Quality of life in people with Type 2 diabetes; a study in a multi-ethnic clinical trial population

SHAIFALI KULKARNI, PAUL WELSH, MYZVOON ALI,* JOHN R PETRIE* ON BEHALF OF THE VICCTA-DIABETES COLLABORATORS**

Abstract
Background: The long-term burden of self-management in type 2 diabetes can impact quality of life.
Aims: To examine associations between demographic and clinical factors, anxiety/depression and perception of health in people with type 2 diabetes.
Methods: Retrospective analyses of anonymised data from completed clinical trials provided by the diabetes subsection of Virtual International Cardiovascular and Cognitive Trials Archive (VICCTA). Data on demographics, polypharmacy, HbA1c, anxiety/depression (EQ-5D-3L) and perception of health (EQ-5D-3L VAS) were extracted. Regression analyses explored associations amongst polypharmacy, HbA1c and quality of life (anxiety/depression and health perception) at baseline.
Results: In 2783 participants with type 2 diabetes (median age 66 years (IQR 61–70), n=1,595 (57%) male), female sex and Caucasian/European ethnicity were each associated with increased anxiety/depression and lower EQ-5D-3L VAS scores. Following adjustment for covariates, each additional prescribed medication was associated with increased anxiety/depression: OR 1.09 (95% CI 1.04 to 1.14; p<0.001) and lower VAS scores: B=−1.06 (95% CI −1.37 to −0.75, p<0.001)).
Conclusion: Demographic factors and polypharmacy are associated with anxiety/depression and lower health perception.

Key words: anxiety, depression, diabetes, quality of life

Introduction
Type 2 diabetes comprises 90% of diabetes cases worldwide.1 People with type 2 diabetes experience a high burden of self-management of their condition and are at an increased risk of depression and lower quality of life2,3 Given the impact on quality of life and the high prevalence of mental health conditions in people with type 2 diabetes, there is a need to better understand these associations.4 Several demographic and clinical factors may affect quality of life and prevalence of anxiety/depression in people with type 2 diabetes: for example, depression is more likely to occur in younger women with diabetes.5 There is conflicting evidence regarding the role of ethnicity, with one study showing that African Americans with type 2 diabetes were less likely to report depressive symptoms compared with other ethnicities, while another showed no link.6,7 Another study of men with type 2 diabetes aged 70–89 years found that the risk of depression was greatest immediately after diagnosis and towards the end of life.8 A previous meta-analysis also reported a link between obesity, depression and type 2 diabetes.9

Type 2 diabetes is a challenging condition due to associations with other morbidities and complications; this often results in polypharmacy, defined as taking five or more medications.10,11 A higher medication burden is twice as likely in people with diabetes and co-existing mental health conditions, including anxiety/depression.12 While an increased medication burden has been shown to adversely affect quality of life, the potential link between anxiety/depression and polypharmacy is under-researched.13 Evidence is somewhat conflicting on the association between glycaemic control and anxiety/depression. However, lower HbA1c levels, reflecting better metabolic control, have been associated with higher quality of life.14

Validated predictors that can be used in the clinic to identify people with type 2 diabetes at risk of anxiety/depression are lacking. One study found that mental health conditions in people with diabetes were only identified by health professionals when symptoms were severe.15 For the present analysis, access to archived data from existing high-quality studies provided an opportunity to further explore these associations. We sought to identify demographic and clinical risk factors, including polypharmacy, associated with a higher risk of anxiety/depression and lower quality of life to inform the management and support of people with type 2 diabetes.

Methods
Transparency and openness
In this article we report how we determined all data exclusions and measures included in the study. Data can be made available...
analyses were reported as odds ratios (OR) and 95% confidence intervals (95% CI) while linear regression models were reported using unstandardised beta coefficients (β) and standardised beta coefficients (β̂). We excluded participants with missing data from the relevant analyses.

Results
Study population characteristics
The analysis population comprised people with a diagnosis of type 2 diabetes mellitus at 30 years of age or older, an age of at least 55 years at the time of study entry and a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease.

Data were available from 2,783 people with type 2 diabetes (57% male, median age 66 years, median duration of diabetes 11 years). Table 1 displays the characteristics of the study population.

Table 1 Characteristics of the study population

| Variable                           | Number | %   |
|------------------------------------|--------|-----|
| Sex                                |        |     |
| Men                                | 1,595  | 57  |
| Women                              | 1,188  | 43  |
| Ethnicity                          |        |     |
| Caucasian/European                  | 1,667  | 60  |
| Chinese                            | 842    | 30  |
| South Asian or South-East Asian    | 217    | 7.8 |
| Others                             | 57     | 2.0 |
| Number of concurrent medications   |        |     |
| 0                                  | 44     | 1.6 |
| 1–3                                | 1,240  | 45  |
| 4–6                                | 1,198  | 43  |
| 7–10                               | 300    | 11  |
| >10                                | 1      | 0   |
| Smoking status                     |        |     |
| Current smokers                    | 169    | 6.1 |
| Ex-smokers                         | 758    | 27  |
| Non-smokers                        | 1,856  | 67  |
| Presence of comorbidities          |        |     |
| Prior stroke                       | 259    | 9.3 |
| Myocardial infarction              | 327    | 12  |
| Chronic ischaemic heart disease    | 174    | 3.7 |
| Transient ischaemic attack         | 115    | 4.1 |
| Heart failure                      | 78     | 2.8 |
| Atrial fibrillation                | 151    | 5.4 |
| Hypertension                       | 1,946  | 70  |
| Leg ulcers                         | 41     | 1.5 |
| Retinopathy                        | 606    | 21.8|
| EQ-5D-3L anxiety/depression score  |        |     |
| 1 (not anxious/depressed)          | 1,988  | 72  |
| 2 (moderately anxious /depressed)  | 745    | 27  |
| 3 (extremely anxious/depressed)    | 37     | 1.3 |
| Age (years)                        | 66     | IQR|
| Diabetes duration (years)          | 7      | 3–11|
| Age of T2D onset (years)           | 58     | 52–64|
| BMI (kg/m²)                        | 27.6   | 24.7–31.1|
| HbA1c (mmol/mol)                   | 55     | 48–66|
| VAS score according to EQ-5D-3L   | 80     | 70–90|

BMI, body mass index; EQ-5D-3L, European Quality of Life Score; HbA1c, glycated haemoglobin A1c; IQR, interquartile range; T2D, type 2 diabetes; VAS, Visual Analogue Scale.
Factors associated with anxiety/depression

In univariable analysis, female sex was significantly associated with an increased prevalence of anxiety/depression (p<0.001). Chinese ethnicity (p=0.046), older age (p=0.007) and a lower BMI (p=0.040) were each significantly associated with lower odds of anxiety/depression (Figure 1).

In multivariable analysis, South/South-East Asian versus Caucasian/European ethnicity (OR, 0.67; 95% CI 0.47 to 0.95; p=0.026), Chinese versus Caucasian/European ethnicity (OR 0.75; 95% CI 0.61 to 0.93; p=0.009) and older age (OR 0.98; 95% CI 0.97 to 0.99; p=0.004) were each significantly associated with lower odds of anxiety/depression. Female sex was significantly associated with increased odds of anxiety/depression (OR 2.03; 95% CI 1.71 to 2.41; p<0.001).

We then examined polypharmacy. In univariable analysis (n=2,770), polypharmacy was significantly associated with increased anxiety/depression (OR 1.09; 95% CI 1.04 to 1.13; p<0.001)) (Table 2).

Multivariable analyses (n=2,714), adjusting for covariates, revealed that polypharmacy remained significantly associated with increased anxiety/depression (OR 1.09; 95% CI 1.04 to 1.14; p<0.001). Within this model, older age (OR 0.98, 95% CI 0.97 to 0.99; p=0.003), Chinese versus Caucasian/European ethnicity (OR 0.79; 95% CI 0.64 to 0.99; p=0.037) and South/South-East Asian versus Caucasian/European ethnicity (OR 0.67; 95% CI 0.47 to 0.95; p=0.024) were each significantly associated with decreased anxiety/depression. Female sex was significantly associated with increased anxiety/depression (OR 2.05; 95% CI 1.72 to 2.43; p<0.001) (Table 3).

There was no association between dependency for ADLs or HbA1c levels (n=2,761) with anxiety/depression (Figure 1, Table 2).

Factors associated with overall perception of health

In univariable analysis (n=2,770), polypharmacy was significantly associated with lower VAS scores (B= −1.40; 95% CI −1.70 to −1.10; p<0.001) (Table 2). In multivariable analyses (n=2,714), following adjustment for covariates, polypharmacy remained significantly associated with lower VAS scores (B= −1.06, 95% CI −1.37 to −0.75, p<0.001). Within this model, Chinese versus Caucasian/European ethnicity (B=3.73, 95% CI 2.30 to 5.16, p<0.001) and South/South-East Asian versus Caucasian/European ethnicity (B=3.77, 95% CI 1.52 to 6.02, p=0.001) were each significantly associated with lower VAS scores.

Table 2 Summary of baseline characteristics and design of studies included in this review

| Independent variable | Anxiety/depression | | VAS score | | |
|----------------------|--------------------|-----------------|-------------|-----------------|-------------|
|                      | N                  | OR              | 95% CI      | P value         | N            | B               | 95% CI      | β               | P value         |
| 1. No of medications (+1) | 2,770              | 1.09            | 1.04        | 1.13            | <0.001        | 2,771          | −1.40        | −1.70           | −1.10          | −0.17          | <0.001         |
| 2. HbA1c (+1 percentage point) | 2,761              | 1.00            | 0.94        | 1.05            | 0.924         | 2,762          | 0.10         | −0.28           | 0.48           | 0.01           | 0.616          |

Odds ratios (OR), 95% confidence intervals (CI) and P values were obtained by logistic regression. Unstandardised beta coefficients (B), 95% confidence intervals (CI), standardised beta coefficients (β) and P values were obtained by linear regression.

HbA1c, glycated haemoglobin A1c; LL, lower limit; UL, upper limit; VAS, Visual Analogue Scale.

Table 3 Summary of baseline characteristics and design of studies included in this review

| Independent variable | Anxiety/depression | | VAS score | | |
|----------------------|--------------------|-----------------|-------------|-----------------|-------------|
|                      | N                  | OR              | 95% CI      | P value         | N            | B               | 95% CI      | β               | P value         |
| Medications          | 2,713              | 1.09            | 1.04        | 1.14            | <0.001        | 2,714          | −1.06        | −1.37           | −0.75          | −0.13          | <0.001         |
| Age                  | 0.98               | 0.97            | 0.99        | 0.003           | −0.06         | −0.15          | 0.03        | −0.03           | 0.181          |
| BMI                  | 0.99               | 0.97            | 1.01        | 0.412           | −0.33         | −0.46          | −0.20       | −0.11           | <0.001         |
| Diabetes duration    | 1.01               | 0.99            | 1.02        | 0.856           | −0.04         | −0.13          | 0.05        | −0.02           | 0.410          |
| Female vs male       | 2.05               | 1.72            | 2.43        | <0.001          | −1.35         | −2.50          | −0.20       | −0.04           | 0.021          |
| Ethnicity            |                    |                 |             |                 |              |                 |             |                 |                 |
| Caucasian/European   | Ref                |                 |             |                 |              |                 |             |                 |                 |
| Chinese              | 0.79               | 0.64            | 0.99        | 0.037           | 3.73          | 2.30           | 5.16        | 0.11            | <0.001         |
| South Asian or South-East Asian | 0.67 | 0.47 | 0.95 | 0.024 | 3.77 | 1.52 | 6.02 | 0.07 | 0.001 |

Odds ratios (OR), 95% confidence intervals (CI) and P values were obtained by logistic regression. Unstandardised beta coefficients (B), 95% confidence intervals (CI), standardised beta coefficients (β) and P values were obtained by linear regression.

BMI, body mass index; HbA1c, glycated haemoglobin A1c; LL, lower limit; UL, upper limit; VAS, Visual Analogue Scale.
significantly associated with higher VAS scores. A higher BMI (B= −0.33, 95% CI −0.46 to −0.20, p <0.001) and female sex (B= −1.35, 95% CI −2.50 to −0.20, p=0.021) were each significantly associated with lower VAS scores (Table 3).

HbA1c levels were not associated with VAS scores in univariable analysis (n=2,761) (Table 2).

Discussion
Main findings
In this analysis of pooled data from the placebo groups of diabetes clinical trials, female sex and Caucasian/European ethnicity were each associated with increased anxiety/depression and a lower perception of health. Increased medication burden was also associated with increased anxiety/depression and lower perception of health.

Strengths and limitations of this study
Strengths of this study include a moderate sample size and a multi-ethnic population; although derived from participants in clinical trials, many characteristics were similar to those of people with type 2 diabetes seen in clinical practice. Anonymised clinical trial data were of high quality, near complete and standardised according to operational definitions. Moreover, the 3-point EQ-5D-3L score is a convenient method of detecting anxiety/depression and has been used in other studies including participants with type 2 diabetes. Our retrospective analysis of an existing dataset meant we were unable to examine the impact of variables such as stressful life events, fear of hypoglycaemia, health literacy and diabetes distress. Finally, we did not adjust for multiplicity in these exploratory analyses.

Interpretation of findings in relation to previously published work
Our study showed that 28% of participants reported having anxiety/depression using the EQ-5D-3L scale. Studies using other self-reporting measures and clinician-led measures show similar figures.

Our observation of sex differences in anxiety/depression supports findings in previous studies. Lower EQ-5D scores both in women with type 2 diabetes and in the general population have also been previously reported.

In addition, there have been previous reports that Caucasian participants with type 2 diabetes are at increased risk of depressive symptoms. Moreover, there is evidence, albeit from populations without diabetes, that people of non-Caucasian ethnicities are less likely to seek help regarding mental health than Caucasians. Non-Caucasian/European participants may therefore have been less likely to self-report anxiety/depression.

We observed that, for each additional prescribed medication, the risk of anxiety/depression increased by approximately 9%. This is in keeping with results from previous research from other populations. Number of prescribed medications may be an indicator of disease severity (ie, a marker of more severe/advanced type 2 diabetes with associated anxiety/depression and lower quality of life). However, clinicians should be aware of the negative impacts of polypharmacy and, where possible, review and/or minimise the number of prescribed medications as this may reduce anxiety/depression and improve quality of life.

Our observation of a lack of association between HbA1c and anxiety/depression differs from previous research. We hypothesise that the lack of association may be due to the fact that the EQ-5D-3L is a general health-related quality of life questionnaire and may not be sensitive enough to detect differences in anxiety/depression.
our sample size was moderate, we acknowledge that there may not have been sufficient statistical power given the relative insensitivity of the anxiety/depression scoring on the EQ-5D-3L (a 3-point ordinal scale).

Implications for future research, policy and practice
Our findings have clinical relevance: anxiety and depression can be a barrier to self-management for people with type 2 diabetes and heighten the risk of severe and life-changing microvascular and macrovascular complications. In addition, diabetes distress (defined as unease occurring due to the self-managing nature of diabetes and the future possibility of complications) is associated with higher HbA1c. Increased awareness of mental health conditions among specific high-risk subpopulations of people with type 2 diabetes, such as women and Caucasians, may contribute to improving outcomes.

Conclusion
Female sex, Caucasian ethnicity and polypharmacy are associated with increased anxiety/depression in people with type 2 diabetes. These findings could contribute to development of future targeted interventions to better manage and support mental health and quality of life in people with type 2 diabetes.

Acknowledgements
The authors would like to thank the VICCTA-Diabetes Steering Committee who commented on the project proposal.

Conflict of interest
None.

Funding
Access to VICCTA-Diabetes was funded by the BSc (MedSci) intercalated degree programme at the University of Glasgow.

Contribution
SK: conceptualisation, methodology, data analysis, investigation, visualisation and writing of the article. PW: supervision of data analysis. MA: conceptualisation, data curation, methodology, supervision and writing of the article. JRP: conceptualisation, methodology, supervision and writing of the article.

References
1. World Health Organisation. 10 facts on diabetes. https://www.who.int/features/factfiles/diabetes/en/ (accessed 5 August 2021).
2. Schram M, Baan C, Pouwer F. Depression and quality of life in patients with diabetes: a systematic review from the European Depression in Diabetes (EDID) Research Consortium. Curr Diabetes Rev 2009;5:112–19. https://doi.org/10.2174/15739909098166828
3. Polonsky WH. Emotional and quality-of-life aspects of diabetes management. Curr Diabetes Rep 2002;2:153–9. https://doi.org/10.1007/s11892-002-0075-5
4. Wylie TAF, Shah C, Connor R, et al. Transforming mental well-being for people with diabetes: research recommendations from Diabetes UK's 2019 Diabetes and Mental Well-Being Workshop. Diabet Med 2019;36:1532–8. https://doi.org/10.1111/dme.14048
5. Zhao W, Chen Y, Lin M, et al. Association between diabetes and depression: Sex and age differences. Public Health 2006;120:696–704. https://doi.org/10.1016/j.puhe.2006.04.012
6. De Groot M, Pinkerman B, Wagner J, et al. Depression treatment and satisfaction in a multicultural sample of type 1 and type 2 diabetic patients. Diabetes Care 2006;29:549–53. https://doi.org/10.2337/diacare.29.03.06-dc05-1396
7. Golden SH, Lee HB, Schreiner PJ, et al. Depression and type 2 diabetes mellitus: The multiethnic study of atherosclerosis. Psychosomatic Med 2007;69:529–36. https://doi.org/10.1097/PSY.0b013e3180f61c5c
8. Almeida OP, McCaul K, Hankey GJ, et al. Duration of diabetes and its association with depression in later life: The Health in Men Study (HIMS). Maturitas 2016;86:3–9. https://doi.org/10.1016/j.maturitas.2016.01.003
9. Luppino FS, De Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: A systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 2010;67:220–9. https://doi.org/10.1001/archgenpsychiatry.2010.2
10. Dobr ic ić EC, Gārmā MA, Cosma MA, et al. Polypharmacy in type 2 diabetes mellitus: Insights from an internal medicine department. Medicina (Lithuania) 2019;55:1–10. https://doi.org/10.3390/medicina55080436
11. Massnoon N, Shakib S, Kalisch-Ellert L, et al. What is polypharmacy? A systematic review of definitions. BMC Geriatrics 2017;17:1–10. https://doi.org/10.1186/s12877-017-0621-2
12. Akhhabali M, Barkhi B, Alhavasi TM, et al. Polypharmacy among patients with diabetes: a cross-sectional retrospective study in a tertiary hospital in Saudi Arabia. BMJ Open 2018;8:1–8. https://doi.org/10.1136/bmjopen-2017-020852
13. Austin RP. Polypharmacy as a risk factor in the treatment of type 2 diabetes. Diabetes Spectrum 2006;19:13–16. https://doi.org/10.2337/diaspect.19.1.13
14. Lau CY, Qureshi AK, Scott SG. Association between glycaemic control and quality of life in diabetes mellitus. J Postgrad Med 2004;50:189–93.
15. Poulsen KM, Pachana NA, McDermott BM. Health professionals’ detection of depression and anxiety in their patients with diabetes: the influence of patient, illness and psychological factors. J Health Psycho 2016;21:1566–75. https://doi.org/10.1177/1359105314559618
16. Aguilar-Salinas CA, Monroy OV, Gómez-Pérez FJ, et al. Characteristics of patients with type 2 diabetes in Mexico: results from a large population-based nationwide survey. Diabetes Care 2003;26:2021–6. https://doi.org/10.2337/diacare.26.7.2021
17. Janssen MF, Lubetkin EI, Sekhob J, et al. The use of the EQ-5D preference-based health status measure in adults with type 2 diabetes mellitus. Diabet Med 2011;28:495–501. https://doi.org/10.1111/j.1464-5491.2010.03136.x
18. Soll I, Stavem K, Kristiansen I. Health-related quality of life in diabetes: the associations of complications with EQ-5D scores. Health and Quality of Life Outcomes 2010;8:18. https://doi.org/10.1186/1477-7525-8-18
19. Abedini MR, Bariar B, Mirti Z, et al. The quality of life of the patients with diabetes type Z using EQ-5D-5L in Birjand. Health and Quality of Life Outcomes 2020;18:18. https://doi.org/10.1186/s12955-020-1277-8
20. Johnson JA, Pickard AS. Comparison of the EQ-5D and SF-12 health surveys in a general population survey in Alberta, Canada. Medical Care 2000;38:115–21.
21. Chen SY, Feng Z, Yi X. A general introduction to adjustment for multiple comparisons. J Thoracic Dis 2017;9:1725–9. https://doi.org/10.21037/jtd.2017.05.34
22. Collins MM, Corcoran P, Perry JJ. Anxiety and depression symptoms in patients with diabetes. Diabet Med 2009;26:153–61. https://doi.org/10.1111/j.1464-5491.2008.02648.x
23. Lloyd CE, Dyert PH, Barnett AH. Prevalence of symptoms of depression and anxiety in a diabetes clinic population. Diabet Med 2000;17:198–202.
24. Rajput R, Gehlawat P, Gehlan D, et al. Prevalence and predictors of depression and anxiety in patients of diabetes mellitus in a tertiary care center. *Indian J Endocrinol Metab* 2016;20:746. https://doi.org/10.4103/2230-8210.192924

25. Gavard JA, Lustman PJ, Clouse RE. Prevalence of depression in adults with diabetes: an epidemiological evaluation. *Diabetes Care* 1993;16:1167–78. https://doi.org/10.2337/DIACARE.16.8.1167

26. Ali N, Iyotsna VP, Kumar N, et al. Prevalence of depression among type 2 diabetes compared to healthy non diabetic controls. *J Assoc Physicians India* 2013;61:619–21.

27. Larijani B, Khoram M, Bayat S, et al. Association between depression and diabetes. *German J Psychiatry* 2004;7:62–5.

28. Parik P, Patel V. Health-related quality of life of patients with type 2 diabetes mellitus at a tertiary care hospital in India using EQ SD SL. *Indian J Endocrinol Metab* 2019;23:407–11. https://doi.org/10.4103/ijem.IJEM_29_19

29. Janssen MF, Szende A, Cabases J, et al. Population norms for the EQ-5D-3L: a cross-country analysis of population surveys for 20 countries. *Eur J Health Econ* 2019;20:205–16. https://doi.org/10.1007/s10198-018-0955-5

30. González-Castro TB, Escobar-Chan YM, Fesam A, et al. Higher risk of depression in individuals with type 2 diabetes and obesity: results of a meta-analysis. *J Health Psychol* 2019;26:1404–19. https://doi.org/10.1177/1359105319876326

31. Bailey RK, Mokinogho J, Kumar A. Racial and ethnic differences in depression: current perspectives. *Neuropsychiatr Dis Treat* 2019;15:603–09. https://doi.org/10.2147/NDT.S128584

32. Schmitt A, Bendig E, Baumeister H, et al. Associations of depression and diabetes distress with self-management behavior and glycemic control. *Health Psychol* 2020;40:113–14. https://doi.org/10.1037/hep0001037

33. Fisher L, Mullan JT, Arean P, et al. Diabetes distress but not clinical depression or depressive symptoms is associated with glycemic control in both cross-sectional and longitudinal analyses. *Diabetes Care* 2010;33:23–8. https://doi.org/10.2337/dc09-1238

34. Polonsky WH, Fisher L, Earles J, et al. Assessing psychosocial distress in diabetes: development of the Diabetes Distress Scale. *Diabetes Care* 2005;28:626–31. https://doi.org/10.2337/diacare.28.3.626

35. Bădescu SV, Tătaru C, Kobylińska L, et al. The association between diabetes mellitus and depression. *J Med Life* 2016;9:120–5.