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Research: Complications

Self-reported non-severe hypoglycaemic events in Europe

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Abstract

Aims Hypoglycaemia presents a barrier to optimum diabetes management but data are limited on the frequency of hypoglycaemia incidents outside of clinical trials. The present study investigated the rates of self-reported non-severe hypoglycaemic events, hypoglycaemia awareness and physician discussion of events in people with Type 1 diabetes mellitus or insulin-treated Type 2 diabetes mellitus.

Methods People in seven European countries aged >15 years with Type 1 diabetes or insulin–treated Type 2 diabetes (basal-only, basal-bolus and other insulin regimens) were recruited via consumer panels, nurses, telephone recruitment and family referrals. Respondents completed four online questionnaires. The first questionnaire collected background information on demographics and hypoglycaemia-related behaviour, whilst all four questionnaires collected data on non-severe hypoglycaemic events in the preceding 7 days.

Results Analysis was based on 11 440 respondent-weeks from 3827 respondents. All participants completed the first questionnaire and 57% completed all four. The mean number of events/respondent–week was 1.8 (Type 1 diabetes) and 0.4–0.7 (Type 2 diabetes, with different insulin treatments) corresponding to annual event rates of 94 and 21–36, respectively. A total of 63% of respondents with Type 1 diabetes and 49–64% of respondents with Type 2 diabetes, treated with different insulin regimens, who experienced hypoglycaemic events, reported impaired hypoglycaemia awareness or unawareness. A high proportion of respondents rarely or never informed their general practitioner/specialist about hypoglycaemia: 65% (Type 1 diabetes) and 50–59% (Type 2 diabetes). Overall, 16% of respondents with Type 1 diabetes and 26% of respondents with Type 2 diabetes reported not being asked about hypoglycaemia during routine appointments.

Conclusion Non-severe hypoglycaemic events are common amongst people with Type 1 diabetes and insulin–treated Type 2 diabetes in real-world settings. Many rarely or never inform their general practitioner/specialist about their hypoglycaemia and the real burden of hypoglycaemia may be underestimated.

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Introduction

The goal of diabetes management for people with Type 1 or Type 2 diabetes mellitus is to maintain normoglycaemia so as to reduce diabetic complications and the risk of mortality; however, the intensification of therapy to achieve this goal may increase the incidence of hypoglycaemic episodes.

Hypoglycaemia remains a common and unpredictable side effect of insulin therapy, and has a negative physical and emotional impact on people with diabetes [1]. Hypoglycaemic episodes are characterized as either severe or non-severe according to whether assistance is required from another individual, or whether the person with diabetes can manage the event alone, respectively [2,3]. Non-severe hypoglycaemic events account for 88–98% of all hypoglycaemic events

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What's new?

- Limited data exist on the frequency of non-severe hypoglycaemic events in people with Type 1 or Type 2 diabetes in real-world practice, as non-severe hypoglycaemic events, by definition, do not require healthcare professional interactions (are not routinely registered).
- The frequency of non-severe hypoglycaemic events in real-world practice may differ from that observed in clinical trials because of the characteristics of clinical trial designs.
- To our knowledge, this is the first study reporting the frequency of non-severe hypoglycaemic events in real--world practice in the seven countries involved in our study.
- Non-severe hypoglycaemic events are common amongst people with Type 1 or insulin-treated Type 2 diabetes.
- Many people with diabetes rarely or never inform their general practitioner/specialist about their hypoglycaemia and the real burden may be underestimated.

[4–6] and have been shown to affect functioning [7], health-related quality of life [4,8], healthcare resource use [4] and work productivity [7]. Furthermore, hypoglycaemia presents a significant barrier to optimum diabetes management, as fear of hypoglycaemic events may cause exaggerated avoidance behaviour and consequently suboptimum insulin therapy and poor glycaemic control [9,10]. Whilst the importance of education about the recognition and treatment of hypoglycaemia is acknowledged in the current European Association for the Study of Diabetes and American Diabetes Association consensus statement [11], the real-world levels of communication between healthcare professionals and people with diabetes regarding hypoglycaemia are not fully understood.

Data on the frequency of hypoglycaemia, specifically non-severe hypoglycaemic events, outside of clinical trial settings are limited and varied [1,5,6,8]. The variability of data is probably attributable to differing study populations (degree of selection, Type 1 diabetes and/or insulin-treated Type 2 diabetes), targets for glycaemic control, duration of treatment, methods of data collection and country coverage within these studies.

Our aim was to investigate the real-world frequency of self-reported non-severe hypoglycaemic events, levels of impaired hypoglycaemia awareness and discussion of hypoglycaemic events within physician consultations. We used a multi-country questionnaire-based survey in a large non-interventional cohort of people with Type 1 diabetes or insulin-treated Type 2 diabetes. The questionnaire also explored the health-related impact and economic burden of hypoglycaemia, the results of which are to be provided in a follow-on publication.

Subjects and methods

The questionnaire-based survey was conducted between November 2011 and May 2012 and recruited respondents from Austria, Denmark, Finland, Norway, Sweden, Switzerland and the Netherlands. Respondents were primarily recruited via existing large consumer panels that were established to reflect a representative sample of the general diabetes population, based on age, gender and other demographic characteristics. Where sufficient numbers of respondents could not be identified via consumer panels, other methods of recruitment were initiated, including the use of advertisements on diabetes-related websites and patient association websites (with a link to the screener for inclusion in the survey), face-to-face recruitment, telephone recruitment and subsequent referrals from friends/family. In addition, some respondents were directly recruited at general practitioner clinics by nurses who were asked to identify participants and seek consent for participation, before providing contact details for those eligible to take part in the survey. All respondents completed a screening stage to determine eligibility for study inclusion. Before study entry, respondents were unaware that the survey related to hypoglycaemia. A target of 600 respondents per country was set with an expectation that the probability of a hypoglycaemic event would have a 95% CI of ±4%.

The inclusion criteria were a diagnosis of either Type 1 diabetes or Type 2 diabetes from a healthcare professional, current insulin treatment and age >15 years. In addition, respondents were required to read and speak the native language of the country in which they resided and have an email address in order to complete the questionnaire online. Respondents were offered a small incentive for completion of the entire survey (€5–25), in line with current market research guidelines and to ensure there was no undue incentive to participate. All respondents were anonymous according to the regulations and practice of the market research governing bodies, the European Society for Opinion and Marketing Research [12] and the European Pharmaceutical Market Research Association [13].

Eligible respondents were invited by email to complete an online questionnaire, in four waves. They received invitations for the second, third and fourth questionnaires 7 days after they had completed the previous questionnaire.

Questionnaires were adapted from those used in a previous study [7], which had been designed using insights collected during focus groups on the impact of hypoglycaemia reported by people with diabetes [14]. Data collected in the first questionnaire included respondent demographics, previous experience with and awareness of hypoglycaemia, the impact of hypoglycaemia and the number of non-severe hypoglycaemic events and severe hypoglycaemic events.

Respondents were also asked about hypoglycaemia-related discussions during general practitioner/specialist consultations. Respondents who had experienced a non-severe hypoglycaemic event were asked whether they normally informed their general practitioner/specialist after they had had a hypoglycaemic event. A non-severe hypoglycaemic event was defined as symptoms of hypoglycaemia (e.g. sweating, shaking, headache) with or without a blood glucose measurement, or a low blood glucose measurement (≤3.1 mmol/L) without symptoms, that the individual managed without assistance from another person. A severe hypoglycaemic event was defined as an event of low blood glucose level needing help from a third party to manage (e.g. help from a family member or a healthcare professional, including emergency room visits and hospitalization). Questions also referred to non-severe hypoglycaemic events occurring during the daytime or the night-time (while the respondent was in bed/asleep). The subsequent questionnaires focused only on the number of non-severe hypoglycaemic events and the impact of these events. Completion of the survey in four waves provided data for the number of non-severe hypoglycaemic events occurring over the past 4 weeks, whilst minimizing the recall period (i.e. four 7-day periods were reported). The estimated total amount of time to complete all four questionnaires was 35 min. Questionnaires were completed anonymously but responses could be tracked across the four waves by an identification number assigned at study initiation.

Limits for upper and lower entry values were included within the questionnaire to minimize erroneous values. In addition, data were cleaned using a logical consistency check that allowed the removal of individual answers for which incorrect calculations had been made by a respondent (e.g. where longer treatment duration than diabetes duration was reported), or the removal of the respondent from the entire analysis in instances where type of diabetes was not known or where erroneous reporting of simple demographic variables occurred (e.g. diabetes duration longer than current age).

The rate of non-severe hypoglycaemic events was calculated using data from all respondents who completed at least one wave of the survey. The first questionnaire collected data for non-severe hypoglycaemic events in the last 4 weeks and the last 7 days. All subsequent waves reported only the number of non-severe hypoglycaemic events in the last 7 days, so the estimated weekly rates from the 4-week rate provided in wave one could be matched with the weekly rates reported by the four times 7-day rates across waves one, two, three and four. Annual event rates were calculated using the subsequent wave mean event rate per respondent-week multiplied by 52.

The relationships between demographic factors and the annual rate of non-severe hypoglycaemic events were analysed in regression models. The continuous dependent variable of the annual event rate was estimated by combining two variables: the 4-weekly non-severe hypoglycaemia event rate and, for respondents who did not experience a hypoglycaemic event in the previous 4 weeks, answers to the question, 'How often do you normally have non-severe hypoglycaemic events?' This analysis used data collected during the first wave of the survey. Analysis on Type 1 and Type 2 diabetes was carried out separately. Regression analyses were conducted for the whole study population, as the study was not designed for cross-country comparisons.

The classification system for awareness of hypoglycaemia was based on a prospectively validated study by Pedersen-Bjergaard *et al.* 2003 [15]. Any respondent who answered 'sometimes' or 'never' to the question, 'Can you feel when your blood sugar is low?' was classified as being unaware of hypoglycaemia, those who answered 'usually' were classified as having impaired awareness and those who answered 'always' were classified as aware.

Standard descriptive methods (means/percentage and standard deviations) were used to report results for respondents in the following four groups: people with Type 1 diabetes, people with Type 2 diabetes receiving basal-only/long-acting insulin-only therapy, people with Type 2 diabetes receiving basal-bolus/both short- and long-acting insulin therapy, or people with Type 2 diabetes receiving another form of insulin therapy. Comparisons were performed using *t*-tests and a P value <0.05 was considered to indicate statistical significance.

Results

A total of 3959 respondents across seven countries were recruited to the study and 132 (3.3%) were excluded as a result of inadequate questionnaire completion. The remaining 3827 respondents completed the initial survey, with 76, 66 and 57% completing waves two, three and four, respectively, resulting in a total of 11 440 respondent-week records.

The demographics for respondents with Type 1 diabetes and those with Type 2 diabetes are shown in Table 1 and were similar across countries (data not shown). Differences between respondents with Type 1 diabetes and respondents with Type 2 diabetes were consistent with those expected (age, diabetes duration etc.). Age and BMI were negatively correlated with the annual rate of non–severe hypoglycaemic events ($P < 0.05$). Female gender and duration of insulin treatment were positively correlated with the annual event rate ($P < 0.05$).

The mean self-reported non-severe hypoglycaemic event rate was 1.8 per respondent-week for respondents with Type 1 diabetes and 0.5 for respondents with Type 2 diabetes (Table 2). Individual country data are also reported in Table 2. Rates for respondents with Type 2 diabetes were 0.4 (respondents receiving basal-only/long-acting insulin-only therapy), 0.7 (respondents receiving basal-bolus/both short- and long-acting insulin therapy) and 0.5 (respondents receiving another form of insulin therapy; Table 2). The calculated mean annual event rates were therefore 91.0, 20.3, 35.4 and 27.0 in the four groups (Table 2). The

Table 1 Respondent-related characteristics

	Type 1 diabetes	Type 2 diabetes
Number of respondents, *n* (%)	1631 (43)	2196 (57)
Mean (SD) age*	44.3 (14.1)	60.3 (10.7)
Gender, female, *n*(%)†	722 (44)	735 (33)
Education, *n* (%)‡		
Primary school	244 (15)	393 (18)
High school	808 (49)	1147 (52)
University (plus PhD. or higher)	517 (32)	558 (25)
Other	62 (4)	98 (5)
Mean (SD) BMI*	25.87 (4.88)	31.54 (6.39)
Smoking, *n* (%)§		
Smoker	458 (28)	450 (20)
Ex-smoker	418 (26)	1008 (46)
Non-smoker	755 (46)	738 (34)
Diabetes duration, *n* (%)		
<2 years	20 (1)	41 (2)
2–5 years	220 (14)	317 (15)
5–9 years	145 (10)	394 (19)
10–14 years	197 (13)	546 (26)
15 + years	957 (62)	806 (38)
Insulin treatment type, *n* (%)¶		
Long-acting insulin only	134 (8)	812 (37)
Both short- and long-acting insulin	1058 (65)	942 (43)
Other insulin types	439 (27)	442 (20)
Duration of insulin treatment, *n* (%)**		
<2 years	113 (7)	311 (14)
2–5 years	189 (12)	741 (35)
5–9 years	136 (9)	394 (18)
10 + years	1101 (72)	659 (32)
HbA_{1c}§		
Mean mmol/mol (SD);	61 (16.1)	60 (16.9)
National Glycohaemoglobin Standardisation Programme%, (SD)	7.7 (1.5)	7.6 (1.5)
Medical complications, none reported, *n* (%)††	1036 (64)	1148 (52)

*Significant negative correlation with yearly number of non-severe hypoglycaemic events (for both Type 1 diabetes and Type 2 diabetes, according to regression analysis; $P < 0.05$).
†Significant positive correlation with yearly number of non-severe hypoglycaemic events (for both Type 1 diabetes and Type 2 diabetes, according to regression analysis; $P < 0.05$).
‡Significant ($P < 0.05$) negative correlation with yearly number of non-severe hypoglycaemic events (Type 2 diabetes only).
§No significant correlation with yearly number of non-severe hypoglycaemic events.
¶Variable not included in the regression analysis.
**Duration of insulin treatment was correlated with diabetes duration, and thus duration of treatment was included in the regression analysis. A significant positive correlation was found between duration of treatment and yearly number of non-severe hypoglycaemic events (for both Type 1 diabetes and Type 2 diabetes; $P < 0.05$).
††Medical complications were correlated with age. Medical complications were not significantly associated with yearly number of non-severe hypoglycaemic events, independent of their association with age. Questionnaire options for medical complications included: None, Eye problems, Neuropathy, Cardiovascular disease, Renal disease, Amputations, Other (please specify).

proportion of nocturnal non-severe hypoglycaemic events were slightly greater in respondents with Type 2 diabetes than in respondents with Type 1 diabetes: 22% (Type 1 diabetes), 32% (respondents with Type 2 diabetes receiving basal-only/long-acting insulin-only therapy), 22% (respondents with Type 2 diabetes receiving basal-bolus/both short- and long-acting insulin therapy) and 27% (respondents with Type 2 diabetes receiving another form of insulin therapy; Table 2). Four-week non-severe hypoglycaemic event rates recalled by respondents in questionnaire one were similar to, although slightly lower than, those collected over the four waves of the study (Table 2).

The mean number of self-reported severe hypoglycaemic events experienced in the last year was 0.7 for respondents with Type 1 diabetes, 0.1 for respondents with Type 2 diabetes receiving basal-only/long-acting insulin-only therapy, 0.2 for respondents with Type 2 diabetes receiving basal-bolus /both short- and long-acting insulin therapy and 0.2 for respondents with Type 2 diabetes receiving another form of insulin therapy (Table 2).

Overall, 76% of study respondents (87% of respondents with Type 1 and 59–78% of respondents with Type 2 diabetes) had previously experienced a hypoglycaemic event at any point (i.e. not just in the study recall period). In respondents who had previous experience of hypoglycaemic events, impaired awareness was reported by 53% of respondents with Type 1 diabetes, 45% of respondents with Type 2 diabetes receiving basal-only/long-acting insulin therapy only, 43% of respondents with Type 2 diabetes receiving basal-bolus/both short- and long-acting insulin therapy and 43% of respondents with Type 2 diabetes receiving another form of insulin therapy (Table 3). A further 10, 19, 6 and 8% were classified as unaware for each respondent type, respectively. Respondents with Type 1 diabetes who were unaware had significantly higher rates of non-severe hypoglycaemic events than those who were always aware ($P < 0.05$; Table 3). Among respondents with Type 2 diabetes receiving basal-only/long-acting insulin-only therapy and respondents with Type 2 diabetes receiving basal-bolus/both short- and long-acting insulin therapy, respondents with impaired awareness had significantly higher non-severe hypoglycaemic event rates than those who were aware ($P < 0.05$). In respondents with Type 2 diabetes receiving another form of insulin therapy, significantly lower non-severe hypoglycaemic event rates were observed in unaware respondents than in respondents who were always aware ($P < 0.05$; Table 3). Significantly higher rates of severe hypoglycaemic events were reported by respondents with Type 1 diabetes classified either as unaware or as having impaired awareness, compared with aware respondents ($P < 0.05$).

A high proportion of respondents who had experienced a non-severe hypoglycaemic event stated that they 'rarely' or 'never' informed their general practitioner/specialist about their hypoglycaemia: 65% (respondents with Type 1

Table 2 Self-reported, recalled rates of hypoglycaemic events

Rates based on 11440 rw reports from 3827 respondents		Total: N = 3827; 11440 rw	Austria: n = 553; 1773 rw	Switzerland: n = 395; 1116 rw	Denmark: n = 601; 1894 rw	Finland: n = 628; 1364 rw	Netherlands: n = 692; 2456 rw	Norway n = 379; 918 rw	Sweden n = 579; 1919 rw
Mean (SD) self-reported NSHE rate per respondent per week*	Type 1 diabetes	1.8 (2.3)	1.6 (2.3)	1.4 (1.8)	1.9 (2.4)	1.3 (2.1)	2.0 (2.5)	1.8 (2.2)	2.0 (2.5)
	Type 2 diabetes: BOT	0.4 (1.1)	0.3 (0.8)	0.4 (0.9)	0.5 (1.5)	0.2 (0.6)	0.5 (1.2)	0.4 (1.0)	0.4 (1.1)
	Type 2 diabetes: BB	0.7 (1.3)	0.5 (1.1)	0.6 (1.0)	0.7 (1.6)	0.5 (1.1)	0.7 (1.2)	1.0 (1.7)	0.9 (1.7)
	Type 2 diabetes: Other	0.5 (1.2)	0.4 (0.8)	0.7 (1.2)	0.4 (1.0)	0.2 (0.6)	0.9 (1.7)	0.6 (1.2)	0.4 (0.7)
Mean annual calculated NSHE rates (52 weeks)*	Type 1 diabetes	91.0	84.8	73.3	98.8	67.1	105.0	93.1	106.1
	Type 2 diabetes: BOT	20.3	15.1	18.7	23.4	10.4	24.4	20.3	22.4
	Type 2 diabetes: BB	35.4	27.6	32.2	38.5	25.0	34.3	50.4	45.8
	Type 2 diabetes: Other	27.0	18.7	36.9	21.8	12.5	44.7	29.6	18.7
Proportion of NSHE that occur whilst sleeping, %*	Type 1 diabetes	22	19	20	22	31	13	19	20
	Type 2 diabetes: BOT	32	22	49	27	22	33	18	39
	Type 2 diabetes: BB	22	22	28	24	33	16	26	20
	Type 2 diabetes: Other	27	15	42	38	39	25	11	19
Based on all respondents completing wave 1, n = 3825									
Mean (SD) self-reported NSHE 4 week rate†	Type 1 diabetes	6.3 (8.2)	5.5 (6.9)	6.0 (7.8)	7.7 (9.3)	4.2 (7.6)	7.9 (9.1)	6.3 (8.0)	7.4 (7.6)
	Type 2 diabetes: BOT	1.2 (3.2)	0.7 (1.7)	0.8 (1.6)	1.6 (4.3)	0.5 (1.4)	1.5 (4.2)	1.2 (2.1)	1.5 (3.5)
	Type 2 diabetes: BB	2.6 (5.1)	1.6 (2.4)	2.1 (3.9)	3.1 (6.2)	1.6 (2.9)	3.1 (5.0)	2.5 (3.3)	3.5 (7.9)
	Type 2 diabetes: Other	1.7 (3.9)	1.3 (2.5)	0.6 (1.3)	1.4 (3.0)	0.8 (1.1)	3.4 (5.7)	2.9 (7.1)	1.5 (2.6)
Based on all respondents completing wave 1, n = 3820									
Mean (SD) number of SHEs in the last year‡	Type 1 diabetes	0.7 (2.4)	0.7 (2.1)	0.6 (2.0)	0.6 (2.3)	0.6 (2.0)	0.9 (2.3)	1.0 (3.2)	0.9 (2.8)
	Type 2 diabetes: BOT	0.1 (0.8)	0.1 (0.5)	0.2 (0.6)	0.1 (0.2)	0.1 (0.3)	0.1 (0.3)	0.2 (0.6)	0.3 (1.6)
	Type 2 diabetes: BB	0.2 (0.8)	0.2 (0.6)	0.5 (1.4)	0.1 (0.6)	0.1 (0.3)	0.2 (0.9)	0.4 (1.4)	0.1 (0.4)
	Type 2 diabetes: Other	0.2 (0.8)	0.2 (0.5)	0.3 (1.1)	0.3 (1.3)	0.1 (0.4)	0.2 (0.5)	0.1 (0.3)	0.1 (0.3)

rw, respondent week; NSHE, non-severe hypoglycaemic event; BOT, basal-only/long-acting insulin-only therapy; BB, basal bolus/short- and long-acting insulin therapy; SHE, severe hypoglycaemic event; Other, e.g. mixed insulin.
*All respondent-weeks reported; includes all respondents regardless of whether completing all four questionnaires.
†All respondents completing wave 1 (two responses were removed because of erroneous answers for this question).
‡All respondents completing wave 1 (seven responses were removed because of erroneous answers for this question).

Table 3 Self-reported respondent awareness of hypoglycaemia and corresponding event rates in respondents who had previously experienced a hypoglycaemic event

Respondents, $N = 2925$*		Type 1 diabetes, $n = 1420$	Type 2 diabetes		
			BOT, $n = 479$	BB, $n = 736$	Other, $n = 290$
Can you feel when your blood sugar is low?	Always aware,%	36	36	51	49
	Impaired awareness,%	53	45	43	43
	Unaware,%	10	19	6	8
Mean (SD) NSHE rates of those respondents who are aware, have impaired awareness or are unaware	Always aware	1.7 (2.3)	0.5 (1.0)	0.8 (1.5)	0.7 (1.4)
	Impaired awareness	1.9 (2.2)	0.6 (1.2)†	0.9 (1.5)†	0.7 (1.2)
	Unaware	2.6 (3.0)†	0.4 (1.0)	0.7 (1.1)	0.3 (0.7)†
Mean (SD) SHE rates of those respondents who are aware, have impaired awareness or are unaware	Always aware	0.4 (1.8)	0.2 (0.6)	0.2 (0.9)	0.2 (0.5)
	Impaired awareness	0.8 (1.9)†	0.2 (1.1)	0.2 (0.7)	0.2 (1.2)
	Unaware	2.7 (5.2)†	0.1 (0.5)	0.4 (1.0)	0.2 (0.5)

BOT, basal-only/long-acting insulin-only therapy; BB, basal-bolus/short- and long-acting insulin therapy; Other, e.g. mixed insulin; NSHE, non-severe hypoglycaemic event; SHE,severe hypoglycaemic event.
*All respondents who had previously experienced a NSHE at any point (i.e. not just in the study recall period; $n = 2925$).
†$P < 0.05$ significance against always aware.

Table 4 Communication between respondents and general practitioners/specialists

All respondents, $N = 3827$*	Type 1 diabetes, $n = 1631$	Type 2 diabetes		
		BOT, $n = 812$	BB, $n = 942$	Other, $n = 442$
General practitioner/specialist did not ask about hypoglycaemia during routine appointments,%*	17	28	26	21

All respondents who have ever experienced a NSHE, $N = 2925$†	Type 1 diabetes, $n = 1420$	Type 2 diabetes		
		BOT, $n = 479$	BB, $n = 736$	Other, $n = 290$
Proportion of respondents rarely or never informing their general practitioner/specialist of a hypoglycaemic event, %†	65	50	59	53
Mean (SD) NSHE rates of those respondents communicating versus those who do not tell their general practitioner/specialist†				
Always/Mostly	1.5 (1.9)	0.4 (0.9)	0.6 (1.0)	0.6 (0.9)
Rarely/Never	2.2 (2.3)‡	0.6 (1.0)‡	1.0 (1.5)‡	0.8 (1.2)

BOT, basal-only/long-acting insulin-only therapy; BB, basal-bolus/short- and long-acting insulin therapy; Other, e.g. mixed insulin; NSHE, non-severe hypoglycaemic event.
*All respondents completing questionnaire one ($n = 3827$).
†All respondents who have ever experienced a NSHE ($n = 2925$).
‡$P < 0.05$ significance.

diabetes), 50% (respondents with Type 2 diabetes receiving basal-only/long-acting insulin-only therapy), 59% (respondents with Type 2 diabetes receiving basal-bolus/both short- and long-acting insulin therapy) and 53% (respondents with Type 2 diabetes receiving another form of insulin therapy; Table 4). The lowest level of communication was reported in the Netherlands (data not shown). The proportion of respondents in the Netherlands who rarely or never informed their general practitioner/specialist about their hypoglycaemic events was 86% (respondents with Type 1 diabetes), 64% (respondents with Type 2 diabetes receiving basal-only therapy/long-acting insulin-only therapy), 77% (respondents with Type 2 diabetes receiving basal-bolus/both short- and long-acting insulin therapy) and 79% (respondents with Type 2 diabetes receiving another form of insulin therapy). Event rates for non-severe hypoglycaemic events were significantly higher for respondents with Type 1 diabetes or Type 2 diabetes who rarely or never informed a physician about their non-severe hypoglycaemic events ($P < 0.05$). When respondents were asked about topics discussed during general practitioner/specialist consultations, 17% (Type 1 diabetes), 28% (Type 2 diabetes receiving basal-only/long-acting insulin-only therapy), 26% (Type 2 diabetes receiving basal-bolus/both short- and long-acting insulin therapy) and 21% (Type 2 diabetes receiving another form of insulin therapy) of respondents stated that their general

practitioner/specialist 'did not ask about hypoglycaemia during routine appointments' (Table 4).

Discussion and conclusions

This study captures the self-reported, recalled rates of non-severe hypoglycaemic events and severe hypoglycaemic events in both people with Type 1 diabetes and those with insulin-treated Type 2 diabetes, and shows that hypoglycaemic events remain a common adverse event of insulin therapy in both groups. The majority of the published literature on hypoglycaemic event rates includes only people with Type 1 diabetes, or is focused on reporting severe hypoglycaemic events only, and may not adequately reflect the frequency of hypoglycaemic events (especially non-severe hypoglycaemic events) across the insulin-treated diabetes population. In contrast, the present study explored the frequency of non-severe hypoglycaemic events and severe hypoglycaemic events in people with Type 1 diabetes and people with insulin-treated Type 2 diabetes across seven European countries.

The recalled rates of non-severe hypoglycaemic events for respondents with Type 1 diabetes (1.8 per respondent, per week) in this study are comparable with results from three previously conducted studies in Northern Europe, which reported non-severe hypoglycaemic event rates of 1.8, 2.0 and 2.2 per respondent, per week [6,16,17]. Rates of non-severe hypoglycaemic events for respondents with Type 2 diabetes in the current study are higher than those reported in a prospective single-centre study in Scotland, UK (0.4–0.7 vs 0.3 per respondent, per week) but this variation may be attributable to differences in the geographical region, Type 2 diabetes treatment regimen, and study sample size, or the way in which hypoglycaemic events had been defined [5]. Hypoglycaemic events occurred less frequently in respondents with insulin-treated Type 2 diabetes compared with respondents with Type 1 diabetes, and previous studies suggest the frequency of severe hypoglycaemic events in Type 2 diabetes to be approximately one-third of that experienced by people with Type 1 diabetes [5,18]. The results reported in the present study for severe hypoglycaemic events are consistent with this trend (Type 1 diabetes 0.7; Type 2 0.1–0.2) and suggest a similar ratio for non-severe hypoglycaemic events (Type 1 diabetes 1.8; Type 2 0.4–0.7). It should be noted that the frequency of hypoglycaemic events in respondents with Type 2 diabetes varies according to the treatment regimen (basal-only/long-acting insulin-only therapy, basal-bolus/both short- and long-acting insulin therapy, or another form of insulin therapy); however, this was to be expected given the different insulin coverage they provide [11].

Overall, nocturnal events represented between one quarter and one third of all non-severe hypoglycaemic events. In the present study, the proportion of overall non-severe hypoglycaemic events occurring at night was 22% (respondents with Type 1 diabetes), 32% (respondents with Type 2 diabetes receiving basal-only/long–acting insulin-only therapy), 22% (respondents with Type 2 diabetes receiving basal-bolus/both short- and long-acting insulin therapy), and 27% (respondents with Type 2 diabetes receiving another form of insulin therapy). Few other studies have reported rates of nocturnal events, although the proportion of nocturnal events would be expected to vary between insulin regimens.

In the present study, we investigated levels of hypoglycaemia awareness and reported 10% (Type 1 diabetes) and 6–19% (Type 2 diabetes) of respondents to be classified as unaware and 53% (Type 1 diabetes) and 43–45% (Type 2 diabetes) to have impaired awareness of hypoglycaemia (based on respondents with experience of hypoglycaemic events). A comparable proportion of respondents with Type 1 diabetes were found to have impaired awareness (47%) or be classified as unaware (13%) in a 1-year prospective study that used the validated question, 'Do you recognise symptoms when you have a hypo?' [15]. Furthermore, a cross-sectional study in a cohort of 401 people with Type 2 diabetes, also using this question, reported a similar proportion of respondents with impaired awareness (46%) to that in the current study (43–45%) [18]. There is no consensus on how to classify awareness, but our method benefits from the use of three categories (instead of two, 'aware' or 'unaware', as in the Clarke *et al.* [19] and Gold *et al.* [20] methods), which enables identification of the gradual loss of awareness. In addition, it is the only method proven to perform similarly across language barriers [21].

Some consideration should be given to the different respondent demographics within the current study. For example, symptoms of hypoglycaemia have been shown to decline with increasing age and the prevalence of impaired awareness of hypoglycaemia is reported to increase with duration of Type 1 diabetes [6]; results may be confounded by these factors. In addition, the study by Akram *et al.* [18] reported impaired awareness of hypoglycaemia to be the most important risk factor for severe hypoglycaemia. Results of the current study show that respondents with Type 1 diabetes classified as unaware or as having impaired awareness of hypoglycaemia reported significantly higher rates ($P < 0.05$) of severe hypoglycaemic events than respondents who were always aware. Unaware respondents with Type 1 diabetes also reported significantly higher rates of non-severe hypoglycaemic events compared with aware respondents ($P < 0.05$). This could be explained by unaware respondents failing to take action to prevent the onset of an event because of an inability to recognize the symptoms of low blood sugar. Additionally, this inability may cause respondents to overcompensate by testing their blood glucose more frequently, resulting in the identification of more events; however, this is an area that requires further investigation, especially as these trends were not observed in respondents with Type 2 diabetes.

An important finding of the current study was the high proportion of respondents with Type 1 diabetes (65%) and

Type 2 diabetes (50–59%) who rarely or never informed their general practitioner/specialist about their hypoglycaemic events. Despite these results, only 17% of respondents with Type 1 diabetes and 21–28% of respondents with Type 2 diabetes said that their general practitioner/specialist did not ask them about hypoglycaemia during routine appointments, suggesting some level of communication regarding hypoglycaemic events is taking place. The reluctance of people with diabetes to discuss their hypoglycaemia may be caused by wider factors such as concerns regarding driving privileges [9], implications for employment, or fear that they may be perceived by their general practitioner/specialist to have poor control of their diabetes. Further research is needed to understand the reasoning behind why people may not actively be reporting their hypoglycaemic events. Along with discussions on the frequency of non-severe hypoglycaemic events and severe hypoglycaemic events, other important aspects such as impaired hypoglycaemia awareness [18] and fear of hypoglycaemia [9,10] should be addressed, given that these are associated with an increased risk of severe hypoglycaemic events [18] and a risk of suboptimum glycaemic control [9,10], respectively. An opportunity exists for more standardized measures of these self-reported outcomes, which may also help to improve understanding for people with diabetes, and improve communication levels. With the endorsement by both the American Diabetes Association and the European Association for the Study of Diabetes of education regarding recognition and treatment of hypoglycaemia [11], it is hoped that communication between people with diabetes and their physicians will increase further. Whilst greater education could be expected to improve blood glucose management, there will still be an underlying increase in hypoglycaemic complications as insulin treatment regimens are intensified over time [1]. This is supported by our current regression analysis, where the number of non-severe events increased with duration of insulin treatment.

The frequency of hypoglycaemic events reported during randomized trials, such as the Diabetes Control and Complications Trial [22], and the United Kingdom Prospective Diabetes Study [23], may not be reflective of the incidence in real-world practice because of trial inclusion and exclusion criteria and because observational studies have reported a higher incidence of hypoglycaemic events in unselected populations [1]. In addition, there are key benefits to obtaining data directly from people with diabetes, particularly since a high number of them are not reporting non-severe hypoglycaemic events to their doctor.

It is important that the limitations of this study are considered. Respondent demographics show that 8% of respondents with Type 1 diabetes receive long-acting insulin-only therapy. It is likely that this figure may be the result of incorrect reporting of diabetes type by respondents with Type 2 diabetes. As a result, given that respondents with Type 2 diabetes have fewer hypoglycaemic events, our study may underestimate the frequency of events for respondents with Type 1 diabetes. The survey is based upon the recall of both severe hypoglycaemic events and non-severe hypoglycaemic events and the interpretation of symptoms is open to bias. A previous study showed that a respondent's ability to remember non-severe hypoglycaemic events during the previous week was not significantly different from the prospective recording of events over 1 week [6]. The current study was therefore designed to maximize the optimum recall period, by asking respondents to record events occurring in the previous week for each of the four questionnaires over 4 consecutive weeks. Also, a previous study has shown that people with Type 1 diabetes and people with Type 2 diabetes are able to accurately recall severe hypoglycaemic events within a 1-year period (corresponding to the recall period in the current study) [15]. There is also the potential that the duration of the study may over- or underestimate the annual frequency of hypoglycaemia, given that seasonal variation was not considered (the study was conducted December–May). The recruitment of respondents, mostly via online panels and the requirement of an email address in order to participate in the study could have introduced selection bias; however, the internet penetration rates for all of the countries studied are high (80–97%) [24]. The anonymous nature of the online panel may allow a better means of obtaining self-reported data on areas such as communication levels with physicians. Recruitment was via broad panels reflective of the general population and respondents were invited via email to participate in the survey by following a link, and were not informed that the survey was about hypoglycaemia before they clicked on the link to enter the survey. There are therefore no reasons to suggest any selection bias towards people struggling with hypoglycaemia in the first wave of the study; however, since the response rates for subsequent waves diminished (76, 66 and 57% of respondents completed waves two, three and four, respectively) we cannot exclude the possibility that later waves were completed by respondents who had more experience of hypoglycaemic events. Nevertheless, a subsequent analysis comparing event rates for the different waves did not suggest any trends towards higher frequency in later waves. The target recruitment rate of 600 respondents per country was not reached in Austria, Norway and Switzerland because of difficulties in accessing people with diabetes; however, results were remarkably consistent across the countries. Some respondents did not complete all four waves, but only small changes in the non-severe hypoglycaemic event rates (1.09 in wave 1 to 0.93 in wave 4) were seen when comparing data across waves. This was a descriptive study, therefore, few comparisons were explored and no adjustments were made for multiple cross-country comparisons; however, variations in non-severe hypoglycaemic event rates across countries were 1.3–2.0 per respondent, per week in Type 1 diabetes, and

0.2–1.0 per respondent, per week in Type 2 diabetes (0.2–0.5 in Type 2 diabetes respondents receiving basal-only/long-acting insulin-only therapy, 0.5–1.0 in Type 2 diabetes respondents receiving basal-bolus/both short- and long-acting insulin therapy and 0.2–0.9 in Type 2 diabetes respondents receiving another form of insulin therapy). This might reflect other demographic differences which were not captured, such as local differences in treatment regimens, different patient education levels or targets for glycaemic control. Additionally, the recruitment method does not differentiate between primary and secondary care patients, which may also have an impact.

Despite these limitations, the present study reports the real-world rates of hypoglycaemic events in a large number of people with Type 1 diabetes and people with Type 2 diabetes across seven European countries and provides evidence for a need to minimize the frequency of hypoglycaemia. It is acknowledged that both severe and non-severe hypoglycaemic events are more frequent in people with Type 1 diabetes, but the associated social and economic burden of events in people with Type 2 diabetes is likely to be substantial given the global epidemic of Type 2 diabetes [25]. Hypoglycaemia presents a barrier to optimum glycaemic control, increasing the risk of diabetic complications and mortality; therefore, discussion during physician consultations and education on the recognition and treatment of hypoglycaemic events for people with diabetes are imperative to encourage greater communication with physicians.

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Competing interests

R. Weitgasser has received honoraria for lectures and as a member of the Advisory Board for Novo Nordisk, Eli Lilly, Sanofi, Novartis, Medtronic, MSD, Takeda, Astra Zeneca/BMS, Boehringer-Ingelheim and Roche Diagnostics. J. Lahtela has received honoraria as a symposium speaker for Novartis, Sanofi, Novo Nordisk, MSD symposia. C. G. Östenson has received honoraria as a symposium speaker for Novo Nordisk Scandinavia. P. Geelhoed-Duijvestijn has received honoraria for lectures from Novo Nordisk and as a member of the Advisory Boards of Medtronic, Sanofi Aventis and Elli Lilly. U. Pedersen-Bjergaard has received honoraria for lectures and consultancy from Novo Nordisk, Sanofi Aventis, and BMS and has served as a member of Advisory Board for Novo Nordisk. M. Markert Jensen is employed by Novo Nordisk Scandinavia AB.

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