not captured by the NHWS database, healthcare resource utilization data could not be definitively attributed to diabetes. However, comorbidities (ie, CCI) were controlled for in the multivariable analyses to better estimate the association between resource use and diabetes/hypoglycaemia. Finally, while the NHWS is designed to be representative of the general US adult population, it is possible that the diabetes subpopulation may have been selectively underrepresented, because of age and/or technology-related limitations; the sample is likely to favour younger, healthier adults (see Table 3 for detailed demographic and clinical patient characteristics), and respondents without Internet or computer access were not represented in the current sample. The study may have picked up a population which was at a higher risk of hypoglycaemia by including only patients who reported having experienced hypoglycaemia in the past. The results may not be generalizable to the wider population.

In conclusion, the results of the present study suggest that, of US patients with T2D using basal insulin \pm OADs or rapid-acting/

premixed insulin, those experiencing severe hypoglycaemia had greater impairment of activity and work productivity, utilized health-care resources to a greater extent, incurred higher associated costs than those with non-severe or no hypoglycaemia, and reported a negative impact on HRQoL outcomes. The study also highlights the burden of non-severe hypoglycaemia, in particular on patients' HRQoL, the number of outpatient visits, and indirect healthcare costs. Reducing the incidence and severity of hypoglycaemia could lead to clinically meaningful improvements in HRQoL, and reduce healthcare utilization and associated costs. These findings highlight a need to reduce hypoglycaemia and minimize its negative effects in patients with T2D on insulin therapy.

ACKNOWLEDGMENTS

This study was funded by Sanofi, Bridgewater, NJ, USA. The authors gratefully acknowledge the contributions to this manuscript of Hongwei Wang and Liyue Tong. The authors received writing/editorial support in the preparation of this manuscript provided by Grace Richmond, PhD, and Tessa Hartog, PhD, of Excerpta Medica, funded by Sanofi, Bridgewater, NJ, USA.

Conflict of interest

L. M. is a consultant and advisory board member for Novo Nordisk and Sanofi and an advisory board member of Intarcia Therapeutics. L.L. and S.G. are employees of Kantar Health, which received funding from Sanofi to conduct this study. R.P. is an employee of Sanofi.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Meneghini LF, Lee LK, Gupta S, Preblich R. Association of hypoglycaemia severity with clinical, patient-reported and economic outcomes in US patients with type 2 diabetes using basal insulin. *Diabetes Obes Metab*. 2018;20:1156-1165. <https://doi.org/10.1111/dom.13208>