January 2014

Risk Of Hypoglycemia Among T1dm Individuals Who Exercise Regularly

Jennifer Audrey Campbell
Yale University, jennifer.a.campbell321@gmail.com

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A Thesis Submitted to the Yale University School of Public Health in Partial Fulfillment of the Requirements for the Degree of Master of Public Health

By

Jennifer A. Campbell

ABSTRACT: Exercise training and sport activity are important for good health among those with type 1 diabetes mellitus (T1DM); however, fear of hypoglycemia is a clear barrier to participation. We examined both the main demographic and exercise training risk profiles for exercise-associated and nocturnal hypoglycemia, including indicators of unawareness. Mode of insulin delivery, whether multiple daily injections (MDI) via pen or continuous subcutaneous insulin infusion (CSII) via pump, was an important consideration. **Research Design**: Our study was based on data from an internet-based survey in the Netherlands that attracted T1DM participants who engage in routine exercise or sport activity. **Results**: The majority of survey participants reported experiencing hypoglycemia either "sometimes" (67.9%) or "regularly" (18.5%) during or after exercise, while 74% reported experience of nocturnal hypoglycemia. In contrast, only a very small number of survey participants reported complete unawareness surrounding symptom severity (< 4%). Overall, regular exercise-associated hypoglycemia predicted the report of nocturnal hypoglycemia (OR= 14.44; P < 0.001). Significant demographic predictors specific for exercise-associated hypoglycemia were sex, age, and number of years of exercise with T1DM (P <0.05). Nocturnal hypoglycemia was influenced by duration of diagnosis and daily basal insulin dose requirements (P < 0.05). Mode of insulin delivery (pen/pump) significantly influenced both exercise-associated (P= 0.002) and nocturnal (P= 0.042) hypoglycemic outcomes, depending on exercise type (endurance/non-endurance). Specifically, pump use, in the context of non-endurance exercise, was associated with high risk for both forms of hypoglycemia. **Conclusions**: While hypoglycemia is prevalent in individuals with T1DM who exercise regularly, hypoglycemia unawareness is not. Given that baseline insulin requirements were broadly tied to the above risk profiles, we conclude that exercise regimens to improve overall insulin sensitivity may be crucial to mitigating risk for hypoglycemic outcomes.

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INTRODUCTION

Cardiorespiratory fitness achieved through regular exercise is vital to overall health quality, and offers a number of health benefits to people with Type 1 Diabetes Mellitus (T1DM) (Huttunen et al., 1989; Lehmann et al., 1997). Measured by maximal oxygen consumption, cardiorespiratory fitness is a simple predictor of good glycemic control as gauged by glycosylated hemoglobin (HbA1c) levels in individuals with T1DM (Lukacs et al., 2012). Unfortunately, low exercise involvement has been identified as a common lifestyle characteristic contributing to cardiometabolic risk in people with T1DM (Leroux et al., 2014). One of the primary barriers to regular exercise participation is the fear of hypoglycemia (Brazeau et al., 2008). While it is recognized that a given person can benefit from keeping track of conditions that promote or seemingly protect them from exercise-associated hypoglycemia (Nagi et al., 2010), regular exercisers as a group have not been queried to gain a collective profile for this risk.

Glycemic control, which is a primary treatment goal for T1DM (American Diabetes Association, 2003), can be disrupted by physical activity (Riddell & Perkins, 2006). Muscle contraction and insulin action are capable of increasing the disposal of glucose in a potentially additive manner (Lai et al., 2010). Rates of glucose uptake during exercise are increased with intensity of physical activity due to muscle contraction mobilizing the glucose transporter (Romijn, et al., 1993; Romijn et al., 2000; Richter, et al., 2001). Normally, insulin decreases during exercise so that muscle contraction is the primary stimulus driving glucose uptake (Marliss &Vranic, 2002). Blood glucose concentrations are maintained constant by glucose production from the liver (Wasserman & Cherrington, 1991). Only during high intensity exercise does glucose production typically outpace demand from the active muscles (Coker & Kjaer, 2005; Marliss &Vranic, 2002). The situation is quite different for a person with T1DM.

There is no mechanism to decrease exogenous insulin levels in response to physical activity (Riddell & Perkins, 2006) placing individuals with T1DM at risk for hypoglycemia both during and after exercise (Tonoli et al., 2012). Moreover, the insufficient release of counter-regulatory stress hormones (often exacerbated by recent episodes of low blood glucose or preceding exercise) can delay symptom presentation surrounding hypoglycemia onset, dangerously promoting unawareness and increasing vulnerability to more severe hypoglycemic events (Mokan et al., 1994; de Gallen et al., 2006). While incompletely understood, nocturnal hypoglycemia is likely promoted by increased peripheral insulin sensitivity due to exercise, coupled with impaired glucose counter-regulatory system response to falling glucose levels (Riddell & Perkins, 2006; MacDonald, 1987; McMahon et al., 2007). Primary prevention of hypoglycemia in T1DM is thus ideal, and careful planning is required to decrease the potential for hypoglycemia that can occur, not only during or after exercise is performed, but also at night. While evidence supports a relatively high level of hypoglycemia unawareness in T1DM (Mokan et al., 1994), the extent of hypoglycemia unawareness in regular exercisers is unknown. Similarly, the risk profiles for both exercise-associated and nocturnal hypoglycemia in people with T1DM who exercise regularly have yet to be fully understood.

As exogenous insulin administration acutely challenges glycemic control during and after exercise, the distinction between multiple daily injections (MDI) via pen and continuous subcutaneous insulin infusion (CSII) via pump is potentially an important consideration. CSII therapy has become an increasingly popular alternative to MDI and is touted for generally allowing T1DM patients the most precise, near-normal physiological experience of blood glucose control (Lenhard & Reeves, 2001; Weissberg-Benchell et al., 2003). Yet, an overwhelming majority of past research endeavors comparing modes of insulin delivery were not executed in the context of exercise (e.g. DeVries et al., 2002; Home et al., 1982; Jakisch et al., 2008; Simon et al., 2008). Indeed, there is little to no evidence suggesting pump use confers protection from hypoglycemia in the case of regular physical activity. Although the general recommendation is for exercisers to reduce their dose before exercise (Mauvais-Jarvis et al., 2003; West et al., 2010), even with an appropriate dose reduction, hyperinsulinemia is possible due to enhanced muscle sensitivity and increased blood flow augmenting the mobilization of insulin from its injection site (Campbell et al., 2013; Marliss & Vranic, 2002; Riddell & Perkins, 2006). Given that intensive insulin therapy generally increases the likelihood of hypoglycemia during or after exercise (The DCCT Research Group, 1993) and at night (The DCCT Research Group, 1993; Yardley et al., 2012), CSII pump use might present an increased risk for regular exercisers.

Despite its challenges, exercise has been widely recommended as an important management strategy for T1DM (IDF, 2011). The present study is the first epidemiological observation of regular exercisers with T1DM; an attempt to describe the basic risk landscape for hypoglycemia and associated unawareness based on real-world experience from recreational exercisers and athletes with T1DM in the Netherlands. This emphasis on "real-world" self-report is crucial, as most T1DM acute exercise studies to date have investigated risk under very controlled research settings (e.g. Huttunen et al., 1989; Mauvais-Jarvis et al., 2003; Yardley et al., 2012). The Dutch population was chosen for study given the high prevalence and steady increase in T1DM incidence in the Netherlands in recent years (Ruwaard et al., 1994) and relative genetic homogeneity of the Dutch population (Abdellaoui et al., 2013). Outcomes of interest are our primary and secondary markers for poor blood glucose control, namely exercise-associated and nocturnal hypoglycemia, and symptom (un)awareness. In addition, we examined the extent to which mode of insulin delivery (pen/pump) is accompanied by an increased likelihood of hypoglycemia and/or unawareness, hypothesizing that CSII pump therapy might present an increased risk due to the potential for over-insulinization and thus disturbed glycemic control.

RESEARCH DESIGN

This study was designed to ascertain feedback from individuals with T1DM who engage in routine exercise activity either on a recreational or competitive basis. Data were acquired from an anonymous, nationally advertised, internet-based survey launched in the Netherlands. Interested participants were directed to the Bas Van de Goor Foundation website to complete the survey. The materials were approved by Yale School of Medicine Human Investigation Committee. No personal health information was linked to participants. Our structured questionnaire collected data from participants ranging from 18 to >70 years of age who were reportedly diagnosed with T1DM and engaged in some level of exercise and/or sport activity on a regular basis. Participants were questioned on relevant demographic and exercise characteristics including sex, age, number of years diagnosed with T1DM, number of years exercising with T1DM, exercise volume/training hours, type of exercise, and the time of day during which they primarily engage in exercise. Exercise volume/training hours referred to either “recreational” or “competitive” status. Recreational status was characterized by physical activity levels ranging anywhere from less than one hour per week up to 4 hours per week. Alternatively, competitive respondents indicated an exercise training volume of 4-20 hours per week. Type of exercise was divided into endurance (i.e. cycling, running, triathlon, large field team sports, etc.) and non-endurance (small field, interval and individual sports) categories. The non-endurance category also included general fitness activities such as golf and Zumba.

Concerning exercise time of day, participants could indicate any combination of the following options: morning, afternoon, evening, weekend. Participants were further asked to specify mode of insulin delivery (pen/pump) as well as their daily basal insulin dose.

With regard to experiencing exercise-associated hypoglycemia during or after exercise or sport activity, participants were asked to reply either 1) "no, never" 2) "sometimes" or 3) "regularly." Alternatively, experience of nocturnal hypoglycemia was probed through a general "yes/no" reply. Both forms of hypoglycemia were queried in general, not referenced to specific exercise sessions. The outcome of (un)awareness was two-fold, in that we assessed 1) participant reaction time and 2) blood glucose concentration surrounding the detection of initial symptoms of hypoglycemia. The first evaluated how soon/well a participant could feel the onset of hypoglycemia, and was grouped and assessed at the following reaction time intervals (ranging from "poor awareness" to "awareness"): 1) combined complete unawareness and 5-10 minute reaction time before symptom escalation (categorized as "poor awareness"), 2) 10-20 minute reaction time before symptom escalation, and 3) 20-30 minute reaction time before symptom escalation. The second marker evaluated the concentration of blood glucose at which a participant typically detected symptoms of hypoglycemia onset. Levels were similarly grouped and assessed at the following intervals (ranging from "poor awareness" to "awareness"): 1) combined complete unawareness and symptom detection at values ≤ 2.9 mmol/l ("poor awareness"), 2) detection at values ranging from 3.0 to 3.9 mmol/l, and 3) detection at values ≥ 4.0 mmol/l. For both markers, we grouped complete unawareness and poor awareness together for the sake of statistical balance, given that so few respondents reported a total lack of symptoms. The resulting category was termed "poor awareness" and would be predicted against increasing levels of awareness in our analysis.

Statistical Analysis

Using frequency distributions, we calculated the overall prevalence of hypoglycemia during/after exercise and at night. The same was done for each level of (un)awareness. Using mean calculations and the independent samples t-test procedure, we examined the potential for significant differences in daily basal insulin dose requirements across mode of insulin delivery, sex, age, duration of diagnosis, number of years exercising with T1DM, exercise volume/training hours, and exercise type. Chi-square analyses were conducted to investigate possible associations between each demographic subject characteristic and mode of insulin delivery, as well as to examine the hypothetical relationship between the use of pen/pump and any number of our 4 key dependent outcome variables. To further explore the potential impact that mode of insulin delivery, in conjunction with other demographic/exercise variables, may have on outcomes of hypoglycemia and symptom (un)awareness, we employed logistic regression modeling. A total of 4 models were analyzed through a combination of ordered and regular logistic regression procedures, depending on the nature of the outcome (ordinal or binary). Each model controlled for the following known and potential confounders: sex, age, number of years diagnosed with T1DM, number of years of exercise with T1DM, exercise volume/training hours, type of exercise, exercise time of day, daily basal insulin dose, and mode of insulin delivery. Effect modification was assessed uniformly across models through the testing of 24 potentially relevant interactions. Interaction terms were included in the final models based on clinical and statistical significance. Values are expressed as odds ratios (OR) accompanied by 95% confidence intervals, and statistical significance was concluded at $p < 0.05$. All calculations and analyses were conducted using SAS 9.3.

RESULTS

A total of 385 subjects responded to the survey. Participants were excluded from analysis if they 1) did not complete the survey in full (n = 78), and/or 2) demonstrated probable type 2 diabetes status through their answer choices (n = 5), leaving an analytic sample of 302 (120 male and 182 female) subjects. Key characteristics of T1DM survey participants are described in **Table 1**, and are stratified by mode of insulin delivery. The sample was relatively balanced, but favored respondents who indicated they had engaged in exercise or sport activity for less than 10 years since their diagnosis of T1DM (63.9%). Participants self-identified as "recreational" exercisers made up the majority of the sample, while over a third of our respondents characterized themselves as "competitive." Endurance and non-endurance exercisers each comprised approximately half the sample. With respect to mode of insulin delivery, 173 participants (57.3%) reported pen use, while 129 (42.7%) reported pump use. As indicated in **Table 1**, a significant difference between pen and pump use was found to exist among a number of our main demographic groups, including sex ($P < 0.001$) and age ($P < 0.003$). The same applied to daily basal insulin dose requirements, for which pump users reported an average insulin dose (27.51 ± 17.38 mmol/l) significantly higher than that of pen users (20.40 ± 12.33 mmol/l) ($P < 0.001$).

Risk of Hypoglycemia (During/After Exercise and at Night)

A high percentage of our survey population of regular exercisers indicated experience with both exercise-associated hypoglycemia and nocturnal hypoglycemia. Specifically, respondents reported experience of hypoglycemia either "sometimes" (67.9%) or "regularly" (18.5%) during or after exercise or sport activity; 74.2% indicated experience with nocturnal hypoglycemia

(**Table 2**). Notably, chi-square test of association revealed potential for a significant relationship between mode of insulin delivery and experience of hypoglycemia during/after exercise and at night ($P < 0.001$ and $P = 0.006$, respectively).

Figure 1 illustrates the results for the logistic regression strictly examining the relationship between the primary dependent outcomes: during/after exercise and nocturnal hypoglycemia. Those who indicated having experienced exercise-associated hypoglycemia "regularly" were over 14 times more likely to experience nocturnal hypoglycemia (OR = 14.44; 95% CI: 5.01, 41.62; $P < 0.001$) compared to those individuals who reported "never" experiencing exercise-associated symptoms. In contrast, the latter group demonstrated increased protection from nocturnal hypoglycemia (OR = 0.07; 95% CI: 0.02, 0.20; $P < 0.001$). Each trajectory was particularly significant among non-endurance exercisers, where experience of exercise-associated symptoms "regularly" was associated with report of nocturnal hypoglycemia (OR = 41.43; 95% CI: 7.95, 215.87; $P < 0.001$).

Table 3 presents separate results for the ordered and regular logistic regression modeling of exercise-associated hypoglycemia ("regularly," "sometimes," or "never") and nocturnal hypoglycemia ("yes"/ "no"), respectively. Sex was a significant predictor of hypoglycemia during or after exercise, with females 2.4 times more likely to experience hypoglycemia "regularly" vs. less often, given all variables held constant (OR = 2.36; 95% CI: 1.20, 4.65; $P = 0.013$). This finding was despite the lack of significant difference in daily insulin requirement (female: 24.34 ± 16.25; male: 22.95 ± 13.87; $P = 0.467$). No significant difference existed between males and females in terms of predicting nocturnal hypoglycemia. Additionally, compared to youngest participants (age 18-30), participants 51 years or older seemed to maintain a level of protection from experiencing hypoglycemia "regularly" vs. less often during or after exercise (OR = 0.30; 95% CI: 0.12, 0.73; P = 0.008), but not from experiencing nocturnal episodes. The average basal dose for those in the 18-30 age range (27.54 ± 17.88 mmol/l) was significantly higher than average dose requirements for the 31-50 (21.72 ± 13.13 mmol/l) and 51+ (20.24 ± 12.22 mmol/l) age ranges (P = 0.004). Diabetes duration proved to be a significant predictor of nocturnal hypoglycemia, in that those who had been diagnosed for more than 10 years were 2.5 times more likely to experience hypoglycemia at night given all variables held constant (OR = 2.51; 95% CI: 1.04, 6.08; P = 0.042). The average daily basal insulin dose for those with a longer duration of diabetes (more than 10 years) (25.85 ± 14.77 mmol/l) was significantly higher than that of individuals who reported a shorter disease duration (less than 10 years) (21.18 ± 15.70 mmol/l) (P = 0.012). Alternatively, the number of years spent engaging in exercise with T1DM was only weakly associated with experience of hypoglycemia "regularly" vs. less often during or after exercise (P = 0.049), and not associated with the risk of nocturnal hypoglycemia. The average daily basal insulin dose of those exercising for more than 10 years since diagnosis (25.31 ± 13.00 mmol/l) was not significantly different from that of those exercising for less than 10 years since diagnosis (22.87 ± 16.53) (P = 0.180). Daily basal insulin dose itself was also a significant predictor of nocturnal hypoglycemic events. That is, for every 5-unit increase in daily basal insulin dose, individuals became 1.2 times more likely to report experience of hypoglycemia at night given all variables held constant (OR = 1.22; 95% CI: 1.06, 1.39; P = 0.004). In comparison, daily basal insulin dose was only marginally associated with experience of hypoglycemia "regularly" vs. less often during or after exercise (P = 0.059).

In addition to main effects shown in **Table 3**, an interaction between type of exercise (endurance/non-endurance) and mode of insulin delivery (pen/pump) was observed in both contexts of exercise-associated (P = 0.002) and nocturnal hypoglycemia (P = 0.042). This significant interaction is shown in **Figure 2.** Compared to the non-endurance exercisers who used pen, those who used a pump demonstrated the largest increased risk for exercise-associated hypoglycemia (OR = 4.02; 95% CI: 1.82, 8.87) and nocturnal hypoglycemia (OR = 2.31; 95% CI: 0.93, 5.73) alike. In contrast, among endurance athletes, pump users were seemingly protected from exercise-associated hypoglycemia (OR = 0.68; 95% CI: 0.28, 1.62) as well as from nocturnal hypoglycemia (OR = 0.59; 95% CI: 0.22, 1.61). In general, report of experiencing exercise-associated hypoglycemia "regularly" was more common in non-endurance exercisers (73.2%), suggesting increased overall risk in this group (P = 0.006). In addition, respondents indicating primary involvement in non-endurance training reported an average daily basal insulin dose significantly higher than that of endurance-trained exercisers (25.62 ± 16.43 mmol/l and 21.54 ± 13.61 mmol/l, respectively) (P = 0.026). Particularly among endurance exercisers, pump users reported an average basal dose (25.33 ± 16.16 mmol/l) significantly higher than that of pen users (18.32 ± 10.04 mmol/l) (P = 0.006). The same pattern was identified among non-endurance pump (29.17 ± 18.19 mmol/l) and pen users (22.21 ± 13.83 mmol/l) (P = 0.010).

Risk of Unawareness and Poor Awareness of Hypoglycemia

We examined (un)awareness by two different indicators: time and blood glucose concentration. Less than 4% of respondents (on average) reported complete hypoglycemic unawareness (specifically, 3.3% based on reaction time, and 1.3% based on blood glucose concentration surrounding hypoglycemia symptom onset). In terms of reaction time, 57.6% of respondents claimed to detect symptoms between just 5 and 10 minutes before symptom escalation, demonstrating general poor awareness based on time. Overall, those reportedly unaware or who indicated awareness of hypoglycemia onset just 5-10 minutes before symptom escalation were

3.6 times more likely to experience hypoglycemia “regularly” vs. less often (OR = 3.60; 95% CI: 1.53, 8.50; P = 0.004). In comparison, individual reports based on blood glucose concentration revealed that the majority of respondents (78.1%) indicated the ability to sense hypoglycemia symptoms at blood glucose concentrations greater than or equal to 3.0 mmol/l (59.6% identified concentration levels in the 3.0-3.9 mmol/l range, and 18.5% identified increasing concentration levels above 4.0 mmol/l) (**Table 2**).

Table 4 presents the ordered logistic regression results reflecting the influence of subject characteristics on poor awareness in each context of reaction time and blood glucose concentration. With respect to reaction time, middle-aged respondents (age 31-50), compared to youngest survey respondents (age 18-30), were 1.8 times more likely to report poor awareness (either complete unawareness or 5-10 minute reaction time) vs. a more reasonable reaction time surrounding symptom escalation given all variables held constant (OR = 1.83; 95% CI: 1.03, 3.28; P = 0.041). Middle-age was similarly associated with poor awareness in terms of blood glucose concentration at the time of symptom detection. Specifically, compared to youngest individuals (age 18-30), middle aged respondents (age 31-50) were 2 times more likely to report poor awareness (either complete unawareness or symptom detection at blood glucose concentrations ≤ 2.9 mmol/l) vs. detection of symptoms at higher blood glucose concentrations given all variables held constant (OR = 2.05; 95% CI: 1.14, 3.67; P = 0.016).

In addition to main effects displayed in **Table 4**, an interaction between daily basal insulin dose and mode of insulin delivery was shown to significantly influence poor awareness in terms of blood glucose concentration at the time of symptom detection (P = 0.021). Specifically, with every 5-unit increase in basal insulin dose, pump users became 1.2 times more likely to report detection of hypoglycemia onset at highest blood glucose concentrations (≥ 4.0 mmol/l) vs. lower concentrations given all variables held constant (OR = 1.18; 95% CI: 1.06, 1.32). In contrast, for every 5-unit increase in basal insulin dose, pen users reported little change in hypoglycemic awareness (OR = 1.05; 95% CI: 0.91, 1.22).

DISCUSSION

Currently, there is a lack of information surrounding hypoglycemia and hypoglycemia unawareness in people who exercise regularly with T1DM. In the present study we surveyed a physically active T1DM population from the Netherlands among which both the risks for exercise-associated and nocturnal hypoglycemia were found to be prevalent. In contrast, reported hypoglycemia unawareness was essentially absent (< 4%). Overall, exercise-associated hypoglycemia was a strong predictor for nocturnal hypoglycemia, with non-endurance exercisers demonstrating the most consistent dual risk. Distinct demographic features such as sex, age, and the number of years exercising with T1DM predicted exercise-associated hypoglycemic outcomes, while duration of diagnosis was shown to influence nocturnal hypoglycemia. Importantly, insulin requirements, marked by daily basal insulin dose, were shown to either marginally or strongly influence outcomes of exercise-associated and nocturnal hypoglycemia, respectively. In addition, both forms of hypoglycemia were similarly marked by a consistent and significant interaction between mode of insulin delivery and type of exercise. This interaction indicted an elevated risk for both exercise-associated and nocturnal hypoglycemia among non-endurance exercisers engaging in CSII vs. MDI therapy; however, no such elevated risks were seen among pump-using endurance athletes.

Exercise is important for good health in people with T1DM (Chimen et al., 2012). However, fear of hypoglycemia is a primary barrier to physical activity (Brazeau et al., 2008) and is likely the reason for which a large percentage of the T1DM population remains widely inactive (Thomas et al., 2004). Here we provide preliminary findings surrounding the demographic and exercise characteristics that impact the risk profile for hypoglycemia in people who exercise regularly. We also explore the extent to which mode of insulin delivery may contribute to T1DM hypoglycemic complications in this physically active population. As emphasized, survey respondents overall were far more likely to report nocturnal hypoglycemia if they were prone to regular hypoglycemic episodes surrounding the time of exercise. The reverse was true in the case of those who reported never experiencing exercise-associated hypoglycemia. Upon examining this relationship more closely, we found that non-endurance exercisers may largely be driving this overall effect. Indeed, stratifying by exercise type revealed that the non-endurance exercise group demonstrated a consistent and significant trajectory from report of regular exercise-associated hypoglycemia to nocturnal hypoglycemia; however, no such significant pattern existed among endurance exercise respondents. It is important to note that, in general, non-endurance exercisers reported an average daily baseline insulin dose significantly higher than that of endurance exercisers, which likely indicates reduced overall sensitivity. In contrast, and as expected (Hall, 2013; Kirwan et al., 1993; Hersey et al., 1994), endurance exercisers reported a significantly lower average basal dose of insulin, indicative of higher insulin sensitivity and likely better glucose control overall. Research is needed to identify whether less insulin sensitivity associated with non-endurance exercise is related to more labile glucose control. In general, non-endurance exercise training is far from well represented in the acute exercise literature (Tonoli et al., 2012).

This overarching relationship between exercise-associated and nocturnal hypoglycemia set the stage for an in-depth investigation of the individual risk factors for each. Our analysis revealed several main effects. Females, for instance, demonstrated a significantly higher risk for exercise-associated hypoglycemia, but not necessarily for nocturnal hypoglycemia. Average basal insulin dosing patterns were no different across males and females. Moreover, there was a lack of model interaction between mode of insulin delivery and sex. Thus, it could be that the difference between the risk for men and women lies within insulin adjustment patterns before, during, and after physical activity or within inherent differences in male and female physiology/metabolism. To date, little research has focused on women, but past work has highlighted female susceptibility and struggle with poor glycemic control (Wild, 2013). Fortunately, females (by and large pump users) were well represented in our sample, but further study is needed in this area to explain the apparent increased vulnerability of women. Also exclusive to the outcome of exercise-associated hypoglycemia, older respondents (51+) indicated decreased risk of regular hypoglycemic events during or after physical activity. In looking into this population we found that their average daily basal insulin dose requirement was unusually and significantly lower than that of younger age groups (18-30), and is thus quite possibly driving this protection from risk. We have seen from the literature that older age is generally associated with a decrease in insulin sensitivity and, consequently, an increase in insulin requirements (Kahn et al., 1990). However, this increased resistance is largely driven by an age-associated decline in physical activity (Kahn et al., 1990). Here, we are dealing with a motivated, physically active older population that appears to be more insulin sensitive as a group. This finding parallels that of previous work which demonstrated the potential for exercise training to improve insulin sensitivity in older adults (Kahn et al., 1990). It is also worth noting that roughly 60% of older age respondents were split almost equally between endurance activities such as cycling and running and low-exertion activities such as walking and golf. It is possible that the latter activities conferred some protection from risk given the flexibility allowing for easy carbohydrate ingestion. In addition, although a marginally significant indicator, increased number of years of regular physical activity with T1DM may prove to enhance the risk for exercise-associated hypoglycemia. Respondents who had engaged in exercise for over 10 years since their diagnosis demonstrated a higher propensity for regular episodes of hypoglycemia during or after exercise compared to those exercising for less than 10 years since diagnosis. We are unaware of previous research that has involved years of training with T1DM. However, the lack of difference between average insulin requirements across years of exercise with T1DM, suggests other factors are important. In contrast, nocturnal hypoglycemic events were strongly influenced simply by the number of years of diagnosis, where respondents diagnosed for more than 10 years were reportedly at increased risk. This same group of individuals reported a significantly higher average basal insulin dose compared to that of individuals characterized by shorter disease duration. We know from the literature that increased duration of diabetes, and thus years of insulin treatment, leads to more frequent and severe hypoglycemic events (McCrimmon & Sherwin, 2010; Leese et al., 2003; The DCCT, 1991) and specifically to nocturnal hypoglycemia (Shalwitz et al., 1990). While daily basal insulin dose may have been weakly correlated with exercise-associated hypoglycemia, it proved to be a highly significant influence in the context of nocturnal hypoglycemia, consistent with what we would expect as defined by the acute literature (Shalwitz et al., 1990; Amin et al., 2003). Indeed, respondents who indicated higher basal insulin dosing patterns were significantly more at risk for nocturnal hypoglycemia, reflective of sustained insulin sensitivity that may persist hours after exercise (MacDonald, 1987; Campbell et al, 2013).

Finally, both outcomes of exercise-associated and nocturnal hypoglycemia were marked by an interaction between mode of insulin delivery and type of exercise, suggesting that the distinction between endurance and non-endurance exercise training plays a substantial, modifying role in the relationship between mode of insulin delivery and hypoglycemia. This is not surprising given that exercise type is known to play a critical role in blood glucose fluctuation (Goodyear & Kahn, 1998; Riddell & Perkins, 2006; Vanelli et al., 2006). Specifically, endurance exercise training has been associated with a decrease in blood glucose concentration during exercise, while non-endurance or anaerobic activity leads to augmentation of blood glucose concentration (Riddell & Perkins, 2006). Yet, to our knowledge, this is the first major data with respect to vulnerability to hypoglycemia comparing non-endurance and endurance activity in the context of regular exercise training. In terms of endurance exercise, the current interaction places pump users at decreased risk for regular episodes of exercise-associated hypoglycemia and nocturnal hypoglycemia. The finding that pump use mitigates the risk of regular hypoglycemia in endurance exercisers appears consistent with past studies suggesting that CSII may promote tighter blood glucose control (McMahon et al., 2004, Pickup et al., 2002, Hunger-Dathe et al., 2003, Schreiver et al., 2013; Misso et al., 2010), and subsequently promote a reduction in severe hypoglycemic events (Misso et al., 2010; Bode et al., 1996). However, the picture was quite different from the standpoint of *non-endurance* exercise activity and, as such, may challenge the common misconception surrounding the insulin pump's ability to generally eliminate severe hypoglycemic events (Lenhard & Reeves, 2001). While past studies have highlighted that pump use, in general, may reduce the occurrence of severe hypoglycemic events by as much as 4-fold compared to MDI treatment (Lenhard & Reeves, 2001; Bode et al., 1996; Haardt, 1997), our findings demonstrate quite the contrary, with pump-using non-endurance trained respondents reporting 4 times *increased* risk for regular experience of exercise-associated hypoglycemia. The substantial increase in risk for both exercise-associated and nocturnal hypoglycemia among pump users in the context of non-endurance exercise activity, suggests that the idea of potential over-insulinization may prevail (Toni et al., 2006; Marliss & Vranic, 2002). However, this hyperinsulinemia may not have to do with pump use *per se*. Despite the survey nature of our study, insulin dosing patterns were in the expected direction, with non-endurance exercisers reporting a significantly higher basal dose requirement. While CSII therapy has generated reports of reduced insulin requirements (Weissberg-Benchell et al., 2003, Kuroda et al., 2011), pump-using survey respondents overall reported *higher* baseline levels. Thus, lower underlying insulin sensitivity offers a likely explanation for why non-endurance pump users were at an amplified risk for regular episodes of hypoglycemia during or after exercise and at night. Interestingly, stratification across exercise type revealed that, among endurance and non-endurance exercisers alike, pump users exhibited, on average, a higher basal insulin dose. Therefore, a difference in insulin requirement does not afford an explanation for why pump use seemingly protected endurance exercisers from risk; although the absolute magnitude of daily insulin was shifted lower overall in the endurance athletes of both modalities. Still, further work is needed to identify whether distinct insulin adjustments or dietary practices may be contributing to this effect among endurance-trained athletes.

Given the observed overarching relationship between basal insulin requirement and risk of hypoglycemia, our findings bring to light an important consideration regarding underlying insulin sensitivity to glucose control that is widely uncaptured by acute exercise research. While it is well documented that physical activity acutely lowers blood glucose concentrations and increases insulin sensitivity in T1DM individuals (Steppel & Horton, 2004; The DirectNet Study

Group, 2006; Landt et al., 1985), very few studies have even come close to being able to demonstrate long-term effects in the context of a lifestyle of routine exercise (Stratton et al., 1987; Lehmann et al., 1997; Wallberg-Henriksson et al., 1982; Heath et al., 1983). Importantly, reduced baseline insulin sensitivity, as gauged by higher average basal insulin dose requirements, repeatedly surfaced where exercisers reported increased risk for regular episodes of exercise-associated or nocturnal hypoglycemia. Alternatively, we found that respondents most sensitive at baseline were overall better protected from risk. These findings are in accordance with Lehmann et al. (1997) whose 3-month exercise training intervention program led to increased insulin sensitivity among participants and a decrease in the overall frequency of severe hypoglycemic episodes. The present outcomes suggest that decreased insulin sensitivity overall potentially leads to impaired glucose metabolism due to exercise-driven swings in glucose control. It is likely that when these individuals (e.g. non-endurance pump-users) become *acutely* insulin sensitive as a consequence of exercise, a less stable regulatory response leads to hypoglycemia. The next question then becomes why are the insulin requirements for these individuals higher in the first place? These levels are essentially necessary for them to best regulate blood glucose in the context of their daily lives, and thus may even reflect exercise requirements external to this study. Ultimately, these results offer a glimpse into what long-term glycemic control (or lack thereof) looks like for these individuals in terms of underlying insulin sensitivity based on exercise routine. While non-endurance exercise warrants further study, endurance training, as previously noted, has been shown to decrease insulin resistance (Kirwan et al., 1993; Hersey et al., 1994), and thus total requirements (Hall, 2013). It therefore may be beneficial for all exercisers with T1DM to supplement their training regimens with endurance exercise to confer an overall better level of insulin sensitivity.

Finally, the present study shows a dramatic shift from the traditional literature assessing hypoglycemia unawareness in T1DM patients. Examining unawareness in the context of regular exercise revealed a much lower overall percentage of unawareness (< 4%) compared to what has been reported in the past (26%) (Mokan et al., 1994). As underscored by our results, T1DM individuals who engage in regular exercise are inherently characterized by better symptom awareness. It is likely that the fear of hypoglycemia may be selecting out of this exercise population anyone who lacks symptoms entirely. However, better symptom awareness leaves the potential that improved awareness is part of an adaptation of regular exercise. While only a minute fraction of our population indicated a total lack of awareness, just over 20% of respondents still reported symptom detection at blood glucose concentration levels ≤ 2.9 mmol/l, rendering this group metabolically hypoglycemic, and thus poorly aware. Therefore, if we were to combine poorly aware respondents with those few lacking symptoms entirely, we approach a prevalence similar to that reported by Mokan et al. (1994). In addition, the majority of respondents indicated detection of hypoglycemia onset within a very small reaction time window (5-10 minutes) before symptom escalation, and thus poor awareness in general. The present study revealed that those who either failed to sense hypoglycemia, or reported a reaction time of just 5-10 minutes, were over 3 times more likely to experience hypoglycemia "regularly" during or after exercise. This finding is consistent with the idea that poor awareness, or total lack thereof, places one at increased risk for regular or severe hypoglycemia (Mokan et al., 1994; Gold et al., 1994). While surprisingly not visible, we would have expected a similar finding with regard to blood glucose, in that those who reported symptom detection at lowest concentrations would have demonstrated increased risk for hypoglycemia. Yet previous research has shown that, among T1DM patients with a general lack of symptom awareness, self-report of hypoglycemic events was significantly at odds with what was otherwise indicated by blood glucose markers (Kubiak et al., 2004; Donnelly et al., 2005). Thus, it stands to reason that while an individual may be hypoglycemic according to blood glucose concentration, they may not always recognize and report it as such. In general, middle-aged respondents (age 31-50) were found to be significantly more at risk for poor awareness in each context of reaction time and blood glucose concentration. It was thus surprising that middle age did not show up as a significant main effect predicting hypoglycemia during or after exercise. Additionally, a significant interaction between daily basal insulin dose and mode of insulin delivery appeared in the context of blood glucose concentration alone. It was promising to see consistency in survey responses in that lower insulin sensitivity, at least in pump users (reflecting general insulin resistance with respect to daily insulin requirements), translated to *increased* awareness. This is what we would expect based on Mokan et al. (1994), who was able to draw an association between increased insulin sensitivity and lack of awareness. Finally, the literature suggests that diabetes duration is also a significant predictor of unawareness (Mokan et al., 1994). While complete unawareness could not be tested due to such a small number of subjects who reported a lack of symptoms, we still may have expected a main effect here for our outcome of *poor* awareness; however, duration of diagnosis did not show up in either of our models predicting this result.

There are several limitations inherent in survey studies. Self-report, for example, may have led to the over- or under-estimation of hypoglycemic events and accompanying markers (reaction time and blood glucose concentration) of poor awareness surrounding symptom severity. Additionally, the fact that our participants were volunteers suggests that we may have been dealing with a motivated subset of T1DM exercisers, one perhaps not fully representative of the entire T1DM exercise population. Nonetheless, given the energy and dedication fundamentally associated with maintaining an exercise routine with T1DM in general, it is likely the external population is not entirely dissimilar. While this survey will generate follow-up studies, probing more deeply into diet and insulin adjustment patterns surrounding exercise, the data presented here were not assessed in the context of having controlled for either of these. Food intake and insulin adjustment are known to have substantial influence on blood glucose control and patterns of hypoglycemia (Toni et al., 2006). In addition, our survey did not gather information regarding overall glucose control (e.g., HbA1c levels) or explore the reasoning behind why individuals may have taken up CSII therapy. In some cases it has been shown that individuals on the pump may have transferred from MDI due to unstable blood glucose fluctuation and recurrent episodes of hypoglycemia (Schreiver et al., 2013; Crenier et al., 2013). Frequent hypoglycemia has, in fact, become a common indication for switching to pump use (Lenhard & Reeves, 2001).

The very nature of our survey design, however, is also what conferred our study its greatest strength: "real-world" feedback. As previously mentioned, this goes far beyond self-report, in the sense that we were able to gather highly uncontrolled exercise data that most closely exemplifies reality for T1DM individuals who regularly engage in physical activity. Here, there were no calibrated exercise machines, no stopwatches, and no laboratory measurements; just authentic testimony based on training habits that may help to inform others with similar profiles. Finally, our sample population was an asset, in and of itself, given that the Netherlands offers a relatively homogenous study base (diminishing the potential for confounding by genetic factors) that has generally exhibited a high prevalence and increasing incidence of T1DM (Ruwaard et al., 1994). To boost external validity, future studies are needed to explore the potential for differences across race and ethnicity.

SUMMARY AND CONCLUSIONS

In the present study we were able to describe the basic hypoglycemia risk profile of the T1DM individual who engages in regular exercise, while observing a number of associations consistent with what we've seen in smaller, more controlled studies both within and outside of the context of physical activity. There were, however, various nuances in our data that will specifically help to inform this unique population of T1DM athletes and help others to join their ranks. Our survey population indicated a wide prevalence of exercise-associated and nocturnal hypoglycemia, yet a general lack of symptom unawareness on the whole. The latter observation demonstrates the likely incompatibility of routine exercise and complete unawareness, but also the potential for improved awareness due to regular exercise. Importantly, we found that exercise-associated hypoglycemia was a strong predictor for nocturnal hypoglycemia, with sex, age, and number of years exercising with T1DM predicting the former, and duration of diagnosis influencing the latter. An overarching theme of higher insulin requirement among those at risk was substantiated by the fact that increased daily basal insulin dose itself was influential in both outcomes of exercise-associated and nocturnal hypoglycemia. Finally, mode of insulin delivery proved to be a significant influence, interacting with exercise type and daily basal insulin dose in the contexts of hypoglycemia and (un)awareness (blood glucose concentration), respectively. Elevated risk for both exercise-associated and nocturnal hypoglycemia among non-endurance exercisers engaging in CSII vs. MDI therapy may have been dictated by over-insulinization in this group due to a lower underlying sensitivity to insulin (and thus higher basal requirements).

It is recommended that future studies explore the reasoning behind this increased relative baseline resistance among pump users and non-endurance trained athletes alike.

Until now, we had yet to solicit feedback from T1DM exercisers that would allow us to establish the basic profile of risk or protection from hypoglycemia and associated (un)awareness in the context of routine physical activity. Survey responses have enabled us to describe this profile, and to importantly highlight the potential of underlying insulin sensitivity, acquired through consistent exercise training (especially endurance), to confer overall protection from regular hypoglycemic events. Our work is a precursor of similar future studies that might help to expand our understanding of T1DM complications associated with a physically active lifestyle. As such, regular exercisers will become better acquainted with how best to gauge and modify their risks. Similarly, individuals deterred by the fear of hypoglycemia may become more comfortable approaching the idea of routine exercise - the cardiorespiratory benefits of which are innumerable for T1DM.

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Table 1. Description of the Sample

Main Demographics	Total (N = 302)	Pen (N = 173)	Pump (N = 129)	P-value†
Sex				$p < 0.001$
Male	120 (39.7)	85 (70.8)	35 (29.2)	
Female	182 (60.3)	88 (48.4)	94 (51.7)	
Age (years)				$p = 0.003$
18-30	119 (39.4)	61 (51.3)	58 (48.7)	
31-50	129 (42.7)	70 (54.3)	59 (45.7)	
51+	54 (17.9)	42 (77.8)	12 (22.2)	
No. Years Diagnosed				$p < 0.001$
Less than 10 years	140 (46.4)	98 (70.0)	42 (30.0)	
More than 10 years	162 (53.6)	75 (46.3)	87 (53.7)	
No. Years Exercising with T1DM				$p = 0.022$
Less than 10 years	193 (63.9)	120 (62.2)	73 (37.8)	
More than 10 years	109 (36.1)	53 (48.6)	56 (51.4)	
Exercise Volume/Training Hours				$p = 0.511$
Recreational	189 (62.6)	111 (58.7)	78 (41.3)	
Competitive	113 (37.4)	62 (54.9)	51 (45.1)	
Type of Exercise				$p = 0.772$
Non-endurance	168 (55.6)	95 (56.6)	73 (43.5)	
Endurance	134 (44.4)	78 (58.2)	56 (41.8)	
Time of Exercise				$p = 0.041$
Combo M/A/E/W*	197 (66.6)	112 (56.9)	85 (43.2)	
Morning only	23 (7.8)	18 (78.3)	5 (21.7)	
Afternoon only	20 (6.8)	7 (35.0)	13 (65.0)	
Evening only	56 (18.9)	31 (55.4)	25 (44.6)	
Daily Basal Insulin Dose (mmol/l/d) ††	23.8 ± 15.3	20.4 ± 12.3	27.5 ± 17.4	$p < 0.001$

Data are in *n* (%) unless otherwise indicated. †P values were obtained using a χ^2 test (categorical) or an independent samples t-test (continuous), comparing the demographics of diabetic participants with regards to mode of insulin delivery. †† Data are expressed as mean ± SD. *W= "weekend". Six respondents who indicated only a weekend exercise routine were excluded from the analysis, as a "weekend-only" survey selection fails to provide sufficient information around exercise "time of day". However, those that indicated "weekend" in some combination of either morning/afternoon/evening exercise remained in the analysis ("Combo M/A/E/W").

Table 2. Primary Dependent Outcomes

Hypoglycemia	**Total (N = 302)**	**Pen (N = 173)**	**Pump (N = 129)**	**P-value†**
During/After Exercise				$p < 0.001$
Never	41 (13.6)	33 (80.5)	8 (19.5)	
Sometimes	205 (67.9)	118 (57.6)	87 (42.4)	
Regularly	56 (18.5)	22 (39.3)	34 (60.7)	
Nocturnal Hypoglycemia				$p = 0.006$
No	78 (25.8)	55 (70.5)	23 (29.5)	
Yes	224 (74.2)	118 (52.7)	106 (47.3)	
Level of Awareness				
Reaction Time				$p = 0.173$
Poor Awareness*	174 (57.6)	94 (54.0)	80 (46.0)	
10-20 minutes	102 (33.8)	60 (58.8)	42 (41.2)	
20-30 minutes	26 (8.6)	19 (73.1)	7 (26.9)	
Blood Glucose Concentration				$p = 0.614$
Poor Awareness* *	66 (21.9)	41 (62.1)	25 (37.9)	
3.0-3.9 (mmol/l)	180 (59.6)	102 (56.7)	78 (43.3)	
≥ 4.0 (mmol/)	56 (18.5)	30 (53.6)	26 (46.4)	

* "Poor awareness" includes those reportedly unaware (total lack of symptoms) (3.3%) as well as those who indicated a short reaction time of just 5-10 minutes before symptom escalation (57.6%). Increasing reaction time is associated with improved awareness.

** "Poor awareness" in the case of blood glucose concentration includes those reportedly unaware (total lack of symptoms) (1.3%) and those who indicated symptom detection at blood glucose concentrations ≤ 2.9 mmol/l (20.5%). Symptom detection at increasing blood glucose concentration is associated with improved awareness.

†P values were obtained using a χ^2 test (categorical), comparing each of our 4 main outcomes with respect to mode of insulin delivery.

Table 3. Risk of Hypoglycemia During/After Exercise and at Night

Hypoglycemic Event	During or After Exercise †		Nocturnal ††	
Covariate	**OR (adj) (95% CI)**	**P**	**OR (adj) (95% CI)**	**P**
Sex				
Male (reference)	1.00		1.00	
Female	2.36 (1.20, 4.65)	**0.013**	0.95 (0.44, 2.06)	0.899
Age (years)				
18-30 (reference)	1.00		1.00	
31-50	0.74 (0.40, 1.38)	0.345	1.53 (0.74, 3.14)	0.251
51+	0.30 (0.12, 0.73)	**0.008**	0.61 (0.23, 1.66)	0.336
No. Years Diagnosed				
Less than 10 years (reference)	1.00		1.00	
More than 10 years	1.05 (0.50, 2.22)	0.891	2.51 (1.04, 6.08)	**0.042**
No. Years Exercising with T1DM				
Less than 10 years (reference)	1.00		1.00	
More than 10 years	2.13 (1.00, 4.52)	**0.049**	1.67 (0.63, 4.46)	0.303
Exercise Volume/Training Hours				
Recreational (reference)	1.00		1.00	
Competitive	1.01 (0.55, 1.85)	0.968	1.23 (0.60, 2.52)	0.566
Type of Exercise				
Time of Exercise				
Combo M/A/E/W (reference)	1.00		1.00	
Morning only	1.63 (0.54, 4.95)	0.388	0.78 (0.24, 2.55)	0.686
Afternoon only	1.58 (0.55, 4.55)	0.399	1.29 (0.38, 4.35)	0.681
Evening only	1.45 (0.71, 2.97)	0.311	1.73 (0.70, 4.28)	0.233
Daily Basal Insulin Dose (/5 mmol/l/d)	1.10 (1.00, 1.20)	**0.059**	1.22 (1.06, 1.39)	**0.004**
Mode of Insulin Delivery (pen/pump)				
***Mode of Insulin Delivery*Type of Exercise**		**0.002**		**0.042**

Data are adjusted odds ratios (95% CIs). †Model data were obtained through ordered logistic regression given the ordinal outcome (“never,” “sometimes,” “regularly”), and are predicting the risk of experiencing exercise-associated hypoglycemia “regularly” vs. less often. ††Model data were obtained through regular logistic regression given the binary outcome (“yes”/”no”), and are predicting the risk of nocturnal hypoglycemia (“yes”). For each model, all variables were mutually adjusted for the other variables in the table. *Covariates *Mode of insulin delivery* and *type of exercise* were involved in a significant interaction predicting risk of hypoglycemia during/after exercise and at night (See **Figure 2**).

Table 4. Risk of Poor Awareness of Severe Hypoglycemia

Sensing Onset of Hypoglycemia	**Time†**		**Blood Glucose Concentration††**	
Covariate	**OR (adj) (95% CI)**	**P**	**OR (adj) (95% CI)**	**P**
Sex				
Male (reference)	1.00		1.00	
Female	1.06 (0.57, 1.96)	0.853	1.17 (0.64, 2.14)	0.609
Age (years)				
18-30 (reference)	1.00		1.00	
31-50	1.83 (1.03, 3.28)	**0.041**	2.05 (1.14, 3.67)	**0.016**
51+	1.10 (0.49, 2.46)	0.813	1.34 (0.59, 3.06)	0.487
No. Years Diagnosed				
Less than 10 years (reference)	1.00		1.00	
More than 10 years	0.72 (0.36, 1.46)	0.366	1.88 (0.93, 3.79)	0.080
No. Years Exercising with T1DM				
Less than 10 years (reference)	1.00		1.00	
More than 10 years	0.97 (0.48, 1.93)	0.919	0.95 (0.47, 1.88)	0.871
Exercise Volume/Training Hours				
Recreational (reference)	1.00		1.00	
Competitive	1.14, 0.65, 2.00)	0.660	1.09 (0.63, 1.91)	0.754
Type of Exercise				
Non-endurance (reference)	1.00		1.00	
Endurance	0.99 (0.57, 1.72)	0.977	1.44 (0.84, 2.49)	0.188
Time of Exercise				
Combo M/A/E/W (reference)	1.00		1.00	
Morning only	1.51 (0.52, 4.35)	0.446	1.43 (0.51, 4.07)	0.499
Afternoon only	2.66 (0.80, 8.86)	0.111	1.92 (0.73, 5.09)	0.189
Evening only	0.53 (0.28, 1.01)	**0.053**	0.74 (0.38, 1.44)	0.380
Daily Basal Insulin Dose (/5 mmol/l/d)	0.99 (0.91, 1.08)	0.894		
Mode of Insulin Delivery				
Pen (reference)	1.00			
Pump	1.57 (0.90, 2.72)	0.111		
***Basal Dose*Mode of Insulin Delivery**	N/A			**0.021**

Data are adjusted odds ratios (95% CIs). †Model data were obtained through ordered logistic regression given the ordinal outcome of increasing reaction times, and are predicting the risk of "poor awareness" vs. levels of increasing awareness. ††Model data were obtained through ordered logistic regression given the ordinal outcome of increasing blood glucose concentrations and are similarly predicting the risk of "poor awareness" vs. levels of increasing awareness. For each model, all variables were mutually adjusted for the other variables in the table. *Covariates *mode of insulin delivery* and *daily basal insulin dose* were involved in a significant interaction predicting risk of poor awareness in the context of blood glucose concentration.

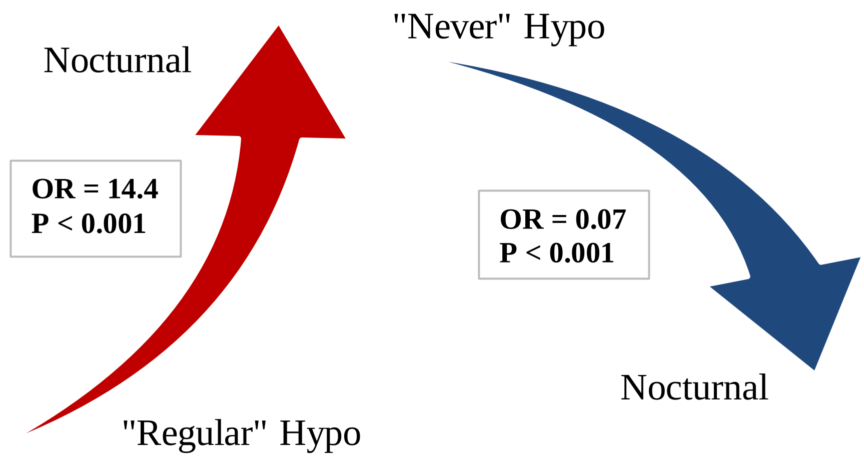

Figure 1. Describes the overall relationship between exercise-associated and nocturnal hypoglycemia outcomes. Experience of exercise-associated hypoglycemia “regularly” was associated with increased report of nocturnal hypoglycemia. Those who reportedly "never" experienced exercise-associated hypoglycemia were significantly protected.

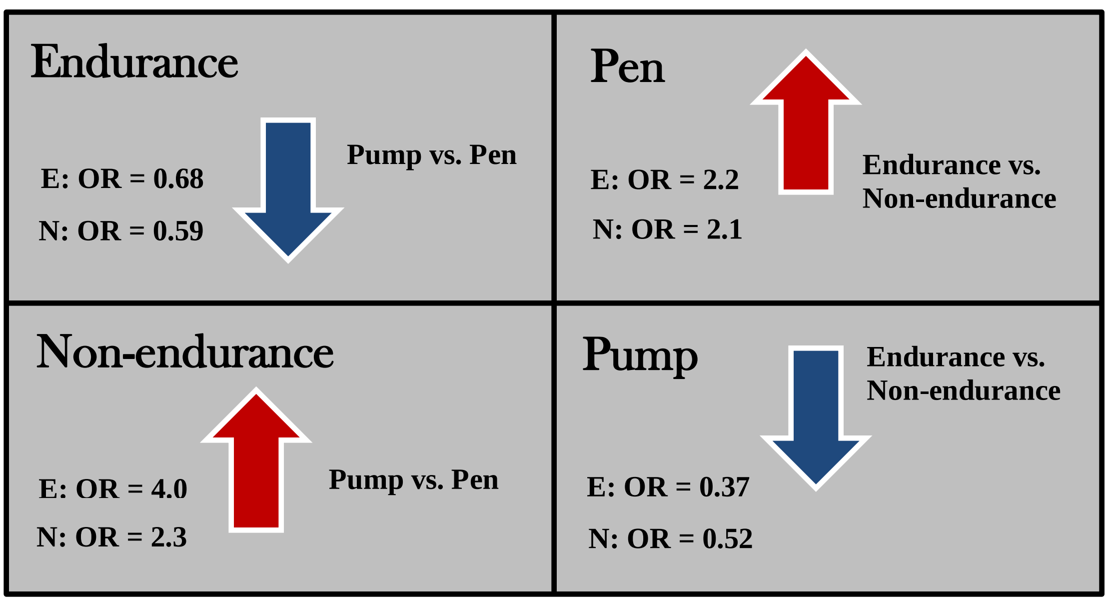

Figure 2. Describes the effect of the significant interaction between type of exercise (endurance/non-endurance) and mode of insulin delivery (pen/pump) on experience of exercise-associated (E) hypoglycemia (“regularly”) (P = 0.002) and nocturnal (N) hypoglycemia (P = 0.042).