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Gender differences in reported frequency and consequences of hypoglycemia among adults living with type 1 diabetes: results from the BETTER registry.

Meryem K. Talbo[a*], Maha Lebbar[b,c*], Zekai Wu[b,d], Andréane Vanasse[b], Marie-Laure Lalanne-Mistrih[b,e], Anne-Sophie Brazeau[a,f], Remi Rabasa-Lhoret[b,c,d,f,g]

* Co-First authors

[a] School of Human Nutrition, McGill University, 21111 Lakeshore Dr, Sainte-Anne-de-Bellevue, Quebec, H9X 3V9, Canada
[b] Institut de Recherches Cliniques de Montréal, 110 Pine Ave W, Montréal, Québec, H2W 1R7, Canada
[c] Département de nutrition, Faculté de médecine, Université de Montréal, 2405 Chem. de la Côte-Sainte-Catherine, Montréal, Québec, H3T 1A8, Canada
[d] University of French West Indies, Guadeloupe, France
[e] Department of Medicine, Division of Experimental Medicine, McGill University, 1001 Decarie Boulevard, Montreal, Quebec, H4A 3J1, Canada
[f] Montreal Diabetes Research Center, 900 Saint-Denis, Montreal, QC H2X 0A9, Canada.
[g] Département de médecine, Service d'endocrinologie, Centre hospitalier de l'Université de Montréal, 1000, rue Saint-Denis, Montréal, Québec, H2X 0C1, Canada

Corresponding author:

Anne-Sophie Brazeau, RD, PhD
anne-sophie.brazeau@mcgill.ca
School of Human Nutrition - McGill University
21111 Lakeshore Rd, room MS2-038
Sainte-Anne-de-Bellevue Québec H9X 3V9, Canada

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Abstract

Aims: To evaluate the frequency and consequences of level 2 (L2H, glucose level <3.0 mmol/L with autonomous management) and level 3 hypoglycemia (L3H requiring external assistance to treat), in adults living with type 1 diabetes (T1D), while investigating the role of gender.

Methods: Self-reported data from a Canadian registry of 900 adults living with T1D were analyzed using logistic regression models adjusted for age, T1D management modalities, hypoglycemia history, and validated patient-reported outcomes scales. Changes in diabetes management, seeking healthcare resources, and impacts on daily well-being were explored.

Results: Of the 900 adults (66% women, mean age 43.7 ± 14.8 years, mean T1D duration 25.5 ± 14.6 years), 87% used wearable diabetes technology. L3H in the past year was reported by 15% participants, similar between genders. Women reported more L2H than men (median (Q1, Q3): 4 (2, 10) vs 3 (1,8), p=0.015), and were more likely to report persistent fatigue after both L2H and L3H (Odds ratio [95% confidence interval]: 1.95 [1.16, 3.28] and 1.86 [1.25, 2.75], respectively) and anxiety (1.70 [1.05, 2.75]) after a L3H.

Conclusions: The findings suggest taking a gender-based differential approach when addressing hypoglycemia and its various consequences for people living with T1D.

Keywords: gender difference, hypoglycemia, type 1 diabetes, patient-reported outcome, primary care

1. Introduction:

Growing evidence suggests that sex and gender differences play a role in chronic disease management including diabetes [1]. Gender and sex could indeed shape diabetes' features, from management strategies in various settings [2], to its consequences in terms of short and long-term complications and adverse events [3]. For instance, some studies suggest a higher risk of hypoglycemia, specifically severe hypoglycemia amongst females compared to males [4], but the results remain conflicting and scarce [5].

Iatrogenic hypoglycemia is a well-recognized barrier to achieving optimal diabetes management for people living with T1D (PwT1D) [6]. International consensus established three levels of hypoglycemia. The two most clinically relevant are level 2 hypoglycemia (L2H, glycemia <54 mg/dL (<3.0 mmol/L)) that warrants immediate action and level 3 or severe hypoglycemia (L3H), which is a state characterized by the individual's inability to treat themselves [7].

The global Hypoglycemia Assessment Tool study (over 8,000 PwT1D from 24 different countries) highlighted the real-world frequency of hypoglycemia, with 83% of participants reporting at least one non-severe hypoglycemic event, and 14% at least one severe hypoglycemic event in the 4-week prospective analysis [8]. Incidence of reported severe hypoglycemia in PwT1D can even go up to 54% a year, one Canadian study found based on anonymous reporting [9]. However, the frequency of L2H is rarely assessed whether it is by using self-reported or continuous Glucose Monitoring (CGM)-based data. A recent CGM-based study found that amongst 257 PwT1D, two-thirds presented at least one L2H event in the last 3 months [10, 11].

Hypoglycemia is associated with several complications such as physical injury, adverse cardiovascular events and/or cognitive impairment [12]. It also carries social and economic

burdens, such as an increase in the use of health services and a decrease in work productivity [13] and can lead to fear of hypoglycemia (FOH) [14]. While data on gender differences and consequences of hypoglycemia are scarce, current literature supports that women with T1D experience more FOH [15] and have a lower quality of life compared to men with T1D [16]. Similarly, women also report more diabetes distress and lower hypoglycemia confidence [17].

Keeping these differences in mind, we hypothesized that the frequency and consequences of hypoglycemia may differ between the genders. Furthermore, there are scarce results about the prevalence of L2H and its consequences on diabetes management, healthcare services' use, and well-being with respect to gender in PwT1D.

This study aims to assess the frequency of L2H and L3H and to better understand the possible gender differences in the way PwT1D experience and manage such events, based on a large Canadian registry.

2. Material and methods:

2.1 Registry

A cross-sectional analysis of data extracted from the BEhaviors, Therapies, TEchnologies, and hypoglycemic Risk in T1D (BETTER) registry in Quebec, Canada [11]. Data from adults (≥18 years old) living with T1D, who completed the baseline questionnaires of the BETTER registry, were collected between April 2019 and January 2022. Pregnant participants and PwT1D diagnosed for less than a year were excluded from this analysis.

2.2 Variables

The current analysis included self-reported socio-demographic data (age, annual household income, health insurance coverage, and living status), diabetes information (duration, most recent HbA1c range level, methods of insulin administration and glycemia monitoring), and hypoglycemia history (L2H and symptomatic nocturnal hypoglycemia in the past month, L3H in the past year).

We surveyed participants' biological sex (male or female) and gender identity (men, women, or other). Reported gender was used as an independent variable to evaluate its association with hypoglycemia consequences.

Participants were asked about their perceived consequences after their last L2H and L3H episodes. Participants were also provided with free text space to add any other consequences that were not suggested. Questions on the consequences spanned three domains: a- diabetes management, b- use of health services and medical follow-up, c- daily life and physical and mental health (supplementary table 1).

Patient-reported outcomes measures (PROMs) were assessed using validated surveys. Impaired awareness of hypoglycemia was defined as a Gold score ≥4 [18]. The Hypoglycemia Fear Score II (HFS II) was used to quantify participants' FOH. HFS-II is a validated 33-item questionnaire, with a total score and two subscale scores (behaviors and worry). Each item is rated on a five-point scale from 0 (never) to 4 (almost always). Higher scores indicate more FOH [19]. While there is validated cut-off for HFS, some authors endorsed the elevated item approach, in which individuals with a concerning FOH were defined as having an elevated score (scoring of 3 or 4) in at least one item of the worry subscale of HFS-II [20]. This approach was used in the current analysis to classify elevated FOH.

The Hypoglycemia confidence scale (HCS) was used to examine the participants' confidence in their ability to manage hypoglycemia. HCS is a validated 9-item questionnaire. Items are rated on a 4-point scale from 0 (not confident at all) to 3 (very confident) and averaged. Higher scores indicate more confidence. A HCS score <3 was used to indicate low confidence [21].

The Diabetes Distress Scale comprised 17 items with 4 subcategories (emotional burden, physician, regimen, and interpersonal distress). Item scores range between 1 (not a problem) to (a very serious problem). An average score between 2.0 to 2.9 is considered moderate distress, while a score ≥3.0 is considered elevated distress [22].

2.3 Ethics

The study protocol was approved by the Montreal Clinical Research Institute ethics board (2022-1146) and all participants signed an electronic consent form.

2.4 Statistical analysis:

Categorical variables are presented as percentages. Continuous variables are presented as mean± standard deviation [SD] or median with interquartile range [IQR]. Outliers and normality were assessed visually, and normality was also assessed using kurtosis<3 and skewness ~0. To compare between genders, independent samples' T-test was used for age and T1D duration and the non-parametric Mann–Whitney U test was used for other continuous variables with asymmetric distribution. The association between the consequences of L2H and L3H and gender was examined using binomial logistic regression, with each consequence modeled as a dichotomous variable (yes/no). First, univariable models were used to explore the associations between each consequence and participants' gender. Multivariable logistic regression models were then built to

adjust for other significant variables (selected based on their statistical and clinical significance) including participants' age, treatment modality, PROMs, and history of hypoglycemia. To evaluate the association between the frequency of hypoglycemia (number of reported episodes) and gender, negative binomial regression was used. The final models were adjusted for treatment modalities and age. The results are expressed as incidence rate ratios (IRRs) with 95% confidence intervals (95% CIs). The minimum sample size needed was estimated to be 550 using the event per variable equation, in addition to a baseline of 100 participants recommended by Bujang et al [23]. The results of the logistic regression analysis were expressed as odds ratios (OR) with 95%CIs. Missing data were minimal (<5%) and no differences were found between the group with missing predictor variable data and the group with available data, thus the missing data is considered negligible, and the regression analysis included only the participants with complete data [24]. The data were analyzed by SPSS version 27 (SPSS Inc., Chicago, IL, USA) and statistical significance was set to $p<0.05$.

3. Results:

Participants' characteristics are presented in Table 1. Of the 900 participants, 66% (n=590) self-identified as women and 33% had an HbA1c ≤7.0% (≤53mmol/mol), similar across genders. On average, women were younger (41.6 ± 14.4 vs 47.5 ± 15.0 years, $p<0.001$), had a shorter duration of T1D (24.6 vs 27.0 years, $p=0.023$), and reported higher use of diabetes technology, especially insulin pumps (49% vs 37%, $p=0.001$) compared to men.

More women reported L2H and symptomatic nocturnal hypoglycemia in the past month (84% vs 76%, $p=0.013$ and 71% vs 62%, $p=0.008$, respectively) compared to men, resulting in higher relative risk even after adjusting for age and diabetes management modality (1.66 [1.15, 2.40] and

1.48 [1.09, 2.02], respectively). The frequency of L2H in the past month (1.19 [1.01, 1.39]) and symptomatic nocturnal hypoglycemia (1.36 [1.15, 1.62]) were also significantly higher in women in the model adjusted for age and treatment modality. The prevalence of reported L3H in the last year was comparable across genders (15% vs 15%, p=0.532). More women reported elevated FOH (61% vs 43%, p<0.001), diabetes distress (22% vs 11%, p<0.001), and low hypoglycemia confidence (32% vs 20%, p<0.001) compared to men.

The consequences of L2H are presented in Figure 1. Up to two-thirds (n=568) of the participants reported experiencing a change in their diabetes management after their last L2H episode, with half (n=463) reporting at least two changes (no statistical difference between genders). The most common diabetes management changes were an increase in glucose monitoring in the days following the episode (36%, n=311) and changes in insulin doses (29%, n=248). Consuming additional carbohydrates and ensuring their availability at all times were also reported by 26% (n=222) and 24% (n=205) of the participants, respectively. Neither of these consequences were significantly different between the genders. Glucagon prescription after a L2H episode was mostly reported by men (4% vs 1%, p=0.016). The majority of participants reported no use of healthcare services after the episode (83%, n=713) with no differences between genders. When reported, the most common consequence on healthcare service use was discussing the hypoglycemic episode at the next usual appointment, although reported by only 14% (n=124) of the participants. Additionally, 42% (n=360) reported experiencing consequences on their daily life, and physical or mental well-being after their last L2H, significantly higher amongst women compared to men (47% vs 33%, p<0.001), such as loss of productivity (13% vs 7%, p=0.003), anxiety (23% vs 14%, p=0.003), and persistent fatigue (33% vs 18%, p<0.001). The descriptive analysis of “Other” consequences shows that 60 participants (7% of the total sample, 80% of which were women)

reported having experienced other consequences than those previously mentioned (Figure 1). The most frequently reported "Other" consequences were headache/migraines (n=9, 15%) and rebound hyperglycemia (n=9, 15%) after a L2H episode (Supplemental Table 3). Thirteen participants (22%) also mentioned adding a new diabetes technology (a continuous glucose monitor (CGM) or an insulin pump)

The consequences of L3H are presented in Figure 1. A majority of participants (76%, n=318) and a higher proportion of women (80% vs 71%, p=0.032) reported changes in their diabetes management after their last L3H episode, with 77% of the participants (n=331) reporting at least 2 changes (similar across genders). The most common changes were an increase in glucose monitoring (55%, n=228), always ensuring the availability of carbohydrates (33%, n=138), and changes to insulin doses (29%, n=119), but neither were significantly different between genders. Glucagon prescription was higher after L3H (16%, n=67) with no significant differences between genders. The frequency of consequences on healthcare service use (64%, n=266) and in daily life and well-being (66%, n=276) were higher than what was noted after L2H, with women reporting more anxiety (44% vs 30%, p=0.004) and persistent fatigue (36% vs 21%, p=0.002) after their last L3H episode compared to men. Details of all L2H and L3H consequences are provided in the supplementary data (Supplemental Table 2). The analysis of "Other" consequences after a L3H show that 45 participants (5% of the total sample) reported having experienced other consequences than those previously mentioned. The proportion of men and women were 31% and 69%, respectively, and the most frequently reported consequences were concerns from others (partners or roommates) (n=8, 18%) and cognitive function impairment (n=6, 13%) after a L3H episode (Supplemental Table 4). Eleven participants (24%) also mentioned they added a new diabetes technology (CGM, or pump) after this episode.

Results from the univariable logistic regression (Supplemental Table 5) informed the selection of consequences significantly associated with gender for the multivariable regression. In the multivariable models (Figure 2), women were more likely to report experiencing persistent fatigue both after a L2H (1.86 [1.25, 2.75]) and after L3H episodes (1.95 [1.16, 3.28]). Women also reported significantly more anxiety after their last L3H (1.70 [1.05, 2.75]) compared to men. No other significant gender differences were found for the remaining consequences of L2H and L3H. Participants experiencing high diabetes distress and elevated FOH were more likely to report higher anxiety, fatigue, embarrassment, and loss of productivity as consequences of L2H and L3H. Moreover, participants with low hypoglycemia confidence were more likely to report additional consumption of carbohydrates and additional consultation with a healthcare provider outside of their scheduled and/or emergency visits, after a L3H episode. Low hypoglycemia confidence was also associated with more anxiety and persistent fatigue (table 2). Of note, diabetes technology use (pump and/or CGM) was not associated with reported consequences of either L2H or L3H.

4. Discussion

Our findings show that L2H and L3H remain frequent [10, 25, 26], despite the high proportion of diabetes technology use in this sample. Moreover, our results also highlight the higher burden related to L2H and L3H in women compared to men, with higher frequency, worse PROMs, and negative consequences on their daily life and well-being.

Few studies explored the association between gender and hypoglycemia burden, as the majority of the literature on the topic explores sex as a biological factor with a focus on L3H, disregarding the role of gender as a social construct in shaping PwT1D experiences [27]. To our knowledge, the only study that specifically looked at L2H found that sex was not a risk factor for L2H or L3H

(CGM-defined, including both symptomatic and asymptomatic episodes) in a 289-participant sample [10]. Yet, our study found that women reported more L2H episodes than men. This could be because women experienced a greater impact from their episodes and were therefore more likely to recall them, compared to men. Furthermore, women have a greater tendency to be attentive to their health which might make them more likely to identify L2H episodes and thus report more episodes [28].

This study found that most consequences reported after L2H and L3H episodes were related to diabetes management, as evidenced by increased glucose monitoring (36% and 55%, respectively) which is reflective of the current guidelines' recommendations [29, 30]. The change in insulin dose following a L2H was slightly higher in our study (29%) compared to a previous report by Brod et al. (24.9%) [25]. This can be explained by the higher proportion of CGM and pump users (83% and 45%, respectively), allowing easier monitoring and insulin dose adjustments. However, there was no unanimity in the reported consequences on diabetes management which indicates that the consequences experienced vary among individuals.

Interestingly, only 16% of participants were prescribed glucagon after their latest L3H event, with no difference between genders. This may be because overall, 80% of the participants were previously prescribed glucagon by their physician even though only 24% of those who had L3H in the past year reported using it. However, a recent observational study (n=264) found that only 68% had a current glucagon prescription, with the majority having the glucagon at home and not elsewhere. Furthermore, only a third received proper training on its use [31]. These findings, including ours, collectively highlight the need for improved access to and training on emergency diabetes kits, including the practical intranasal form of glucagon [32].

While hypoglycemia in clinical trials can be underreported (e.g. due to exclusion of participants with L3H history) [33], our study shows that both L2H and L3H remain frequent and can generate a variety of consequences, including increased healthcare service use. However, PwT1D rarely discuss L2H and its consequences with their healthcare provider [25]. In our sample, only 18% of the participants discussed their L2H with a healthcare professional, compared to 39% after a L3H episode. Due to its clinical relevance and high frequency, L2H should be more systematically addressed during consultation, and CGM data could help initiate the conversation [34]. Additionally, the impact of L3H on healthcare service use (64% of participants) was expected as these episodes can be life-threatening and require assistance to treat.

A significant portion of participants reported having consequences related to their well-being and everyday life for both levels of hypoglycemia after both L2H and L3H (42% and 66%, respectively), with persistent fatigue (28% and 30%) and anxiety (20% and 39%) being most common. Similarly, a European study with over three thousand people with diabetes (including 1631 PwT1D) found that after a non-severe event, fatigue was the most frequent well-being outcome reported by 58% of their participants [13]. The discrepancy can be attributed to the questionnaire terminology (tiredness/fatigue vs persistent fatigue in our study) and the non-severe hypoglycemia definition used [13]. Of note, anxiety was reported in slightly less than 20% of the sample, similar to our results. Furthermore, even after adjusting for relevant factors such as technology use and frequency of hypoglycemia, women are still more likely than men to report persistent fatigue after L2H and L3H episodes, and more anxiety after L3H episodes. This difference in the physical and psychological burden between men and women following a L2H or L3H might be attributed in part to an already unequal mental load between the genders that exacerbates hypoglycemia burden among women [16, 35]. Aside from their psychological

consequences, all the above hypoglycemia consequences can amount to additional direct (e.g., hospitalization and clinical visits) and indirect (e.g., work absenteeism or sick leaves) costs estimated to be close to 3000$ per year per person [36]. Recognizing that women reported a higher L2H rate and its well-being consequences than men, a significant loss of productive days might put them at risk of loss of income or slower career advancement, in an already disadvantageous workplace for women [37].

Even though gender was associated with some well-being-related consequences, most associations were no longer significant after adjusting for PROMs. In fact, high diabetes distress, elevated FOH, and low hypoglycemia confidence were frequently associated with the reported consequences. Given the cross-sectional nature of this analysis, these associations could be explained in two ways. PwT1D who experience significant hypoglycemia consequences would develop higher fear and distress or lose confidence in their ability to manage hypoglycemia [15]. On the other hand, PwT1D with baseline elevated FOH or distress might experience these consequences more often and therefore would be more likely to report them [38]. Either way, these PROMs can provide valuable insights and should be included and further explored in both clinical and research settings [39].

A surprising finding of this study was that use of diabetes technology, such as pump and CGMs, was not associated with hypoglycemia consequences in our multivariable regression analysis. While these technologies can reduce hypoglycemia events [36], certain outcomes such as anxiety and fatigue may persist. Additionally, the cross-sectional nature of the data limits our ability to assess the timing of the initiation of these technologies compared to the timing of the episode and its consequences.

This study is the first to thoroughly assess a variety of consequences of two clinically significant levels of hypoglycemia, in a large contemporary sample while comparing between genders. The large sample size allowed for adjusted regression models to further assess the associations and account for participants' characteristics. The use of validated surveys to measure PROMs (HFS-II, HCS, and DDS) is another strength and allows our findings to be compared to other similar samples and eventually translated into clinical practice. Additionally, patients' reported outcomes and patients' experience measures are essential to assess the burden of hypoglycemia [39].

As our sample has possibly highly motivated participants with high diabetes technology use, might not be representative of all PwT1D, especially those who cannot benefit from such devices due to lack of health or financial coverage. Other limitations include the cross-sectional design only allowing a correlation to be established, the limited propositions (which was mitigated by providing the possibility to write other consequences if experienced), the lack of a validated survey on the consequences of hypoglycemia, and the possible recall bias although some studies found an accurate recall up to 12 months for severe episodes, non-severe hypoglycemia was more subject to underestimation and thus the reported frequency in this sample might be higher [26]. Moreover, while both gender and sex were assessed, all our participants self-identified according to their sex. The findings of this study may therefore not be applicable to other genders, which warrants study designs that target gender minorities.

In conclusion, the frequency of L2H and L3H remains high in a T1D registry cohort in Canada. Women report more L2H events and consequences as well as higher psychological burdens following hypoglycemia events. Multilayer constructs, particularly on stress management, may explain the observed gender differences and suggest taking a gender-based differential approach

when addressing hypoglycemia, while also accounting for hypoglycemia history and mental health-related quality of life in PwT1D.

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Declaration of Interest:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data sharing: The BETTER registry's variable list can be found at https://www.maelstrom-research.org/study/better. De-identified individual participant data used in the analysis and results reported in this article can be available following acceptance by BETTER scientific committee and a duly authorized ethics board. The Cost of providing access to data and maintenance of the registry must also be covered. To explore the possibility of having access to the BETTER registry data, please contact the research team at better@ircm.qc.ca.)

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Table 1. Participant characteristics by gender.

	Total sample (n=900)	Men (n=310)	Women (n=590)	p
Age (years)	43.7 ± 14.8	47.5 ± 15.0	41.6 ± 14.4	<0.001
Living alone [a]	146 (16)	47 (15)	99 (17)	0.524
Household Income by year [b]				0.074
Less than 50 000$	222 (24)	68 (31)	154 (28)	
Between 50 000 and 100 000$	295 (38)	107 (38)	188 (38)	
More than 100 000$	266 (34)	108 (38)	158 (32)	
Medical insurance type [c]				0.357
Public	214 (24)	79 (26)	135 (23)	
Private	591 (66)	195 (63)	396 (68)	
Both	89 (10)	35 (11)	54 (9)	
Diabetes duration (years)	25.5 ± 14.6	27.0 ± 15.5	24.6 ± 14.1	0.023
Diabetes management [d]				0.005
MDI+CBG	111 (13)	46 (15)	65 (12)	
MDI+isCGM	296 (35)	117 (39)	179 (32)	
MDI+rtCGM	66 (8)	26 (9)	40 (7)	
pump+CBG	41 (5)	7 (2)	34 (6)*	
pump+isCGM	136 (16)	34 (11)	102 (18)*	
pump+rtCGM	208 (24)	70 (23)	133 (24)	
HbA1c range [e]				0.160
≤7.0% (≤53mmol/mol)	293 (33)	110 (37)	183 (33)	
7.1% to 8.0% (54 - 64 mmol/l)	374 (42)	131 (45)	243 (43)	
8.1% to 9.0% (65 - 75 mmol/l)	139 (15)	39 (13)	100 (18)	
≥ 9.1% (76 mmol/l)	49 (5)	13 (4)	36 (6)	
Had level 3 hypoglycemia in past year [f]	131 (15)	45 (15)	86 (15)	0.915
Number of level 3 episodes in past year median (IQR)[†]	1 (1, 2)	1 (1, 3)	1 (1, 2)	0.744
Had level 2 hypoglycemia in the past month [g]	726 (81)	235 (76)	491 (84)	0.005

Number of level 2 episodes in past month median (IQR) [h]	4 (1, 9)	3 (1, 8)	4 (2, 10)	0.015
Had symptomatic nocturnal hypoglycemia in the past month [i]	598 (68)	188 (62)	410 (71)	0.008
Number of symptomatic nocturnal hypoglycemia in the past month [j]	1 (0, 3)	1 (0, 3)	2 (0, 4)	0.001
Impaired hypoglycemia awareness as defined by a Gold score >4	179 (20)	64 (21)	115 (20)	0.680
Hypoglycemia Confidence Score [k], median (IQR)	3.3 (2.9, 3.6)	3.4 (3.0, 3.8)	3.3 (2.9, 3.6)	<0.001
Low hypoglycemia confidence	236 (27)	61 (20)	175 (32)	<0.001
Elevated fear of hypoglycemia [l]	463 (51)	128 (43)	335 (61)	<0.001
High diabetes distress m	157 (17)	34 (11)	123 (22)	<0.001
Have used glucagon in the past year †	34 (24%)	9 (21%)	23 (27%)	0.449

Data are presented as mean±SD for continuous data and n(%) for categorical data unless indicated otherwise.
All participants included in the analysis self-identified according to their sex (n=1 didn't know their gender and was therefore excluded).
† n=131 who reported a level 3 hypoglycemia in the past year.
Missing data: [a] n=4 (0.4%),[b] n=117 (13%), [c] n=6 (1%), [d] n=47 (5%), [e] n=45 (5%), [f] n=14 (2%), [g] n=8 (1%), [h] n=29 (3%), [i] n=15, [j] n=15 (2%), [k] n=40 (4%), [l] n=50 (6%), [m] n=50 (6%).

Table 2. Patient-reported outcome measures (PROMs) associated with level 2 and level 3 hypoglycemia consequences.

Consequence	PROMs	Level 2 OR [95%CI]	Level 3 OR [95%CI]
More frequent measurements of blood sugar in the following days	Elevated FOH	1.30 [0.92, 1.82]	1.81 [1.15, 2.88] *
	Low confidence of hypo	1.20 [0.82, 1.75]	0.71 [0.43,1.18]
	High DDS	1.42 [0.89, 2.29]	1.07 [0.56, 2.05]
Additional consumption of carbohydrates	Elevated FOH	1.08 [0.74, 1.57]	1.12 [0.64, 1.96]
	Low confidence of hypo	1.15 [0.76, 1.73]	2.11 [1.19, 3.75] *
	High DDS	2.44 [1.48, 4.01] *	1.34 [0.64, 2.80]
Having a source of carbohydrates on you at all times	Elevated FOH	1.56 [1.06, 2.31] *	1.31 [0.80, 2.15]
	Low confidence of hypo	1.29 [0.85, 1.97]	1.54 [0.91, 2.61]
	High DDS	1.42 [0.84, 2.40]	1.06 [0.55, 2.07]
Skipped insulin injection(s)	Elevated FOH	3.14 [0.86, 11.51]	1.91 [0.37, 9.89]
	Low confidence of hypo	1.11 [0.43, 2.89]	1.33 [0.34, 5.20]
	High DDS	2.81 [0.80, 6.36]	8.28 [0.78, 8.76]
Had change in type 1 diabetes management	Elevated FOH	1.27 [0.90, 1.78]	1.47 [0.86, 2.50]
	Low confidence of hypo	1.28 [0.85, 0.93]	1.12 [0.61, 2.05]
	High DDS	1.80 [1.08, 2.98]	1.02 [0.46, 2.26]
Additional consult or contact with a healthcare provider	Elevated FOH	2.24 [0.72, 6.91]	1.12 [0.64, 1.96]
	Low confidence of hypo	3.47 [1.29, 9.39]	2.11 [1.19, 3.75] *
	High DDS	1.46 [0.45, 4.78]	1.34 [0.64, 2.80]
Discussion about the last hypoglycemic episode at the next usual appointment with your doctor for diabetes	Elevated FOH	1.93 [1.17, 3.18] *	1.74 [1.08, 2.78] *
	Low confidence of hypo	1.49 [0.90, 2.46]	1.05 [0.63, 1.75]
	High DDS	1.72 [0.91, 3.24]	0.86 [0.45, 1.65]
Had consequences on health service use	Elevated FOH	2.06 [1.28, 3.32] *	1.70 [1.07, 2.72] *
	Low confidence of hypo	1.61 [1.00, 2.59] *	0.90 [0.53, 1.52]
	High DDS	1.76 [0.96, 2.50]	1.27 [0.64, 2.51]
Changes in exercise habits	Elevated FOH	1.58 [0.83, 3.02]	1.99 [0.88, 4.48]
	Low confidence of hypo	1.51 [0.80, 2.87]	1.25 [0.57, 2.78]
	High DDS	1.58 [0.67, 3.71]	2.45 [0.88, 6.78]
Loss of productivity (absence from work or school)	Elevated FOH	2.47 [1.27, 4.81] *	1.74 [0.90, 3.35]
	Low confidence of hypo	1.46 [0.83, 2.56]	0.99 [0.52, 1.89]
	High DDS	3.33 [1.63, 6.79] *	3.91 [1.77, 8.63] *
Anxiety (important concern or intense fear)	Elevated FOH	3.01 [1.84, 4.93] *	1.62 [1.00, 2.64] *
	Low confidence of hypo	2.02 [1.30, 3.15] *	1.31 [0.78, 2.19]
	High DDS	4.23 [2.38, 7.41] *	4.23 [2.15, 8.34] *

Persistent fatigue (that lasts a long time)	Elevated FOH	1.83 [1.24, 2.71] *	1.83 [1.08, 3.10] *
	Low confidence of hypo	1.79 [1.20, 2.67] *	1.97 [1.16, 3.34] *
	High DDS	2.26 [1.37, 3.72] *	1.76 [0.89, 3.47]
Embarrassment	Elevated FOH	3.81 [1.92, 7.53] *	1.86 [1.11, 3.14] *
	Low confidence of hypo	0.84 [0.47, 1.48]	1.02 [0.60, 1.75]
	High DDS	6.41 [3.13, 13.10] *	2.83 [1.44, 5.56] *
Had consequences on daily life	Elevated FOH	1.92 [1.36, 2.72] *	1.78 [1.10, 2.84] *
	Low confidence of hypo	1.92 [1.30, 2.82] *	1.93 [1.08, 3.44] *
	High DDS	3.87 [2.37, 6.32] *	2.66 [1.21, 5.83] *

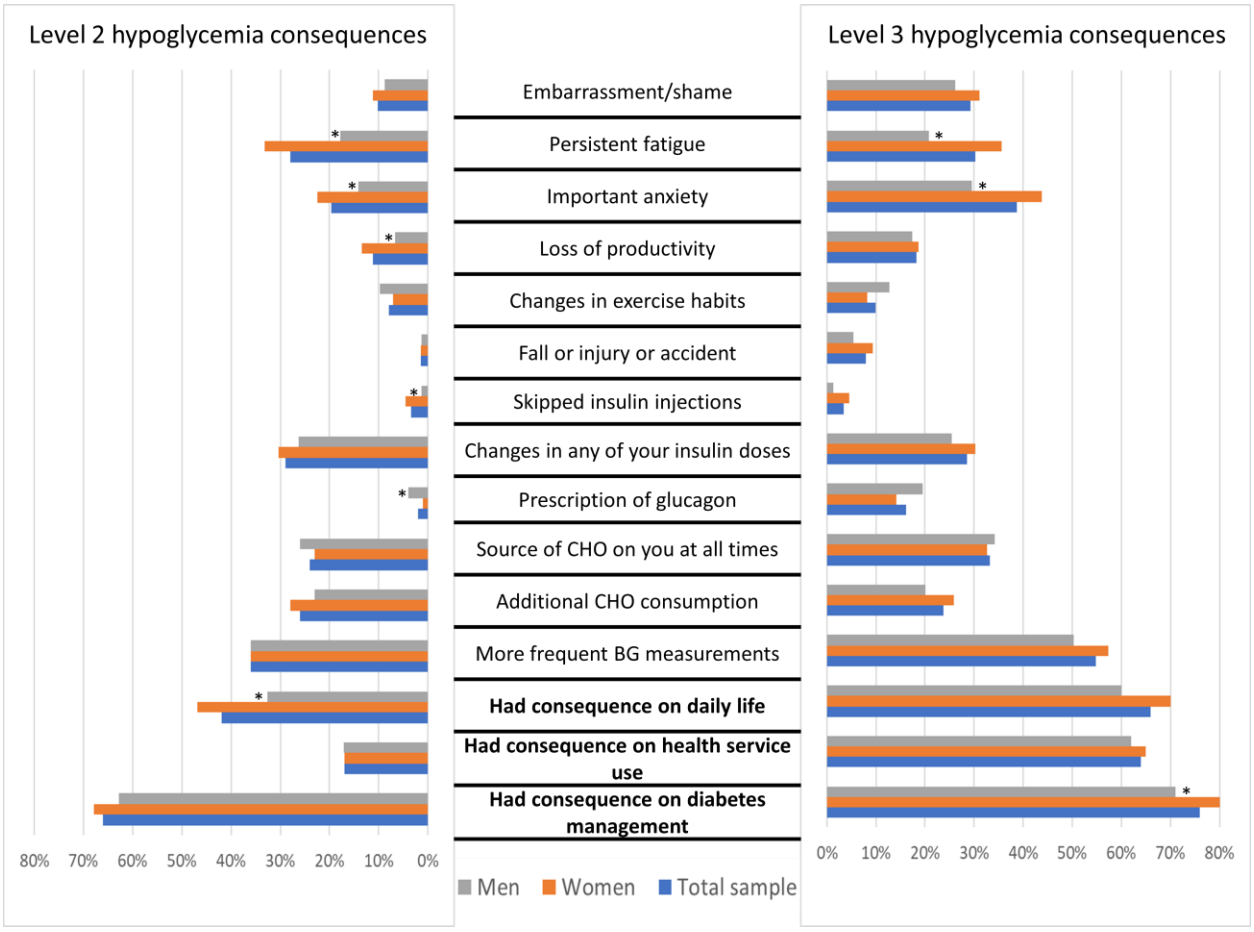
*Statistically significant results ($p<0.05$).

Level 2 hypoglycemia multivariable logistic regression models included gender, age, insulin administration and glucose monitoring modality, number of level 2 hypoglycemia in the past month, and the number of symptomatic nocturnal hypoglycemia in the past month, if they have elevated fear of hypoglycemia (FOH), low hypoglycemia confidence, and elevated diabetes distress scores (DDS).

Level 3 hypoglycemia multivariable logistic regression models included gender, age, insulin administration and glucose monitoring modality, if they have elevated fear of hypoglycemia, low hypoglycemia confidence, and elevated diabetes distress.

Reference categories (OR=1): Low FOH, high confidence of hypoglycemia, and low DDS.

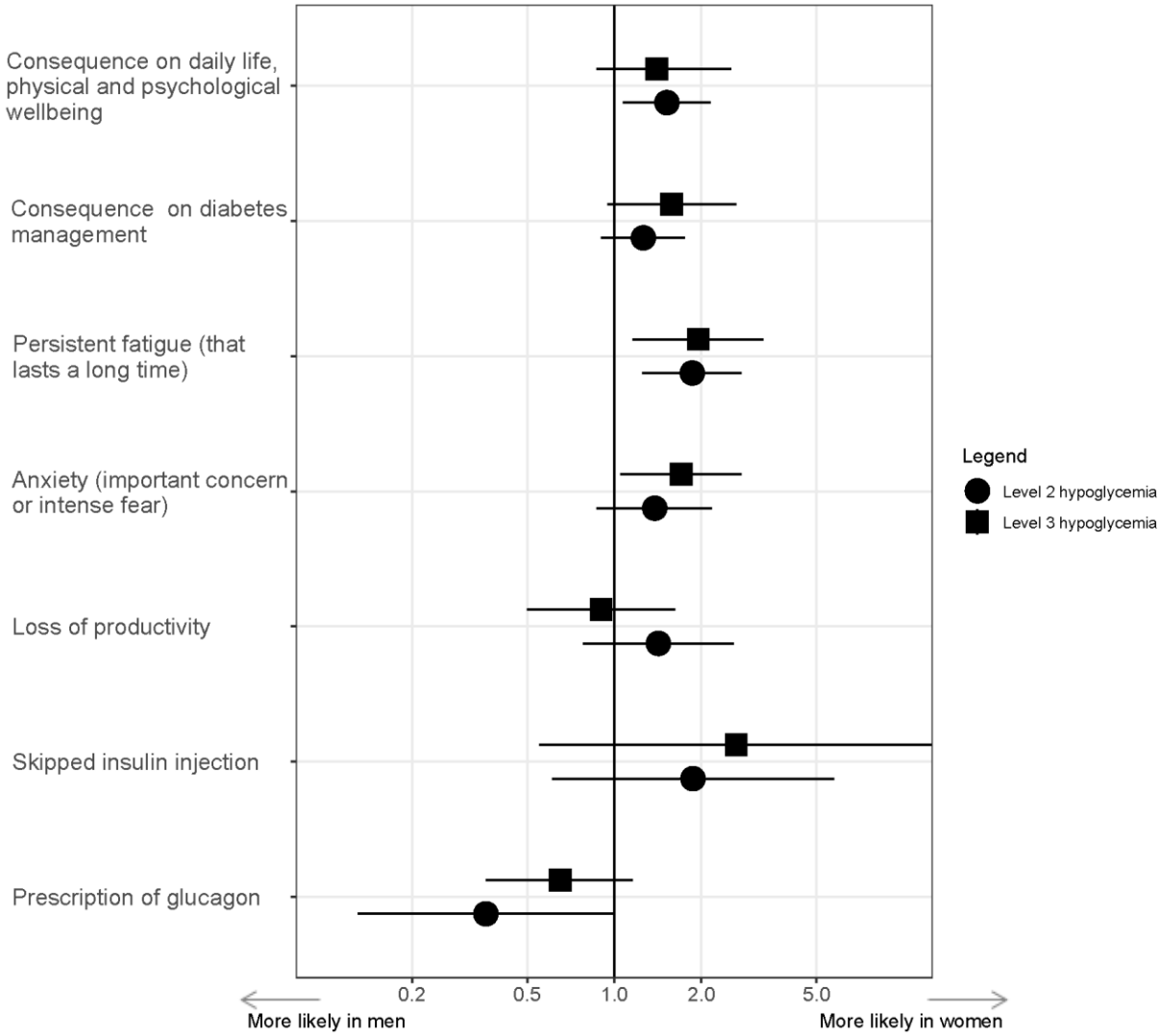
Figure 1. Consequences of level 2 and level 3 hypoglycemia for the total sample and by gender.



* Statistically significant results ($p<0.05$).

CHO: carbohydrates,

Figure 2. Level 2 and level 3 hypoglycemia consequences associated with gender.



Multiple logistic regression analysis was only run for consequences showing significant association with gender in the univariate analysis.

Level 2 hypoglycemia multivariable logistic regression models were adjusted for age, insulin administration and glucose monitoring modality, number of level 2 hypoglycemia in the past month, number of symptomatic nocturnal hypoglycemia in the past month, if they have elevated fear of hypoglycemia (HFS-II), low hypoglycemia confidence, and elevated diabetes distress.

Level 3 hypoglycemia multivariable logistic regression models were adjusted for age, insulin administration and glucose monitoring modality, if they have elevated fear of hypoglycemia, low hypoglycemia confidence, and elevated diabetes distress.

Odds ratio (OR) = 1.0 for the reference categories (men). The centers of the shape are placed at the point estimates (OR) and the horizontal lines represent the corresponding 95%CIs.

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