Sex-based disparities in perceived versus objective glycaemic control in type 1 diabetes: a cross-sectional cohort study

Managing type 1 diabetes has a substantial impact on quality of life and psychological health. Indeed, insulin overdosing can lead to hypoglycaemia, which has potentially damaging consequences, and consistent underdosing can lead to hyperglycaemia-associated complications or diabetic ketoacidosis.[1] Therefore, the accuracy with which individuals assess their risk of hyperglycaemia and hypoglycaemia is important for long-term diabetes management and safety.

Sex differences have been described in multiple aspects of social behavior and are especially pronounced in risk assessment in social behaviour.[2] This warrants the question of whether sex differences occur in risk assessment of diabetes and whether this could lead to differences in health perception or disease management. Furthermore, objective measures of glycaemic control might play a different role in perception of diabetes management between the sexes.[1]

Continuous glucose monitors (CGMs) have made it possible to assess glucose levels in real time for individuals with type 1 diabetes.[3] This technology enables the comparison of continuous measurements with self-reported metrics, providing a means to evaluate subjective versus objective measurements of diabetes management. In light of these considerations, this pilot study aimed to assess the role of sex in perceived, relative to objective, glycaemic control and hypoglycaemia assessment in type 1 diabetes using the GUTDM1 cohort in the Netherlands.[4] To assess the difference between self-rated glycaemic control and CGM metrics between men (n=180) and women (n=316), we calculated a diabetes management index (appendix pp 3–5) and a hypo-estimation-index (appendix pp 3–5). Participants were asked to rate their diabetes management and provide their CGM data during a single study visit in the Amsterdam University Medical Centre (appendix p 5). Statistical analyses were performed as appropriate by the distribution and type of outcome data and linear model and spline regressions were used for multivariate analyses (appendix pp 8–9). The diabetes management index was derived by dividing self-rated glycaemic control (on a 0 to 10 scale) by 14-day time in range (TIR; in tenth percentiles for scale), leading to a scale of 0 to 10. Here, 1 reflects agreement between the subjective and objective glycaemic control (appendix p 17), 0 to <1 reflects underestimation (ie, where the self-rated glucose control is lower than the objective TIR) and above 1 reflects overestimation. The hypo-estimation-index was defined as the difference between the measured hypoglycaemia frequency and the self-reported hypoglycaemia frequency per week (appendix p 7). The hypo-estimation-index was Ln-transformed. Therefore, here 0 reflected agreement between the subjective and objective hypoglycaemic events, negative values reflected underestimation, and positive values represented overestimation (ie, reporting more hypoglycaemic events than recorded by CGM).

Participant characteristics are provided in the appendix (pp 10, 13–15). Objectively, women and men had similar metrics of diabetes management. Women and men had similar TIR (women 67·0% [IQR 52·0–80·0] *vs* men 66·0% [51·0–80·4, p=0·66, figure 1A, appendix pp 13–15) and HbA_{1c} (mean 56·2 mmol/mol [SD 11·5] *vs* 54·3 mmol/mol [13·2], p=0·085, appendix pp 13–15). Time above range and the glucose coefficient of variance were also not significantly different between women and men (appendix pp 13–15).

In contrast to their similar objective diabetes management, women and men rated their subjective diabetes management very differently. Women rated their management as worse than men (self-reported diabetes control 6·0 [IQR 5·0–7·0] *vs* 7·0 [6·0–8·0], p<0·0001, figure 1B), but their diabetes impacted their life more (self-reported diabetes

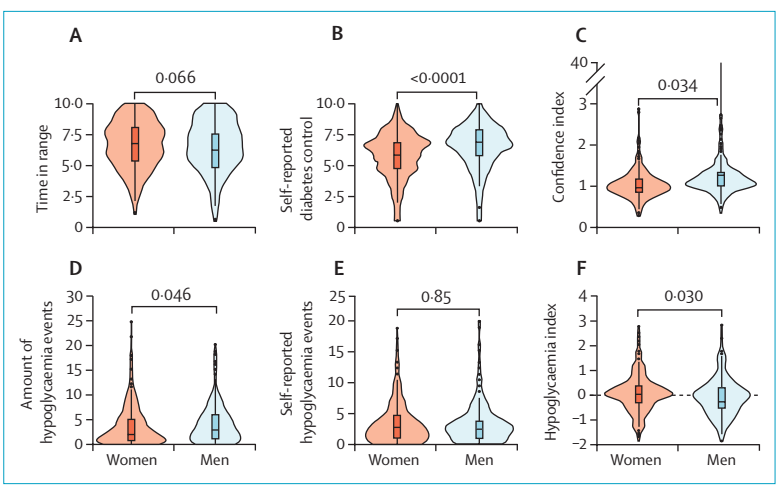

Figure: **Violin plots of CGM measured time in range and sex (A), self-reported diabetes management and sex (B), diabetes management index and sex (C), CGM measured number of hypoglycaemic events per week and sex (D), self-reported hypoglycaemic events per week and sex (E), and hypoglycaemia-index and sex (F)**

The violin plots are displayed with an interruption of the axis to accomidate outliers. CGM=continuous glucose monitor.

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See Online for appendix

burden 6·9 [SD 2·1] *vs* 6·1 [2·1], p<0·0001; appendix pp 13–15). Women underestimated their level of glycaemic control by a non-significant 3% (diabetes-management-index 0·97 [SD 0·35], figure 1C), whereas men overestimated their glycaemic control by 31%, with a significantly higher diabetes-management-index (1·31 [SD 2·94], p<0·034, figure 1C). The correlation between self-rated diabetes management and objective TIR was higher in women (*r*=0·565 [95% CI 0·50–0·62], p<0·0001) than in men (*r*=0·461 [0·39–0·53], p<0·0001; $p_{interaction}$=0·037, appendix p 16). This difference between women and men in diabetes management index (geometric mean ratio [GMR] for men relative to women 1·16 [95% CI 1·08–1·24]) remained significant after adjustment for diabetes duration, age, BMI, residual islet function, amount of insulin, insulin mode of delivery, and CGM type (GMR 1·16 [95% CI 1·07–2·25], appendix pp 10, 16).

Furthermore, women experienced significantly less time below range despite similar median patterns (TBR; 2·0% [1·0–4·0] *vs* 2·0% [1·0–5·0], p=0·028, appendix pp 13–15), a shorter duration of hypoglycaemic events (57·0 min [29·0–91·0] *vs* 64·0 min [34·3–100·0], p=0·078, appendix pp 13–15), and a lower frequency of CGM-reported hypoglycaemic events (2·0 per week [0·7–5·0] *vs* 3·0 per week [1·0–6·0], p=0·046, figure 1D) than men. However, the self-reported number of hypoglycaemic events was similar between women and men (appendix pp 13–15, figure 1E). Both sexes underreported hypoglycaemic events, but less so in women than in men (hypo-estimation-index, –0·38 [SD 0·83] *vs* –0·55 [SD 0·85], p=0·030; figure 1F); we found a significant association between the hypo-estimation-index and sex (GMR for men 0·84 [95% CI 0·72–0·99], appendix p 16). The correlation between self-reported hypoglycaemic events and CGM-measured number of hypoglycaemic events was significantly stronger in women (*r*=0·610, [95% CI 0·55–0·66], p<0·0001) than in men (*r*=0·544, [0·48–0·60], p<0·0001; $p_{interaction}$<0·0001, appendix p 16). This was similar for the correlation between self-reported hypoglycaemic events and TBR in women (*r*=0·582 [95% CI 0·52–0·64], p<0·0001) versus men (*r*=0·493 [0·42–0·56], p<0·0001; $p_{interaction}$<0·0001, appendix p 16). These results remained significant when adjusting for age and diabetes duration, BMI, c-peptide and glucagon levels, amount of insulin, insulin mode of delivery, and CGM type (GMR for men relative to women 0·84 [95% CI 0·71–0·99], appendix p 11, 16).

This study investigated the associations between sex and risk estimation in diabetes, by indexing self-rated and CGM measured glycaemic control and hypoglycaemia in people with type 1 diabetes. Here, men exhibited a self-rated overestimation of their glucose control of 31% relative to objectively measured TIR, but women did not. This difference was not explained by men having lower HbA_{1c} or better TIR than women. Subjective overestimation in men, referred to as overconfidence in social science literature, has been reported in multiple fields, such as risk assessment in corporate leadership, postoperative outcomes, wage expectations, and accident rates.[5–7] Subjective diabetes management in direct comparison to its objective measurement has rarely been considered when addressing gender and sex differences in medicine.

Objectively, TIR and HbA_{1c} showed no discrepancy between women and men in this study, which aligns with the literature on HbA_{1c} and sexual dimorphism, where studies report either no difference or slightly higher levels in women.[1] Our study shows that men had similar HbA_{1c} and TIR (but more hypoglycaemia) with seemingly less use of advanced technological aids, as more men used insulin injections instead of pumps (appendix p 13). This discrepancy raises the question of whether overestimation of diabetes management in men results in physician bias and less counseling for diabetes aids. These questions warrant future research.

Both women and men underreported hypoglycaemic events, however men had a 16% lower hypo-estimation-index than women, despite spending more TBR, having longer hypoglycemic events, and experiencing hypoglycaemia more often. Women were less likely to underreport hypoglycaemic events and both frequency and duration of hypoglycaemic events and TBR were lower in women. This is in line with literature where women report more hypoglycaemic events.[8] Underreporting could be dangerous, as hypoglycaemia is still a major cause of mortality in young individuals with type 1 diabetes and therefore, differences in managing type 1 diabetes could create a higher risk of severe hypoglycaemia with potentially damaging consequences.[9]

These results remained significant when correcting for mode of insulin delivery and type of CGM device. It might be that women take less risks,[10] and as a result are less likely to underestimate hypoglycaemia, resulting in shorter duration of hypoglycaemia and less frequent hypoglycaemic events. An alternative hypothesis for the higher diabetes management index observed in men could be that the relative overconfidence in men is associated with more risky behavioral patterns leading to similar TIR but with more frequent hypoglycaemia.

This study has several strengths and limitations. First, the study design introduced measurement error in several confounders. Second, CGM type and accuracy varied, leading to a potential change of the association of time in and below range with subjective measures of diabetes control, to account for this we corrected the analyses for CGM type and found the results did not

change after correction. Third, data on sex hormones, menstrual cycle, and menopause were not included but might play a role in the sexual dimorphism displayed in the indices. Fourth, women on average were younger, but correction for the age difference did not alter any of the associations. Fifth, this study does not address differences between transgendered and cisgendered individuals or gender related socio-cultural factors since participants' recorded gender-identity was in concordance with their sex based on single nucleotide polymorphism arrays. Finally, women are over-represented in this cohort, which could lead to a potential underestimation of the diabetes management index in men.

In conclusion, this study shows that there are significant differences in subjective estimation of diabetes management between women and men, where women are more accurate and men self-rate their disease management higher in relation to measured hypoglycaemic events and TIR. These findings have important clinical implications. They can help people with type 1 diabetes better align their perception of glucose control with actual CGM data. Furthermore, the results also highlight the importance of using recent CGM metrics instead of relying on general impressions when assessing glycaemic control.

The sex disparity that we discovered warrants further investigation into the role of sex differences in disease management, perception, and possibly pathophysiological heterogeneity.

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Thyroid eye disease and the IGF-1 receptor

I have read the Review by Wilmar M Wiersinga and colleagues,[1] in which the authors have raised several important points that invite additional perspectives.

Regarding the role of insulin-like growth factor-1 receptor (IGF-1R) in thyroid eye disease (TED; also known as Graves' orbitopathy), the authors correctly point out that immunisation with IGF-1R fails to elicit a disease phenotype in mice; however Moshkelgosha and colleagues found that immunising mice with thyrotropin receptor results in a generation of both anti-thyrotropin receptor and autoantibodies against IGF-1R in most cases.[2] Additionally, Pritchard and colleagues published evidence supporting Graves' orbitopathy-derived IgGs directly binding to IGF-1R and activating signalling and gene expression not elicited by recombinant human thyrotropin.[3] Thus, the issue of whether anti-IGF-1R autoantibodies play a consequential role in TED remains controversial.

Concerning the US Food and Drug Administration approval of teprotumumab for TED, several adverse events were identified in two pivotal clinical trials attributable to