Using Distribution-based Methods to Determine Minimal Important Differences with the Hypoglycemia Fear Survey-II in Adults with Type 1 Diabetes

PCR194

Adriana Boateng-Kuffour[1], Patrick Callahan[1], Keval Chandarana[1], Dianne Barry[1], Liang Chen[1], Caitlin S. Kelly[2], Huyen Nguyen[2], Katherine S. Chapman[2], Emilee M. Cornelius[2], Wendy A. Wolf[2], William H. Polonsky[3]

[1]Vertex Pharmaceuticals, Boston, MA, USA; [2]T1D Exchange, Boston, MA, USA; [3]Behavioral Diabetes Institute, San Diego, CA, USA

INTRODUCTION

- Type 1 diabetes (T1D) is a chronic metabolic condition caused by autoimmune destruction of beta cells resulting in a lifelong dependence on exogenous insulin therapy and glucose monitoring[1]
  - In the past 15+ years, advancements in diabetes technology such as continuous glucose monitors (CGM) have become part of the standard of T1D care to help people with T1D achieve more regulated glucose levels and avoid complications[2]
- Despite advances in T1D treatments, many adults with T1D continue to experience distressing hypoglycemic events, in which glucose values fall below a healthy range and can result in a medical emergency[3-6]
  - The experience of hypoglycemic events can lead some individuals to develop a fear of hypoglycemia[7-8]
- Fear of hypoglycemia (FoH) is an especially important patient-reported outcome, with one of the most widely used scales being the hypoglycemic fear scale (HFS-II)[9]
  - This scale has been used in both non-interventional studies and clinical trials,[1,10] but it is unclear as to whether FoH has meaningfully improved for adults with T1D as T1D care has advanced
- Minimum Important Difference (MID) values can be calculated and used to understand meaningful change in FoH,[11] however MID values for HFS-II in adult CGM users with T1D has yet to be established

OBJECTIVES

- To estimate the MID for HFS-II in a cohort of adult CGM users with T1D
- To numerically compare two separate samples to understand whether advances in diabetes management in the past 15+ years create a meaningful difference in FoH among adult CGM users

METHODS

Study Design

- An online cross-sectional survey was administered to people with T1D from the T1D Exchange Registry

Key Inclusion Criteria

- Self-reported clinical diagnosis of T1D ≥5 years
- Current CGM user
- Aged ≥18 years old

Survey Design & Administration

- Participants completed the HFS-II survey[12] (score 0 - 132; higher score = greater hypoglycemia fear), as part of a larger study
  - HFS-II has two domains:
    - Behavior (HFS-B, score 0 – 60): evaluates how fear of hypoglycemia influences the person's behavior, such as avoiding activities that might lead to hypoglycemia
    - Worry (HFS-W, score 0 – 72): assesses the level a person feels about experiencing low blood sugar

Statistical Analysis

- Distribution-based methods were used to estimate the MID for the HFS-II and each domain (Behavior [HFS-B], Worry [HFS-W]) using each score's standard deviation and theoretical score range[11,13-16]
  - A distribution-based approach compares the difference in a scale-based outcome measure to a pre-specified threshold value of its uncertainty (e.g. standard error, standard deviation [SD])
- There is no consensus in the literature as to which approach is preferred,[11] thus a range of values is calculated
  - This range provides useful insights into whether a variable is more or less likely to be meaningful
- Three MID values were calculated based on conventions in the literature[13]:
  - One-half the standard deviation of each score (0.5 * SD)[14]
  - 8% of theoretical range[15]
    - Theoretical range: HFS-II = 0-132; HFS-B = 0-60; HFS-W = 0-72
  - Standard error of measurement (calculated using each score's standard deviation and Cronbach's alpha)[16]
- To contextualize how distributional MID scores can be utilized, we descriptively compared our sample means to the published sample means in Gonder-Frederick et al. (2011) original study to validate the HFS-II[12]
  - This numerical comparison explores if the *time* observed between these two samples (i.e., 15+ years) created a meaningful difference in HFS-II scores

RESULTS

- Mean (SD) age of participants was 45.9 (15.3) years old and 67.5% were female. The mean most recent hemoglobin A1c (HbA1c) reported was 6.7% (SD = 1.0) (**Table 1**)

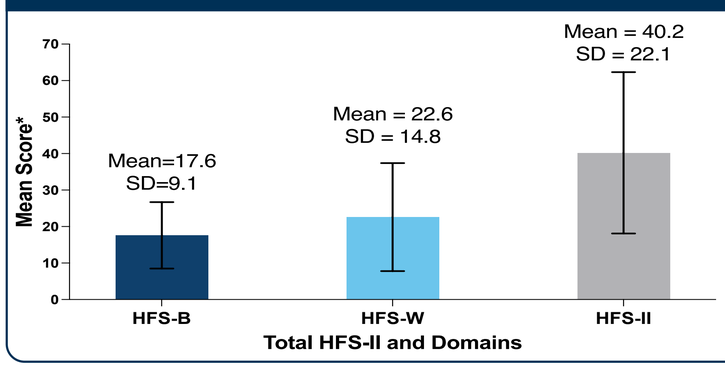
Table 1. Participant Demographics & Clinical Characteristics[a]

	Overall Sample (N=1847, 100%)
Age (years)	
Mean (SD)	45.9 (15.3)
Median (Min, Max)	44 (18, 88)
Gender, n (%)	
Male	582 (31.5)
Female	1247 (67.5)
Non-binary / genderqueer	15 (0.8)
Prefer to self-identify	2 (0.1)
Prefer not to answer	1 (0.1)
Marital status, n (%)	
Single	390 (21.1)
Divorced	130 (7.0)
Cohabitating/living with partner	139 (7.5)
Married/legal civil partnership	1159 (62.8)
Widowed	29 (1.6)
Most recent HbA1c, mean (SD)	6.7 (1.0)
HbA1c <7%,[b] n (%)	
Yes	1240 (67.1)
No	607 (32.9)
Duration of T1D (years)	
Mean (SD)	29.0 (15.1)
Median (Min, Max)	27 (5, 84)

SD: standard deviation; **HbA1c:** hemoglobin A1c; **T1D:** type 1 diabetes
[a]Table 1 was previously presented elsewhere
[b]American Diabetes Association recommended HbA1c target

- **Figure 1** summarizes the mean HFS-B, HFS-W and HFS-II scores for adult CGM users. Mean scores were numerically higher on the HFS-W relative to HFS-B

Figure 1. Mean HFS-B, HFS-W and HFS-II Scores



*Error bars = standard deviation
HFS-II: hypoglycemia fear scale; **HFS-B:** hypoglycemia fear scale-behavior; **HFS-W:** hypoglycemia fear scale-worry

- The MID for HFS-II using distribution-based approach are presented in **Table 2**
- The range of MID scores calculated from our sample highlight how much of a difference in the HFS-II, HFS-W, and HFS-B scales would need to be observed to suggest meaningful change
  - For HFS-II, the MID range is between 5.2 and maximum of 11.0, suggesting a score difference of *at least* 5.2 and ideally above 11.0 is necessary to be meaningful
  - Differences below this range of values are unlikely to be meaningful and differences *within* these values are uncertain

Table 2. Minimum Important Difference for HFS-II

	Overall Sample (N=1847)
MID HFS-B	
SD multiplied by 0.5	4.6
8% of theoretical score range	4.8
SE of measurement	3.6
MID HFS-W	
SD multiplied by 0.5	7.4
8% of theoretical score range	5.8
SE of measurement	3.4
MID HFS-II	
SD multiplied by 0.5	11.0
8% of theoretical score range	10.6
SE of measurement	5.2

HFS-II: hypoglycemia fear scale; **MID:** minimum important difference; **SD:** standard deviation; **SE:** standard error

- In these two samples, based on distribution calculations of MID, FoH did not meaningfully improve numerically for adults with T1D from the time of Gonder-Frederick et al.'s (2011)[12] study to our sample in 2021
  - Mean differences were below all calculated values of MID

Table 3. HFS-II MID Mean Differences Between Current Study and Literature HFS-II

	Current Sample Means (N=1847)	Sample Mean in Gonder-Frederick (2011)[a] (N=777)	Mean Differences Two Samples	Mean Differences Needed for MID (Range)
HFS-B	17.6	17.9	-0.3	3.6-4.6
HFS-W	22.6	22.3	0.3	3.4-7.4
HFS-II	40.2	44.1	-3.9	5.2-11.0

HFS-II: hypoglycemia fear scale II; **HFS-B:** hypoglycemia fear scale-behavior; **HFS-W:** hypoglycemia fear scale-worry; **MID:** minimum important difference
Mean difference comparisons are descriptive; no inferential statistics were performed.
[a] Gonder-Frederick's (2011)[12] sample was comprised of secondary data collected between 1998-2009. Their sample consisted of 777 total participants: 289 participants completed both subscales of HFS-II and 488 participants completed only the HFS-W subscale. Sample characteristics were 53.3% female, 95.9% White race, and 41.9 years old on average; average HbA1c was 7.7%, 44.4% used insulin pumps, and 63.1% reported no severe hypoglycemic events in the previous year.

Limitations

- Study participants were from the T1D Exchange Registry, a cohort of individuals with T1D who tend to be highly engaged, have a high degree of diabetes technology use, and have historically been shown to be more likely to achieve glycemic targets
- Study participants were mostly White, non-Hispanic or Latino, identified as female, highly educated, were self-selected and needed access to the internet and email, which may all impact the generalizability of these results
- All data were self-reported; eligibility and clinical data were not verified by a clinician
- Data were cross-sectional and the application of estimated MIDs to within person change or changes from over time are limited

CONCLUSIONS

- **This is the first study to calculate the MID for HFS-II in adult CGM users with T1D**
- **Based on distribution calculations of MID, FoH did not meaningfully decrease numerically for adults with T1D over the past 15+ years, using the Gonder-Frederick et al.[12] sample as our comparison sample**
  - **Results suggest that greater efforts beyond general improvements in diabetes technology/management that have occurred in the past 15+ years are needed to improve quality of life for adults with T1D**
- **Future research should supplement these findings with anchor-based approaches of MID for HFS-II and use longitudinal within-person designs to determine what other factors create meaningful difference in FoH to people with T1D**

References

1. Hering, B. et al. *Islet Transplantation of Type 1 Diabetes*. 2007; Version 2.0F
2. Diabetes Technology: Standards of Care in Diabetes—2024. *Diabetes Care*. 2024;47(Supplement_1):S126–S144
3. Farsaei S et al. *Primary Care Diabetes*. 2014; 8(4):338–45
4. Cryer PE. *Endocrinol Metab Clin N Am*. 2010; 641-654
5. Nathan DM. *Diabetes Care*. 2013;37(1):9–16
6. Jacobson AM et al.*The Lancet Diabetes & Endocrinology*. 2021;9(7):436–45.
7. Cryer PE. *Diabetes*. 2014;63:2188–2195
8. Fidler C. et al. *J Med Econ*. 2011; 14:646-655.
9. Maclean et al. *Diabetes Care.* 2022;45(3):538–546
10. Marknman J.F. et al. *Am J Transplant*. 2021; 21(4): 1477 – 1492
11. Stargardt T. et al. *Health Qual Life Outcomes*. 2009; 7:91
12. Gonder-Frederick et al., *Diabetes Care*. 2011; 34:801-806.
13. Ousman A. et al. *Health and Quality of Life Outcomes*. 2018;16:228
14. Norman, Geoffrey et al. *Medical Care*. 2003; 41(5):p 582-592
15. US FDA. *Health Qual Life Outcomes*. 2006;11;4:79
16. Javier Rejas et al. *Journal of Clinical Epidemiology*. 2008; 61: (4)-350-356

Author Disclosures

CSK, **HN**, **KSC**, **EMC**, and **WAW** are employees of T1D Exchange. **WHP** has served as a consultant for Dexcom, Abbott Diabetes, Eli Lilly, Sanofi, Novo Nordisk, Vertex Pharmaceuticals, Embecta, Mannkind, Ascensia, and Sequel. **WHP** received research support from Dexcom and Abbott Diabetes. **ABK**, **PC**, **KC**, **DB**, and **LC** are employees of Vertex Pharmaceuticals and may hold stock or stock options in the company

Acknowledgments

The T1D Exchange Registry is funded by The Leona M. and Harry B. Charitable Trust grant G-2103-05086. We thank the participants of the T1D Exchange Registry for their participation in this study.

The study was supported by Vertex Pharmaceuticals. Editorial coordination and support were provided by Zara Petzoldt, PharmD (ZP) and Allison Lord, PhD (AL). Graphic support was provided by Alexandra Battaglia (AB). **ZP**, **AL**, and **AB** are employees of Vertex Pharmaceuticals who hold stock and/or stock options at the company.