Fear of hypoglycaemia and its relation to hypoglycaemia awareness and symptom intensity in Type 1 diabetes

Running head: Fear of hypoglycaemia, awareness and symptom intensity

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Abstract

Aims: To investigate fear of hypoglycaemia (FoH) in relation to hypoglycaemia awareness, history of severe hypoglycaemia (SH) and hypoglycaemia symptoms in adults with Type 1 diabetes.

Methods: Questionnaire-based cross-sectional survey. We assessed FoH with the Hypoglycaemia Fear Survey-II Worry subscale, hypoglycaemia awareness status with the Gold score, and used the Edinburgh Hypoglycaemia Scale to grade the presence and intensity of hypoglycaemia symptoms. All these measures have previously been validated for research application. We used multivariable linear regression to examine associations between FoH and hypoglycaemia awareness status, history of SH and hypoglycaemia symptom score.

Results: Of 636 invitees, 445 (70%) responded, with 435 responses eligible for analyses. Seventy-four persons had IAH (17%). Among those, 47 (64%) reported ≥1 SH during the preceding year, in contrast to this being reported by 113 (31%) of persons with normal awareness. The mean (SD) FoH worry score was 1.33 (0.78). This score was 0.64 (95% CI, 0.45-0.83) higher among people with impaired vs. normal hypoglycaemia awareness and 0.53 (95% CI, 0.33-0.73) higher among people with ≥3 episodes of SH the preceding year vs. people with no such episode. A higher number and intensity of hypoglycaemia symptoms was associated with higher FoH, as demonstrated by an increase in mean FoH worry score of 0.30 (95% CI, 0.23-0.36) per point increase in mean Edinburgh hypoglycaemia score.

Conclusions: Impaired awareness of hypoglycaemia, history of SH and higher Edinburgh hypoglycaemia scores were all associated with increased FoH in adults with Type 1 diabetes.

Keywords: Type 1 diabetes; hypoglycaemia; awareness; fear; symptom intensity

1. Introduction

Fear of hypoglycaemia (FoH) is common in people with Type 1 diabetes (1, 2). Some fear or worry may be appropriate, since severe hypoglycaemia (SH) may lead to loss of consciousness and accidents (3). Non-severe hypoglycaemia with unpleasant symptoms may also lead to FoH, with possible negative effects on metabolic control, diabetes management, subsequent health outcomes and quality of life (2, 4).

The most commonly used questionnaire to assess FoH is the Hypoglycaemia Fear Survey (HFS), the prevailing version being HFS-II (4). Studies using the HFS (1, 4-6) or a similar questionnaire (7) have consistently showed higher FoH among persons with a history of SH. Women tend to have higher FoH than men (1). Higher measures of anxiety (4) and depression (4, 8) are also related to increased FoH. Furthermore, two studies found an association between FoH and higher number of symptoms during mild hypoglycaemia (9, 10). However, the relation between hypoglycaemia symptom intensity and FoH has not been examined.

Impaired awareness of hypoglycaemia (IAH), i.e. a reduced ability to perceive the onset of hypoglycaemia (11), is present in 17-25% of people with Type 1 diabetes (6, 11-13) and is associated with a six-fold increased risk of SH (12, 14). Treatment programs aiming to improve awareness of hypoglycaemia in Type 1 diabetes have demonstrated a reduction in FoH (15, 16). Three previous studies (7, 9, 17) have reported an association between FoH and reduced hypoglycaemia awareness. However, in these previous studies, hypoglycaemia awareness was classified by different measures that have not been validated for research application. To our knowledge, no previous study has investigated the relationship between FoH and IAH, using validated instruments for both measures.

In the present study, we have investigated whether IAH, as measured by the method by Gold et al. (14), is associated with FoH, as assessed with the HFS-II Worry subscale (4, 18), in a large and representative population of adults with Type 1 diabetes. In addition, we have examined the association between FoH and the presence and intensity of hypoglycaemia symptoms, as graded with the Edinburgh Hypoglycaemia Scale.

2. Subjects, materials and methods

In a cross-sectional survey performed in 2011, questionnaires were posted to all adults with Type 1 diabetes (n=636) who attended the diabetes outpatient clinic at St. Olavs Hospital in Trondheim, Norway. The inclusion criteria, prevalence of IAH, and hypoglycaemia symptom profiles in this cohort (13), and the differences in aspects of FoH between women and men (19), have been published previously. The questionnaires used in the survey were forward-backward translated (20) into

Norwegian by professional translators, as recommended. The frequency of SH (with loss of consciousness, seizures, or the need for assistance) and self-measurement of blood glucose was queried (13, 19). Information on diabetes duration and the most recent HbA1c was obtained from medical records. Participants gave informed consent, and the study was approved by the regional committee for medical and health research ethics (REC Central), who also consented to our collection of limited demographic and disease-specific data for non-responders.

2.1. Assessment of fear of hypoglycaemia and hypoglycaemia symptoms and awareness

To assess FoH, we employed the HFS-II questionnaire which originally consists of two subscales ('Behavior' and 'Worry') (4). A Norwegian translated version has previously been validated by Graue et al. (18), who found the Behavior subscale to be less reliable with a suboptimal factor structure. We therefore administered only the Worry subscale. The Worry subscale consists of 18 items exploring areas of worry about having hypoglycaemia. The item score was 1-5 (1 being the least and 5 the highest degree of worry), but was recoded to 0-4 in our analyses for comparability with previous publications (4, 8). We used the mean worry score, i.e. the mean score across all worry items with a valid response, for group comparisons of FoH. Participants with valid responses on ≥14/18 of the items were included in the analyses. Among the 435 included participants, 404 (93%) completed all 18 items.

We assessed hypoglycaemia awareness status using the validated questionnaire by Gold et al. (14), which asks the question 'Do you know when your hypos are commencing?'. The participants responded by selecting a number on a Likert scale from 1 ('always aware') to 7 ('never aware'). A score of ≥4 was taken to represent IAH, and a score of 1-3 was considered as normal awareness of hypoglycaemia.

Participants were asked to score the symptoms they usually experience during a typical daytime hypoglycaemic episode. We used the symptoms listed in the Edinburgh Hypoglycaemia Scale (21, 22), with the addition of some symptoms that have been incorporated in later studies (21). Each symptom was scored using a Likert scale from 1 ('not present') to 7 ('present a great deal'). Neuroglycopenic (confusion, drowsiness, weakness, dizziness, warmth, difficulty speaking, inability to concentrate, blurred vision and tiredness), autonomic (sweating, pounding heart, hunger, anxiety and trembling) and general malaise (nausea and headache) symptoms were presented in a mixed order. We calculated the mean symptom score for all symptoms as well as for each subgroup of symptoms.

2.2. Statistical analyses

We used linear regression analysis to examine the association of IAH with FoH and adjusted all results for age (continuous), sex, and diabetes duration (continuous). In a second model, we adjusted for the number of SH episodes in the preceding year (0, 1-2, or ≥3), which may be a reason for, as well as a result of IAH (23, 24), and may thus either confound or mediate the association of IAH with FoH. We similarly examined the association between a history of SH and FoH. Plausible two-way interactions were explored. The mean worry score showed a slightly skewed distribution, but tests on the residuals of the regression model showed acceptable fit. Nonetheless, we also repeated the regression analyses after a square root transformation of the mean worry score, with similar results (data not shown).

Using linear regression analysis, we also examined the associations of symptom scores (continuous and as quartile categories) with FoH adjusted for age, sex, and diabetes duration. In a second model, we additionally adjusted for IAH, which may affect symptom perception. We analyzed total as well as neuroglycopenic and autonomic symptom scores, and additionally explored the association of symptom scores with FoH separately among patients with IAH and normal awareness.

In an additional analysis, we explored any possible association between FoH and living alone (i.e. not living with any other person ≥16 years of age) or not, adjusted for age, sex, and diabetes duration. As factors associated with FoH may differ between women and men (9), interaction by sex was examined.

Characteristics of responders and non-responders were compared using Chi square test, Fisher`s exact test, t-test or Mann-Whitney test, as appropriate. The statistical analyses were performed using SPSS version 22.0.

3. Results

3.1. Participant characteristics

We posted the questionnaire to 636 persons, and 445 responded (70%), 435 of whom had completed all the questionnaires and could be included in the analyses. Seventy-four persons had IAH (17%), and 47 (64%) of those reported ≥1 SH during the preceding year, in contrast to this being reported by 113 (31%) of persons with normal awareness. Among the responders, 78% monitored blood glucose at least once daily; 24% used insulin pump and 2% used continuous glucose monitoring. Non-responders were on average 8 years younger, had 4 years shorter diabetes duration, and 0.5% (5 mmol/mol) higher HbA1c than responders, but there was no difference in sex distribution between responders and non-responders (Table 1).

3.2. Fear of hypoglycaemia score

In all responders, the mean (SD) score on the HFS-II Worry subscale was 1.33 (0.78), with median (IQR) 1.22 (0.77-1.72). The mean score of the individual items varied between 0.90 and 2.04, and the median item score was 1 or 2 for all items except for the item 'Embarrassing myself or my friends in a social situation', which had a median score of 0. The subscale had good internal consistency (Cronbach's Alfa = 0.93).

3.3. Relationship between FoH and hypoglycaemia awareness, severe hypoglycaemia and symptom intensity

3.3.1. FoH vs. reduced hypoglycaemia awareness

Attenuated hypoglycaemia awareness (i.e. higher Gold score) was associated with higher FoH (Figure 1a). Mean (95% CI) worry score was 1.99 (1.82-2.16) in people with IAH and 1.20 (1.13-1.28) in those with normal awareness. The difference in mean worry score between people with impaired (i.e. Gold score ≥4) and normal awareness (Gold score 1-3) was 0.79 (95% CI, 0.60-0.98) after adjustment for age, sex and diabetes duration, and the association was only moderately attenuated after additional adjustment for history of SH (0.64; 95% CI, 0.45-0.83; Table 2). Participants with IAH reported higher FoH than participants with normal awareness irrespective of previous SH (Figure 1c).

3.3.2 FoH vs. history of severe hypoglycaemia

Mean (95% CI) worry score increased from 1.14 (1.06-1.23) in patients with no episodes of SH during the preceding year, to 1.55 (1.41-1.70) and 1.85 (1.67-2.04), respectively, in those having experienced 1-2 or ≥3 such episodes (Figure 1b). Compared with people with no episodes of SH in the preceding year, mean worry score was 0.71 (95% CI, 0.51-0.92) higher among people with ≥3 such episodes after adjustment for age, sex and diabetes duration, and the estimate was moderately attenuated after additional adjustment for IAH (0.53; 95% CI, 0.33-0.73; Table 2).

3.3.3. FoH vs. scores in the Edinburgh Hypoglycaemia Scale

Higher hypoglycaemia symptom scores were associated with higher FoH with an increase of 0.30 (95% CI, 0.23-0.36) in mean worry score per point increase in overall symptom score, adjusted for age, sex, diabetes duration and awareness status (Table 3 and Figure 2). The increase (95% CI) in mean FoH score per point increase in neuroglycopenic symptom score was 0.25 (0.19-0.31) and, similarly, in autonomic symptom score 0.17 (0.11-0.23). The association between symptom score and FoH did not convincingly differ by hypoglycaemia awareness status.

3.4 FoH in people living alone or not living alone

Overall, there was little difference in mean worry score between people living alone vs. not living alone (-0.07; 95% CI, -0.27 to 0.14), adjusted for age, sex, and diabetes duration. There was some evidence that this differed by sex ($p_{interaction}$=0.05). The difference in mean worry score between those living alone vs. not living alone was -0.30 (95% CI, -0.59 to -0.01) in men and 0.13 (95% CI, -0.17 to 0.42) in women.

4. Discussion

By employing validated measures to assess hypoglycaemia awareness and FoH in a large cross-sectional study in adults with Type 1 diabetes, we found that IAH as well as previous episodes of SH were associated with increased FoH. Furthermore, a higher symptom score during episodes of daytime hypoglycaemia was associated with increased FoH in people with impaired as well as normal hypoglycaemia awareness. This association between increased symptom number and intensity, as assessed by the Edinburgh Hypoglycaemia Scale, and FoH has to our knowledge not been described previously. It may seem counterintuitive that IAH as well as increased symptom intensity is associated with FoH. However, IAH implies reduced awareness of the *initial* symptoms of hypoglycaemia, whereas the Edinburgh Hypoglycaemia Scale grades the intensity of symptoms *during* hypoglycaemia (22). A high intensity of neuroglycopenic symptoms has previously been reported in people with IAH (13), and it is intuitively reasonable that people with intense hypoglycaemia symptoms may develop greater FoH.

The major strength of the present study is the use of validated questionnaires for assessing both hypoglycaemia awareness and FoH. Our results confirm previous reports of an association between reduced hypoglycaemia awareness and FoH (7, 9, 17). However, in those previous studies, the definitions of reduced hypoglycaemia awareness have varied. In the study by Hepburn et al. (17), self-reported hypoglycaemia awareness was partitioned into a 3-level scale (‘always/sometimes/never get good warning‘). In a study from Sweden (9), hypoglycaemia unawareness was defined as having experienced >5 blood glucose levels <4 mmol/l without symptoms during the previous year, and in a study from Spain, participants were to state whether they were ’aware of hypoglycaemia or not‘ (7). Neither of these definitions has, to our knowledge, been validated for research application.

Another strength of the present study is the large and unselected study cohort, and the high response rate at 70%. In the study by Anderbro et al. (9), the response rate was 55%. In the study by

Anarte Ortiz et al. 92% responded (7), but the presented data do not inform whether the invitees were a representative sample of patients with Type 1 diabetes.

Our clinic serves the general population of Type 1 diabetes patients in our region, and we invited all outpatients aged 18-75 years with type 1 diabetes for ≥2 years and sufficient understanding of Norwegian to complete the questionnaire (13). Differences in age, diabetes duration and glycaemic control between responders and non-responders were of minor magnitude. In the Norwegian Diabetes Registry (25), the average age, diabetes duration and HbA_{1c} in people with Type 1 diabetes was 41.8 years, 20.8 years and 8.0%, respectively, i.e. quite similar to the measures in the present study, and thus our results are likely representative for the general adult Type 1 diabetes population in Norway. In our responders, the prevalence of IAH (6, 12), history of SH and FoH score were broadly similar to previous reports (4, 26).

The present study was cross-sectional, and we cannot investigate whether IAH and SH episodes preceded FoH. The association between IAH and SH is likely bidirectional, and IAH and SH could be either confounders or mediators of the associations with FoH. We lacked temporal information on the onset of IAH and SH, and it is uncertain which statistical model – with or without adjustment for IAH or SH – that yielded the most valid estimates. Nonetheless, IAH and SH were strongly associated with FoH in both models.

We recognize that, in some people, anxiety traits may inappropriately influence the FoH score. We did not include measures of anxiety, which is a limitation of the present study. Anderbro et al. found higher measures of anxiety in a subgroup of patients with high FoH, but low risk of hypoglycaemia (10). Symptoms of anxiety overlap to some extent with autonomic hypoglycaemia symptoms, and it may be difficult for people with a high level of anxiety to differentiate between symptoms of anxiety and symptoms of hypoglycaemia (27). It is evident that there are complex relationships between factors contributing to FoH, and anxiety measures should be included when FoH is studied.

Another potential limitation of our study is that we used only the Worry subscale, and not the Behavior subscale, of the HFS-II, mainly because the Norwegian translation of the Behavior subscale had a questionable factor structure (18). After initiation of our study, such restricted use of the HFS-II Worry subscale has been addressed by the authors of the original version, who advocate that both subscales should be used (26).

Intuitively, impaired hypoglycaemia awareness might appear to be the most important reason for elevated FoH. This notion is supported by studies in which several strategies to improve

hypoglycaemia awareness resulted in a reduction in FoH (15, 16). However, the reduced FoH observed might also have been promoted by additional support and hypoglycaemia education in these studies. Since IAH is a strong risk factor for SH (12, 14), and intervention also led to a reduction in SH (16), the association between IAH and FoH may in part be mediated by experience of SH. In support of that suggestion, the excess FoH in people with IAH was moderately attenuated after statistical adjustment for history of SH in our study. Furthermore, given the possible consequences of SH, some degree of FoH in people with Type 1 diabetes is considered appropriate (3), which is even more relevant to those with IAH due to their increased risk of SH. Nevertheless, due to the putative negative effects of FoH on clinical treatment goals and quality of life in people with Type 1 diabetes (2, 4), we suggest that it is appropriate to assess awareness status in addition to history of SH in people with excess FoH.

The novel finding of the association between FoH and hypoglycaemia symptom intensity, as graded with The Edinburgh Hypoglycaemia Scale, extends the previously demonstrated relationship between the number of symptoms during hypoglycaemia and FoH (9, 10). The association with symptom intensity was somewhat stronger for neuroglycopenic symptoms than autonomic symptoms. This is consistent with neuroglycopenic symptoms being related to more profound hypoglycaemia (21), but may also reflect fear of the consequences of neuroglycopenia, i.e. the increased risk for injury and accidents due to cognitive dysfunction (3).

Previously, the possible effect of living alone on the level of FoH has scarcely been explored. Anderbro et al. did not find the factor 'nights spent alone' to be associated with FoH (10). We found that men living alone expressed lower levels of FoH than men not living alone, adding to known sex differences in factors associated with FoH (9). However, this exploratory subgroup finding should be interpreted with caution until replicated by others.

The present study adds to the validation of the Norwegian translation of HFS-II Worry subscale, which did not report data on previous SH (18). Our data demonstrate the expected increase in FoH score by increased exposure to SH. The presently described association between FoH and the hypoglycaemia symptom score further supports the validity of the HFS-II Worry subscale, whose internal consistency and acceptability was excellent.

In conclusion, by using validated questionnaires in a large and representative sample of adults with Type 1 diabetes, we found that impaired awareness of hypoglycaemia, previous episodes of SH and high intensity of hypoglycaemia symptoms were associated with increased fear of hypoglycaemia. We suggest that awareness status as well as history of SH should be assessed in people with excess fear of hypoglycaemia.

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Conflicts of interest

None declared.

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Table 1. Characteristics of the study population.

	All participants	Normal awareness	Impaired awareness	Non-responders
Number of participants, n (% women)	435[$] (49)	361 (49)	74 (47)	179[#] (43)[¥]
Age, median (IQR) years	41 (29-53)	39 (28-51)	48 (40-57)	33 (25-45)[*]
Diabetes duration, median (IQR) years	21 (14-32)	19 (12-29)	29 (22-36)	17 (10-26)[*]
Most recent HbA1c,				
%, mean (SD)	8.0 (1.2)	8.0 (1.2)	7.8 (1.2)	8.5 (1.5)[*]
mmol/mol, mean(SD)	64 (13)	64 (13)	62 (13)	69 (16)
Living alone[‡], n (%)	67 (15)	58 (16)	9 (13)	
Insulin regimen, n (%)				
Long + rapid acting analogues	246 (57)	202 (56)	44 (60)	
NPH insulin + rapid acting analogue	77 (18)	68 (19)	9 (12)	
Insulin pump with rapid acting analogue	102 (24)	82 (23)	20 (27)	
Other	7 (2)	7 (2)	0	
RT-CGM[§]	10 (2)	4 (1)	6 (8)	
Frequency of blood glucose measurements, n (%)				
>4 times/day	177 (41)	142 (39)	35 (47)	
1-4 times/day	162 (37)	130 (36)	32 (43)	
1-6 times/week	62 (14)	57 (16)	5 (7)	
<1 time/week	34 (8)	32 (9)	2 (3)	
Severe hypoglycaemia the preceding year, n (%)				
No episodes	275 (63)	248 (69)	27 (37)	
1-2 episodes	100 (23)	78 (22)	22 (30)	
≥3 episodes	60 (14)	35 (10)	25 (34)	
Hypoglycaemia Fear Survey II Worry subscale,				
mean (SD) score	1.33 (0.78)	1.20 (0.69)	1.97 (0.86)	
median (IQR) score	1.22 (0.77-1.72)	1.11 (0.67-1.61)	1.72 (1.32-2.69)	

[$]of 445 responders, ten did not complete the questionnaires regarding fear of hypoglycaemia, history of severe hypoglycaemia and awareness status and were not included in analyses.

[#]12/191 non-responders declined participation and were not included in any calculations.

[*]p≤0.001 for difference vs responders.

[¥]p=0.15 for difference vs responders.

[‡]Not living with any person ≥16 years of age.

[§]Real-time continuous subcutaneous glucose monitoring

Table 2. Difference (95% CI) in fear of hypoglycaemia (mean worry score) according to awareness status and history of severe hypoglycaemia (SH)

Characteristic	n	Unadjusted	Adjusted for age, sex and diabetes duration	Adjusted for age, sex, diabetes duration, history of SH and awareness status
Awareness status				
Normal (Gold score 1-3)	361	reference	reference	reference
Impaired (Gold score ≥4)	74	0.77 (0.59-0.95)	0.79 (0.60-0.98)	0.64 (0.45-0.83)
SH episodes in the preceding year				
0	275	reference	reference	reference
1-2	100	0.39 (0.22-0.56)	0.41 (0.25-0.58)	0.35 (0.19-0.51)
≥3	60	0.74 (0.54-0.95)	0.71 (0.51-0.92)	0.53 (0.33-0.73)

Table 3. Difference (95% CI) in fear of hypoglycaemia (mean worry score) per one-point higher total, neuroglycopenic and autonomic mean symptom scores.

Symptoms	Unadjusted	Adjusted for age, sex and diabetes duration	Additionally adjusted for awareness status
All	0.35 (0.28-0.42)	0.35 (0.28-0.42)	0.30 (0.23-0.36)
Neuroglycopenic	0.30 (0.24-0.36)	0.30 (0.24-0.35)	0.25 (0.19-0.31)
Autonomic	0.19 (0.13-0.25)	0.21 (0.14-0.27)	0.17 (0.11-0.23)

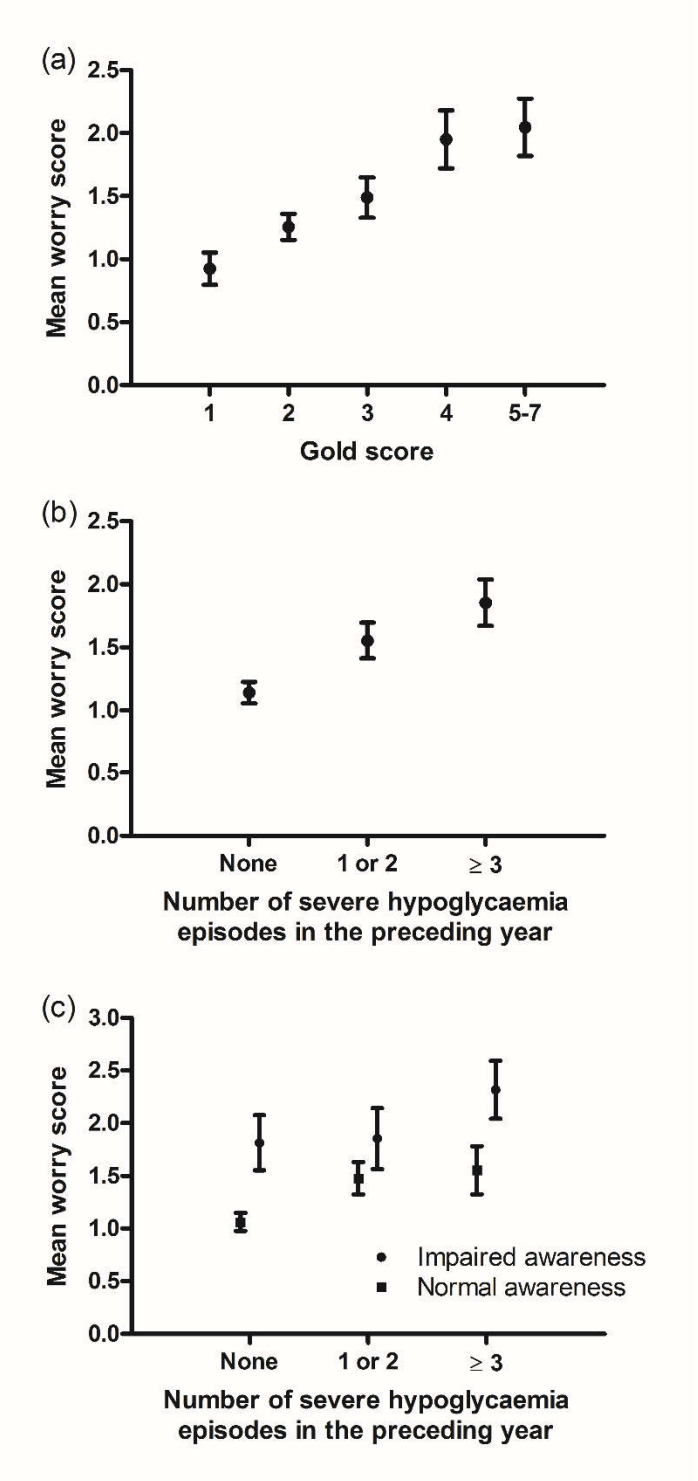

Figure 1. Fear of hypoglycaemia (mean (95% CI) worry score) by (a) Gold score[1], (b) number of severe hypoglycaemia (SH) episodes in the preceding year, and (c) awareness status and number of SH episodes in the preceding year, all adjusted for age, sex, and diabetes duration.

[1] measure of hypoglycaemia awareness on a Likert scale from 1 to 7; a score ≥4 represents impaired awareness, and a score of 1-3 represents normal awareness of hypoglycaemia.

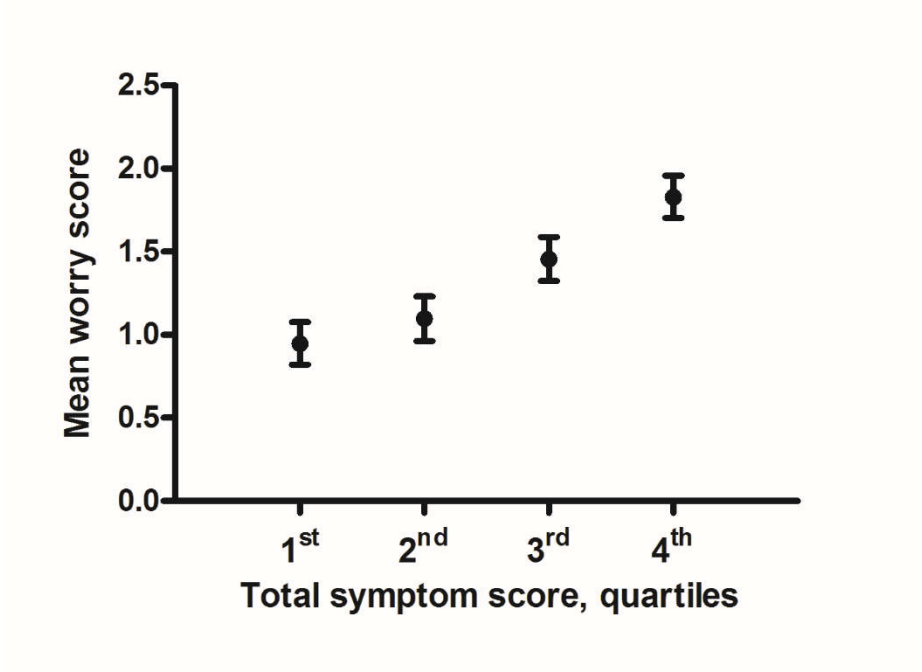

Figure 2. Fear of hypoglycaemia (mean (95% CI) worry score) by quartiles of total symptom score (<2.88, 2.88-3.44, 3.50-4.06, and >4.06, respectively), adjusted for sex, age and diabetes duration.