

Severity of hypoglycaemia and health-related quality of life, work productivity and healthcare costs in patients with type 2 diabetes in Europe

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Summary

Aims: Hypoglycaemia in patients with type 2 diabetes mellitus (T2DM) is associated with poor health outcomes, such as reduced health-related quality of life (HRQoL). This study aimed to assess the impact of hypoglycaemic events by severity on HRQoL, work productivity and healthcare costs in patients with T2DM.

Materials and Methods: European patients with T2DM selected from the National Health and Wellness Survey who were currently receiving pharmacologic therapy were stratified into 3 groups based on the reported history and severity of hypoglycaemic events (no event, nonsevere, severe) experienced in the previous 3 months. Patients' work productivity, HRQoL, healthcare resource use (HCRU) and associated costs were assessed as self-reported outcomes.

Results: Of 1269 patients included in the study, 652 (51.4%) patients had not experienced an event, while 533 (42.0%) and 84 (6.6%) patients had experienced nonsevere and severe hypoglycaemic events, respectively, in the previous 3 months. An increase in hypoglycaemia severity was associated with a decrease in HRQoL, and an increase in HCRU and healthcare costs.

Conclusions: The impact of hypoglycaemia varies by severity and has a negative impact on HRQoL and overall HCRU and costs.

KEYWORDS

economic burden, healthcare resource use, health-related quality of life, hypoglycaemia, type 2 diabetes mellitus, work productivity

1 | INTRODUCTION

The treatment of type 2 diabetes mellitus (T2DM) aims to maintain glycaemic control by optimizing the drug and dose regimen to prevent long-term microvascular and macrovascular complications.¹ However, the positive impact of tight glycaemic control is counteracted by the negative impact of an increased incidence of hypoglycaemia.²

Hypoglycaemia is a recognized risk that is associated with the use of a number of treatments for T2DM, particularly insulin and sulfonylureas,^{3,4} that can expose patients to potential harmful effects.⁵ Indeed, the clinical impact of severe hypoglycaemia is substantial, including confusion, seizures, coma or even death.⁶⁻¹¹

Existing health outcome research on hypoglycaemic events tends to focus on severe events that are reported or treated by clinicians.¹²

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However, most hypoglycaemic events are mild to moderate in nature. There is limited evidence describing the impact of mild-to-moderate hypoglycaemia in the current literature; hence, it is likely that the burden of these events may be underestimated. The present study aimed to assess the impact of hypoglycaemic events, by severity, on health-related quality of life (HRQoL), work productivity loss, healthcare resource use (HCRU) and costs in Europe.

2 | MATERIALS AND METHODS

2.1 | Patients

Patients were selected from the 2013 National Health and Wellness Survey (NHWS) conducted in 5 European countries: France, Germany, Italy, Spain and the United Kingdom (UK). The NHWS is an annual, cross-sectional, Internet-based survey of demographics, disease status, healthcare attitudes, behaviours and outcomes in adults aged 18 years and older. Sampling of the survey is designed to reflect the population of the surveyed countries. Each year, data on age and gender distributions in each country are obtained from the International Database—a database maintained by the United States Census Bureau. These proportions are then mimicked during the recruitment of panel members through a sampling framework, stratified by age, gender and race/ethnicity, and verified against national health statistics to ensure the final sample matches the demographic composition of the surveyed countries.¹³ To further ensure a representative sample (particularly in the population aged 65 years and older), the online panel recruitment is supplemented by computer-assisted web interviews, whereby respondents are recruited over the telephone and given the choice of being interviewed live or receiving a link to the survey via email to complete it on their own.

This study included patients in the NHWS who self-reported a diagnosis of T2DM and were currently receiving pharmacologic therapy for this condition. Analyses were conducted on the combined data from all 5 countries. Baseline demographic and clinical characteristics included age, gender, marital status (married/living with partner or not-married), education (university degree or greater versus less than university degree), household income (<€20 000, €20 000–50 000, >€50 000 or decline to answer), body mass index (BMI; underweight, normal, overweight, obese or decline to answer), smoking status (% who currently smoke), alcohol use (% who currently drink), exercise behaviour (% who currently exercise), insulin/sulfonylureas use, duration of diagnosis, HbA1c and comorbidities recorded in the Charlson Comorbidity Index (CCI).¹⁴ The CCI weights the presence of the following comorbidities and sums the result, with the total index score representing the comorbid burden: HIV/AIDS, metastatic tumour, lymphoma, leukaemia, any tumour, moderate/severe renal disease, hemiplegia, diabetes, mild liver disease, ulcer disease, connective tissue disease, chronic pulmonary disease, dementia, cerebrovascular disease, peripheral vascular disease, myocardial infarction, chronic heart failure and diabetes with end-organ damage.

2.2 | Assessments

In this study, the primary independent variable was hypoglycaemic event severity. Respondents were asked whether or not they had experienced a hypoglycaemic event in the previous 3 months, and the type of hypoglycaemic event they experienced. Respondents were categorized into 1 of 3 groups (no event, nonsevere event or severe event) based on their responses. Nonsevere events were described as symptomatic episodes that could be managed by the patient themselves, whereas severe events were episodes that required assistance from a healthcare professional or other person as defined by the American Diabetes Association Workgroup on Hypoglycemia.⁵ In view of the nature of the survey, respondents were given no additional instructions on how to choose the event that was described and could only select 1 event, even if they had experienced multiple events during the time period of interest.

2.3 | Health-related quality of life

Health-related quality of life was assessed using the Medical Outcomes Study 36-Item Short Form Survey Instrument version 2 (SF-36v2).¹⁵ The SF-36v2 is a multipurpose, generic health status instrument comprising 36 questions that map onto 8 health domains: physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations and mental health. The relevant scores from these 8 domains are summarized in 2 component scores: the physical component summary (PCS) and the mental component summary (MCS).

Each domain and summary score are calculated using a norm-based scoring algorithm that allows for all measures to be viewed together and to be interpreted relative to population values. Higher scores represent better health status and a shift in the score of 6–8.5 for each domain can be considered clinically meaningful.¹⁶ The items from the SF-36v2 can also be used to derive a preference-based health utility index (SF-6D) for health economic assessment.^{17,18}

Using the SF-6D classification system, the response pattern of the SF-36v2 items was converted to a health utility score, which conceptually varies from 0 (a health state equivalent to death) to 1 (a health state equivalent to perfect health), and represents an individual's judgement around a variety of concepts related to overall health and quality of life. Previous research suggests that the minimal important difference (MID) for component scores is 3 points, 5 points for the norm-based domain scores and 0.041 points for the health utilities index.^{15,19,20}

2.4 | Work productivity

Work productivity was assessed in the subset of patients who reported being in full-time or part-time employment using the Work Productivity and Activity Impairment (WPAI) General Health Questionnaire, a validated 6-item instrument consisting of 4 metrics: absenteeism (the percentage of work time missed because of one's health), presenteeism (the percentage of impairment experienced

while at work because of one's health), overall work productivity loss (an overall impairment estimate as a combination of absenteeism and presenteeism) and activity impairment (the percentage of impairment in daily activities because of one's health).²¹ Only those respondents who reported being employed full-time or part-time provided data for absenteeism, presenteeism and overall work impairment, while all respondents provided data for activity impairment. The measures are expressed as a percentage of the time missed in the previous 7 days.

2.5 | Healthcare resource use and the costs

Healthcare utilization was assessed by a number of variables, including the reported number of traditional healthcare provider visits, the number of Emergency Room (ER) visits, and the number of times the patient were hospitalized in the past 6 months. These data were used in conjunction with information on income and the average cost of medical services to estimate the average direct costs associated with HCRU, and indirect costs associated with lost productivity.

Unit costs were derived from the Medical Expenditure Panel Survey (MEPS) database²² and are presented as 2013 €. Indirect costs associated with lost productivity were calculated from the number of hours missed due to absenteeism and the number of hours missed due to presenteeism multiplied by the associated hourly wage, and this amount annualized.²³⁻²⁶ The final estimates represent the total costs of HCRU for participants over the prior year.

2.6 | Statistical analyses

Descriptive statistics are reported as means and standard deviations for continuous variables and percentages for discrete variables. Ordinary least squares regression models were used for SF-36 measures, and negative binomial regressions with log-link distributions were used for WPAI measures. The following demographic and

health characteristics were used as covariates in the multivariate regression models: age, gender, insulin/sulfonylureas use, smoking, CCI, diagnosis length, number of diabetic complications and HbA1c. In addition, a sensitivity analysis was conducted using an expanded list of covariates in a regression model of the SF-6D utilities, including age, gender, insulin/sulfonylureas use, smoking, diagnosis length, HbA1c, exercise, depression, stroke, transient ischaemic attack, myocardial infarction, congestive heart failure, peripheral arterial disease, chronic kidney disease, chronic liver disease, peripheral vascular disease, cerebrovascular disease, dementia and diabetic complications (foot/leg ulcer, kidney disease, macular oedema/diabetic retinopathy, neuropathic pain and diabetes with end-organ damage). In all regression models, the trend in mean values was tested for statistical significance ($P < .05$).

3 | RESULTS

3.1 | Study population

A total of 1269 patients met the inclusion criteria, of whom 652 (51.4%) had not experienced a hypoglycaemic event, 533 (42.0%) had experienced a nonsevere hypoglycaemic event and 84 (6.6%) had experienced a severe hypoglycaemic event in the past 3 months.

3.2 | Patient baseline characteristics

Patient characteristics by country are shown in Table 1 and by severity of hypoglycaemic event in Table 2. Additional demographic data stratified by severity of hypoglycaemic events by country, are presented in Tables S1-S5; the proportion of patients taking insulin, sulfonylureas, either insulin or sulfonylureas, insulin only and sulfonylureas by severity of hypoglycaemia is presented in Table S6. While patient characteristics were generally similar among countries,

TABLE 1 Study population demographics by country

% (n), unless otherwise stated	France (n = 266)	Germany (n = 401)	Italy (n = 130)	Spain (n = 121)	UK (n = 351)
Age, yrs (mean, SD)	60.5 (10.6)	59.8 (11.4)	63.7 (12.4)	60.7 (10.6)	57.4 (12.1)
Sex					
Female	32 (85)	32 (129)	49 (64)	23 (28)	40 (140)
Male	68 (181)	68 (272)	51 (66)	77 (93)	60 (211)
BMI, kg/m ² (mean, SD)	30.4 (6.3)	31.1 (6.1)	28.3 (5.7)	29.4 (4.3)	32.1 (7.4)
Currently smoke	14.3 (38)	26.2 (105)	22.3 (29)	28.1 (34)	20.5 (72)
Currently drink	71.4 (190)	68.8 (276)	50.8 (66)	72.7 (88)	73.8 (259)
Currently exercise	48.9 (130)	44.6 (179)	47.7 (62)	58.7 (71)	40.5 (142)
CCI (mean, SD)	0.75 (2.21)	0.87 (1.39)	0.72 (1.21)	0.74 (1.15)	0.67 (1.15)
Rate of hypoglycaemia severity within country					
No event	53.4 (142)	54.6 (219)	53.1 (69)	47.1 (57)	47 (165)
Nonsevere event	40.2 (107)	39.7 (159)	40.0 (52)	45.5 (55)	45.6 (160)
Severe event	6.4 (17)	5.7 (23)	6.9 (9)	7.4 (9)	7.4 (26)

BMI, body mass index; CCI, Charlson Comorbidity Index; SD, standard deviation; UK, United Kingdom.

% (n), unless otherwise stated	No hypoglycaemic event (n = 652)	Nonsevere event (n = 533)	Severe event (n = 84)	P-value
Age, yrs (mean, SD)	60.7 (11.4)	59.3 (11.1)	56.2 (14.7)	.001
Sex				.131
Female	32.7 (213)	38.3 (204)	34.5 (29)	
Male	67.3 (439)	61.7 (329)	65.5 (55)	
BMI, kg/m ² (mean, SD)	30.8 (6.6)	30.7 (5.9)	30.6 (8.6)	.918
Currently smoke	20.4 (133)	21.4 (114)	36.9 (31)	.014
Currently drink	69.2 (451)	69.4 (370)	69.0 (58)	.995
Currently exercise	46.6 (304)	45.0 (240)	47.6 (40)	.821
CCI (mean, SD)	0.67 (1.17)	0.71 (1.23)	1.74 (3.66)	<.001
Duration of diabetes, yrs (mean, SD)	12.2 (8.7)	13.5 (9.7)	10.9 (7.5)	.006
Complications				
Foot or leg ulcer	6.6 (43)	7.1 (38)	11.9 (10)	.207
Kidney disease	6.9 (45)	8.4 (45)	23.8 (20)	<.001
Macular oedema or diabetic retinopathy	8.6 (56)	15.0 (80)	10.7 (9)	.002
Neuropathic pain	13.2 (86)	19.5 (104)	25.0 (21)	.002
Diabetes with end-organ damage	3.7 (24)	3.4 (18)	9.5 (8)	.024
None of these	71.0 (463)	63.8 (340)	47.6 (40)	<.001
Use of insulin	36.8 (240)	55.7 (297)	58.3 (49)	<.001
Use of sulfonylureas	22.7 (148)	24.6 (131)	15.5 (13)	.177

BMI, body mass index; CCI, Charlson Comorbidity Index; SD, standard deviation.

regression analysis of the total study population identified a significant trend for patients who experienced a severe hypoglycaemic event to be younger (mean age 60.7, 59.2 and 56.2 years for no event, nonsevere event and severe event, respectively; $P = .001$) and to have a higher comorbidity burden (mean CCI 0.67, 0.71 and 1.74, respectively; $P < .001$; Table 2). On average, patients who experienced a severe hypoglycaemic event also had a higher rate of kidney disease, neuropathic pain and macular oedema or diabetic retinopathy relative to other groups ($P < .05$; Table 2). Insulin use was higher in the nonsevere and severe groups relative to those who did not experience a hypoglycaemic event (55.7%, 58.3% and 36.8%, respectively; $P < .001$), while sulfonylureas use did not differ significantly among these groups (Table 2).

3.3 | Health-related quality of life

After controlling for covariates, increasing severity of hypoglycaemia was inversely associated with mean health utility scores (0.64, 0.62 and 0.58 for no event, nonsevere and severe groups, respectively; $P < .001$; Figure 1). Health utility scores were similar to those previously reported for patients with T2DM receiving basal-bolus insulin therapy (0.68 for patients without hypoglycaemia, and 0.60 for those with severe hypoglycaemia).²⁷ The robustness of the regression model was confirmed by the consistent results of the sensitivity

TABLE 2 Total study population demographics by severity of hypoglycaemia

analysis (0.6371, 0.6212 and 0.5877 for no event, nonsevere and severe groups, respectively).

A similar pattern was observed for MCS and PCS scores across no event, nonsevere and severe groups (mean MCS scores: 45.1, 43.5 and 40.5, respectively, $P = .002$; mean PCS scores: 42.2, 41.3 and 38.7, respectively, $P = .008$; Figure 1). The differences in MCS, PCS and health utilities between patients who experienced no hypoglycaemia event compared with those who experienced a severe hypoglycaemic event exceeded the MID threshold. Increased severity of hypoglycaemia was also associated with a significant decrease in all individual SF-36 subscales, except for General Health ($P < .05$; Figure 2).

3.4 | Work productivity

A total of 395 (31.1%) employed participants completed the WPAI (no event: 204; nonsevere: 163; severe: 20). Although increased severity of hypoglycaemia was associated with increased overall activity impairment (Figure 3), no significant differences were observed in absenteeism, presenteeism or overall work impairment.

3.5 | Healthcare resource utilization and direct costs

Regression analyses showed that an increase in severity of hypoglycaemia was associated with an increase in HCRU (Table 3),

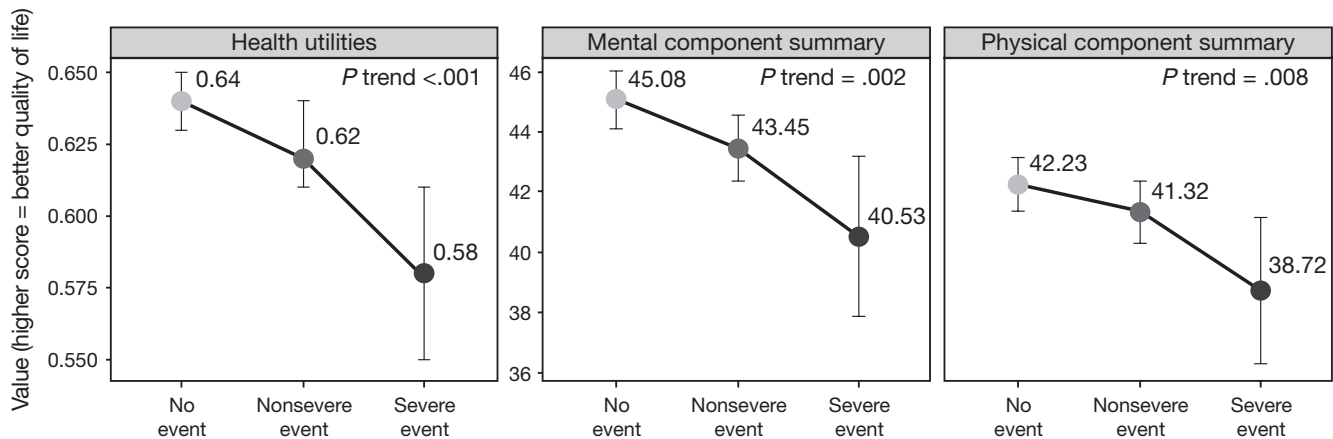


FIGURE 1 Health utilities and overall mental and physical component summary scores of the SF-36 by severity of hypoglycaemic event. SF-36, 36-Item Short-Form Health Survey

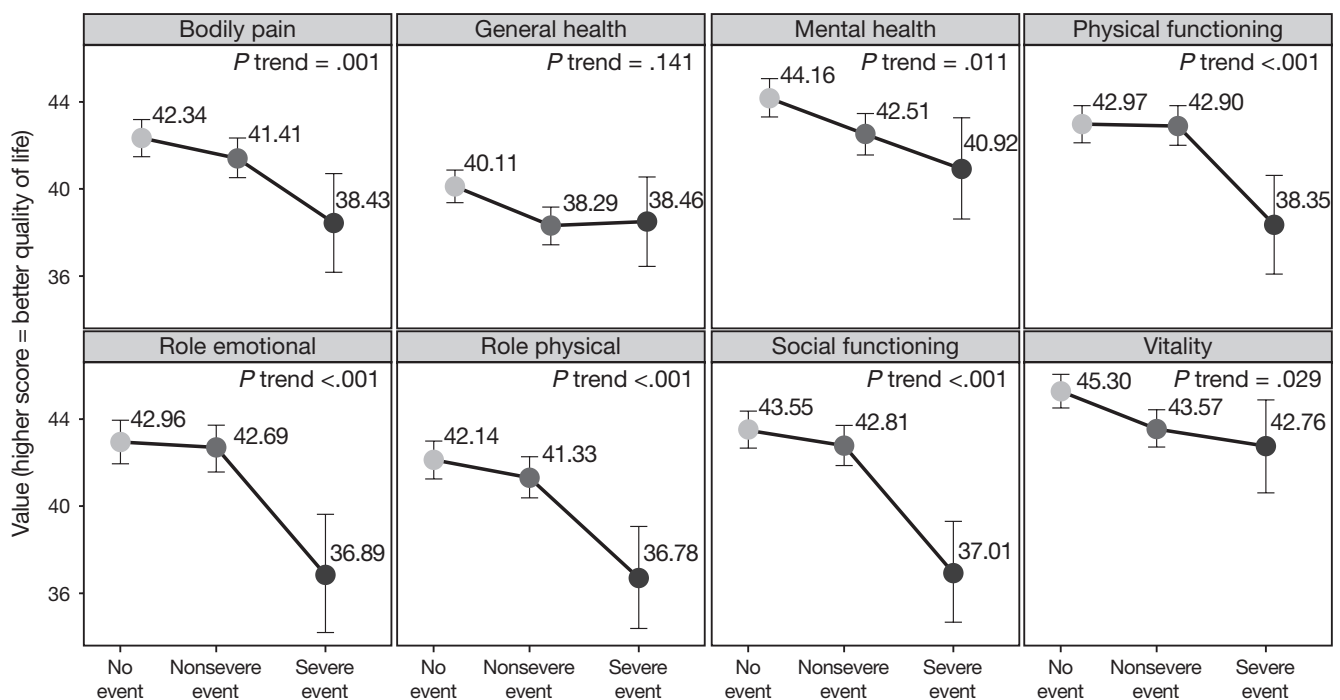


FIGURE 2 SF-36 domain scores by severity of hypoglycaemia.^a SF-36, 36-Item Short-Form Health Survey. ^aData presented are the results of multivariate regression analysis controlling for covariates

with the mean number of both ER visits and hospitalizations increasing significantly with the severity of hypoglycaemia ($P < .001$; Table 3). This also resulted in significantly higher direct costs of healthcare practitioner and ER visits, as well as hospitalizations ($P < .001$; Table 4). The indirect cost associated with presenteeism was also significantly greater with increased severity of hypoglycaemia ($P = .003$), but there was no difference in the cost associated with absenteeism between the groups.

4 | DISCUSSION

To our knowledge, this is the first study that evaluates the association between severity of hypoglycaemia and a comprehensive set of patient outcomes (eg, HRQoL, productivity loss, HCRU and costs) conducted in 5 European countries utilizing a nationally representative sample by age and gender. It differs from most other studies of hypoglycaemia in that it investigates the relative impact of nonsevere

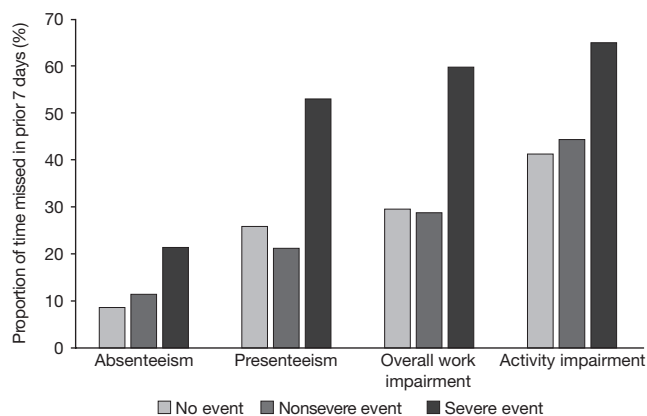


FIGURE 3 Work productivity (WPAI-GH) scores by severity of hypoglycaemia.^a WPAI-GH, Work Productivity and Activity Impairment—General Health. ^aData are a percentage of time missed in the last 7 d for employed participants

and severe hypoglycaemia, whereas previous studies have mainly focused on severe hypoglycaemia. Overall, hypoglycaemia was shown to have a significant impact on HRQoL as well as on HCRU and costs.

Almost half of the patients analysed in this study (42%) reported experiencing a hypoglycaemic event in the 3 months prior to completing the survey. Of these patients, only 7% reported experiencing a severe hypoglycaemic event, suggesting that the majority of hypoglycaemic events in adult patients with T2DM were nonsevere in nature. These observations are consistent with previous studies, which report that nonsevere hypoglycaemic events occur in

24%–60% of patients with diabetes, accounting for 88% of all hypoglycaemic events,²⁸ and have a substantial impact on productivity,²⁸ emotional and social functioning, diabetes management, sleep and decreased well-being.^{29–31}

A statistically significant association between insulin use and the severity of hypoglycaemic events (consistent with the drug's side-effect profile) was observed in this study. This observation is consistent with the outcomes of the HAT study in patients with T1DM or T2DM treated with insulin (conducted in 24 countries), which reported an association between the rate of hypoglycaemia and an increased duration of diabetes and insulin therapy.³² There was no significant association between the severity of hypoglycaemic events and the use of sulfonylureas, with very low numbers in the severe subgroup ($n = 13$) precluding any meaningful interpretation (Tables S1, S2 and S5). It is plausible that patients taking sulfonylureas experience more nonsevere events than severe events, unlike patients taking insulin.

Although the regression model utilized controlled for a number of the covariates, to account for any potential influence on outcomes, further stratification by different age groups or duration of diabetes in future research may be insightful.

Our study found that an increase in severity of hypoglycaemia was associated with a significant and clinically relevant decrement in both physical and mental health component of HRQoL and overall health utility. Previous studies conducted in the UK, United States, Canada and Brazil have also shown self-reported hypoglycaemic symptoms to be independently associated with reduced HRQoL,^{12,33–35} and that

	No hypoglycaemic event (n = 652)	Nonsevere event (n = 533)	Severe event (n = 84)	P-value
HCP visits	9.04 (8.22, 9.94)	9.72 (8.73, 10.82)	12.66 (9.78, 16.38)	.036
ER visits	0.22 (0.17, 0.27)	0.25 (0.20, 0.32)	1.03 (0.72, 1.47)	<.001
Hospitalizations	0.18 (0.14, 0.23)	0.12 (0.09, 0.16)	0.66 (0.44, 0.98)	<.001

CI, confidence interval; ER, emergency room; HCP, healthcare practitioner.

^aData presented are the results of multivariate regression analysis controlling for covariates.

TABLE 3 Healthcare resource utilization in the past 6 months by severity of hypoglycaemia^a

TABLE 4 Direct and indirect costs (€) by severity of hypoglycaemia^a

Mean (SD)	No hypoglycaemic event (n = 652)	Nonsevere event (n = 533)	Severe event (n = 84)	P-value
Direct (€)				
HCP	531.16 (538.00)	587.79 (570.50)	1011.64 (1728.25)	<.001
ER	67.66 (292.09)	78.05 (216.02)	368.87 (787.52)	<.001
Hospitalizations	424.60 (1436.36)	323.16 (1150.10)	2376.68 (5877.27)	<.001
Total	1023.42 (1707.62)	989.01 (1427.06)	3757.18 (7545.38)	<.001
Indirect (€)				
Absenteeism	1737.26 (5116.70)	2491.69 (6051.31)	3310.36 (6243.94)	.234
Presenteeism	4027.81 (4745.04)	3641.03 (4590.87)	7139.68 (6192.67)	.003
Total	5626.86 (7227.42)	5887.00 (7451.60)	9940.06 (10 950.73)	.019

ER, emergency room; HCP, healthcare practitioner; SD, standard deviation.

^aData presented are the results of multivariate regression analysis controlling for covariates.

the magnitude of this reduction increases with both the severity and frequency of the symptoms.^{8,35,36} A recent study also demonstrated a significant relationship between experiencing low blood sugar symptoms and decreased HRQoL, decreased utility and greater difficulties with mobility, daily activities, pain/discomfort and anxiety/depression, relative to patients who did not report those symptoms.¹²

These results are of considerable importance due to the notable humanistic and economic burden associated with hypoglycaemic events. The present study builds on the current literature by demonstrating the impact that the severity of hypoglycaemia has on this burden, but showing that even nonsevere events impose a considerable burden on patient outcomes and resource use. In addition, the increased severity of hypoglycaemia was also associated with an increase in activity impairment in this patient population. This increase is notable, as the group with no hypoglycaemic events also reported a higher degree of activity impairment than that shown in the general population.³⁷

Our study also showed that increasing severity of hypoglycaemia was associated with an increase in HCRU, which resulted in higher estimated direct medical costs. A previous analysis indicated that the direct and indirect costs associated with a hypoglycaemic event increased with severity, with the indirect costs associated with nonsevere hypoglycaemia, severe hypoglycaemia requiring medical assistance and severe hypoglycaemia requiring nonmedical assistance predicted to be US\$11, US\$176 and US\$579, respectively, for patients with T2DM.³⁸ Hypoglycaemic events requiring medical assistance were associated with a high economic burden (US\$1161 per episode in T1DM and T2DM patients) compared with events requiring nonmedical assistance and those managed by self-treatment (US\$66 and US\$11, respectively). Hospital treatment of severe events was also shown to be a major cost in Germany, Spain and the UK, with average treatment costs being higher for patients with T2DM (Germany, €533; Spain, €691; UK, €537) than those with T1DM (€441, €577 and €236, respectively).³⁹

4.1 | Limitations

The current results should be considered within the context of several limitations. The NHWS is a patient-reported, cross-sectional, web-based survey, and the data were not verified against clinicians' diagnoses or chart reviews, nor were reports of low blood sugar confirmed by blood glucose monitoring. Moreover, the cross-sectional nature of the analysis does not allow for inference on the causation of the results nor the temporal association.⁸ Due to the nature of the survey design, patients with hypoglycaemia were able to report only 1 hypoglycaemic event experienced in the previous 3 months, but may have experienced multiple events over that time period; hence, the true impact of the events may be underreported. In addition, almost half of patients surveyed were on insulin (Table 2), which was associated with the reporting of hypoglycaemic events. Yet, the recent legislation in the UK—whereby individuals taking insulin are required to report this information to the transport authorities—may have affected the responses in this country, leading to an underestimation of the number of severe hypoglycaemic events (a smaller proportion of patients in the UK compared with

France and Germany reported these events; Tables S1, S2 and S5, respectively).

Overall, the results of this study show that the impact of hypoglycaemia on patient outcomes varies by severity, and that both severe and nonsevere events are associated with decreased HRQoL and higher HCRU. This study highlights the importance of managing hypoglycaemia to enable the most favourable glycaemic control and avoid the increased humanistic and economic burden related to these events.

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CONFLICT OF INTEREST

Research was funded by Merck & Co., Inc., Kenilworth, NJ, USA. MP, KI, SSE and SR are current or former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and may own stock and/or stock options. EAW has acted as a consultant to Merck & Co., Inc.

AUTHOR CONTRIBUTIONS

MP contributed to the design of the study; data acquisition, analysis and interpretation; and drafting, critically reviewing and revising the manuscript. EAW contributed to the design of the study; data analysis and interpretation; and drafting, critically reviewing and revising the manuscript. SSE contributed to data interpretation, and critically reviewing and revising the manuscript. SR contributed to the design of the study, data interpretation, and critically reviewing and revising the manuscript. KI contributed to the design of the study, data interpretation, and critically reviewing and revising the manuscript.

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SUPPORTING INFORMATION

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

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