



Chiang, J. I., Manski-Nankervis, J.-A., Thuraisingam, S., Jenkins, A., O'Neal, D., Mair, F. S., Jani, B. D., Nicholl, B. I. and Furler, J. (2020) Multimorbidity, glycaemic variability and time in target range in people with type 2 diabetes: a baseline analysis of the GP-OSMOTIC trial. *Diabetes Research and Clinical Practice*, 169, 108451.

(doi: [10.1016/j.diabres.2020.108451](https://doi.org/10.1016/j.diabres.2020.108451))

This is the Author Accepted Manuscript.

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

<https://eprints.gla.ac.uk/223746/>

Deposited on: 6 October 2020

1 **Multimorbidity, glycaemic variability and time in target range in people with type 2 diabetes: a**
2 **baseline analysis of the GP-OSMOTIC trial**

3

4 **Authors:**

5 **Jason I Chiang**¹

6 **Jo-Anne Manski-Nankervis**¹

7 **Sharmala Thuraisingam**¹

8 **Alicia Jenkins**²

9 **David O'Neal**³

10 **Frances S Mair**⁴

11 **Bhautesh Dinesh Jani**⁴

12 **Barbara I Nicholl**⁴

13 **John Furler**¹

14 1. Department of General Practice, University of Melbourne, Australia

15 2. NHMRC Clinical Trials Centre, University of Sydney, Australia

16 3. Department of Medicine, St Vincent's Hospital, University of Melbourne, Australia

17 4. General Practice and Primary Care, Institute of Health and Wellbeing, University of Glasgow, UK

18 **Contact for corresponding author:**

19 Mr Jason I Chiang

20 Address: Department of General Practice, University of Melbourne, Level 3 780 Elizabeth Street,

21 Melbourne, Vic 3010, Australia

22 Email: jason.chiang@unimelb.edu.au

23

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27

ABSTRACT

Aims:

To explore associations between multimorbidity condition counts (total; concordant (diabetes-related); discordant (unrelated to diabetes)) and glycaemia (HbA1c; glycaemic variability (GV); time in range (TIR)) using data from a randomised controlled trial examining effectiveness of continuous glucose monitoring (CGM) in people with type 2 diabetes (T2D).

Methods:

Cross-sectional study: 279 people with T2D using baseline data from the General Practice Optimising Structured MOonitoring To Improve Clinical outcomes (GP-OSMOTIC) trial from 25 general practices in Australia. Number of long-term conditions (LTCs) in addition to T2D used to quantify total/concordant/discordant multimorbidity counts. GV (measured by coefficient of variation (CV)) and TIR derived from CGM data. Multivariable linear regression models used to examine associations between multimorbidity counts, HbA1c (%), GV and TIR.

Results:

Mean (SD) age of participants 60.4 (9.9) years; 40.9% female. Multimorbidity was present in 89.2% of participants. Most prevalent comorbid LTCs: hypertension (57.4%), painful conditions (29.8%), coronary heart disease (22.6%) and depression (19.0%). No evidence of associations between multimorbidity counts, HbA1c, GV and TIR.

Conclusions:

While multimorbidity was common in this T2D cohort, it was not associated with HbA1c, CV or TIR. Future studies should explore factors other than glycaemia that contribute to the increased mortality observed in those with multimorbidity and T2D.

Keywords:

multimorbidity; glycaemia; HbA1c; glycaemic variability; time in range; continuous glucose monitoring (CGM); general practice; primary care

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34

1. INTRODUCTION

Multimorbidity is defined as the co-occurrence of two or more long term health conditions (LTCs) in an individual (1, 2). This is common in people with type 2 diabetes (T2D) where approximately 85% have at least one other LTC (3, 4). The often complicated clinical management of T2D can be more challenging in the presence of multimorbidity and the associated higher treatment burden related to having multiple LTCs (5). This can result in poorer outcomes including suboptimal glycaemic management which is a key component of clinical guidelines for T2D (6-8).

Although HbA1c is traditionally recognised as the gold standard for monitoring glycaemia, it does not characterise daily fluctuations in blood glucose including acute hyper- and hypoglycaemic events (9). In 2017 the Beyond A1c Movement, initiated by nine diabetes organisations around the globe, presented a unified case for the need to incorporate outcomes beyond HbA1c into regulatory decisions and clinical care (10). Two outcomes of importance identified were glycaemic variability (GV) and time in range (TIR) derived from data from continuous glucose monitoring (CGM) systems. CGM technology measures interstitial fluid glucose levels on a regular basis (every five to 15 minutes, depending on the device), providing insights into short-term fluctuations in glucose levels. Several measures of GV exist. The Beyond HbA1c Movement recommended that the coefficient of variation (CV) should be considered the primary measure of glycaemic variability (11) and that a CV $\geq 36\%$ is considered high variability. In 2019 another international consensus recommended that a range of 3.9-10.0 mmol/L be used to calculate TIR in people with T2D (12). This involves calculating the percentage of time that a person spends with their blood glucose levels within the recommended target range, which is usually measured over a defined time period. Both GV and TIR are dependent on medication, physical activity and diet, and GV is known to be associated with the development of micro- and macrovascular complications (13-15). However, no studies have explored the association between TIR and macrovascular complications (16, 17).

We recently conducted a systematic review of the effect of multimorbidity on mortality and glycaemic outcomes in people with T2D (18, 19). We identified 14 cross-sectional studies that demonstrated that the associations between multimorbidity and HbA1c were variable. Importantly, the review also identified that no studies had explored the relationship between multimorbidity, GV and TIR. An important limitation of our review was that we were not able to explore the effect of different types of multimorbid conditions. This is an important consideration in studies of multimorbidity in T2D (20). LTCs can be considered as either concordant or discordant with T2D (7).

1 LTCs that are closely related to T2D, such as hypertension and cardiovascular disease, are considered
2 concordant whereas unrelated conditions like asthma and cancer are considered as discordant.

3

4 It was therefore our aim to explore the associations between multimorbidity count (total,
5 concordant and discordant) and blood glucose (reflected by HbA1c, GV and TIR) using baseline data
6 from a randomised controlled trial examining the effectiveness of CGM in people with T2D in general
7 practice in Australia (21, 22).

8

9 **2. SUBJECTS, MATERIALS AND METHODS**

10 **2.1 Study design and participants**

11 This is a cross-sectional study consisting of 279 people with T2D using baseline data (October 2016 –
12 November 2017) from the General Practice Optimising Structured Monitoring To Improve Clinical
13 outcomes (GP-OSMOTIC) randomised controlled trial (RCT) (21, 22). To summarise, the GP-OSMOTIC
14 trial aimed to explore the effectiveness of a CGM device (FreeStyle Libre Pro® Flash Glucose
15 Monitoring System, Abbott Diabetes Care, Witney, Oxon, UK) used in the clinical care of people with
16 T2D in 25 general practices in Victoria, Australia (23). The inclusion criteria for the trial only included
17 adults (≥ 18 years) with a diagnosis of T2D, whose most recent HbA1c level (within 30 days prior to
18 recruitment) was 0.5% (6mmol/mol) above the general Australian target of 7% (53mmol/mol) (24). A
19 detailed description of the GP-OSMOTIC trial is provided elsewhere (21, 22).

20 **2.2 Procedures**

21 Multimorbidity is measured as a condition count of LTCs based on previous published literature (4,
22 20). This condition count was adapted for use in our cohort and consists of 35 individual LTCs where
23 eight conditions were concordant with T2D and the remainder discordant with T2D (Table S1). We
24 identified the LTCs based on the participant's medical history retrieved from their clinical electronic
25 medical records and on enrolment nurse-led survey interviews. Three variables were created for
26 multimorbidity: total number of LTCs, number of concordant conditions and number of discordant
27 conditions.

28 CGM data were collected at baseline of the GP-OSMOTIC trial, prior to any therapeutic intervention.
29 The CGM device was applied by clinically trained research assistants to the underside of the
30 participant's upper arm to measure individual interstitial fluid glucose levels in 15 minute intervals
31 for two weeks. After two weeks, the sensor was removed, and data were uploaded to Microsoft
32 Office Excel 365 (Microsoft Corp., Seattle, WA, USA) on a secure computer. The CGM data was not
33 available to the participants during the two-week period (i.e. it was masked). Survey and clinical data

1 were entered into REDCap® (REsearch Data CAPture software), a secure, web-based application
2 designed to support research data capture (25).

3 **2.3 Clinical outcome**

4 We had three glycaemic outcome measures of interest, all treated as continuous variables: HbA1c,
5 GV, and TIR. We used the most recently collected HbA1c at baseline. Both GV and TIR were
6 calculated using baseline CGM data. CV was used as the measure of GV based on the international
7 consensus (11) and was calculated using EasyGV® (26). TIR is defined as the percentage of time
8 spent in the consensus suggested target range of 3.9-10.0 mmol/L (12). The duration of CGM for
9 inclusion in the study was five to 14 days which is consistent with recommendations from the CGM
10 manufacturer (27).

11 **2.4 Statistical analysis**

12 Descriptive statistics were used to summarise overall characteristics of the participants. The
13 multimorbidity counts and prevalence of individual LTCs were also summarised. Summaries include
14 means and standard deviations for normally distributed continuous data and medians and
15 interquartile range for skewed continuous data, frequencies and percentages for categorical data.
16 Multivariable mixed-effects linear regression models were used to examine the association between
17 each of the multimorbidity counts (total; total of concordant conditions; total of discordant
18 conditions) and each of our outcomes of interest (HbA1c; CV; TIR) adjusting for age, gender,
19 socioeconomic status (measured by Index of Relative Socioeconomic Disadvantage (IRSD) deciles)
20 (28), body mass index (BMI), smoking status, insulin use, and number of non-insulin hypoglycaemic
21 medications. Duration of diabetes was excluded from the adjusted model due to multicollinearity
22 with age. In our regression models, all co-variables were treated as fixed effects and the general
23 practice as a random effect to allow for the correlation of our outcomes of interest within each
24 practice. All analyses were carried out using STATA version 15.1 (StataCorp, College Station, Texas).
25 Ethics approval for this study was obtained from the Human Research Ethics Committee at the
26 University of Melbourne (Ethics ID 1647151.1).

27

1

2 **3. RESULTS**

3 In our cohort of 279 people with T2D attending Victorian general practice the mean (SD) age was
 4 60.4 (9.9) years and 40.9% were female. Mean (SD) HbA1c was 8.9 (1.2)% (74 (13)mmol/mol), CV
 5 30.0 (8.3)% and TIR 41.1 (25.6)% and number of days that CGM was worn was 12.3 (2.4) days.
 6 Multimorbidity was present in the majority (249 (89.2%)) of participants. Table 1 describes the
 7 overall characteristics of our study participants.

8 **Table 1. Characteristics of participants with type 2 diabetes**

Demographics	Total (n = 279)
Potential confounding variables	
Age, years, mean (SD)	60.4 (9.9)
Female, n(%)	114 (40.9)
IRSD Decile, n(%)	
Decile 1- most deprived	24 (8.7)
Decile 2	59 (21.5)
Decile 3	13 (4.7)
Decile 4	34 (12.4)
Decile 5	9 (3.3)
Decile 6	41 (14.9)
Decile 7	45 (16.4)
Decile 8	23 (8.4)
Decile 9	22 (8.0)
Decile10 – least deprived	5 (1.8)
Missing	4 (1.4)
Current smoker, n(%)	39 (14.0)
BMI, kgm⁻², median (IQR)	33.9 (7.8)
Know diabetes duration, years, median (IQR)	12 (9, 20)
Duration of r-CGM use, days, mean (SD)	12.3 (2.4)
Prescribed insulin, n (%)	143 (51.3)
Number of non-insulin hypoglycaemic agents, n(%)	
0 agents	11 (3.9)
1 agent	35 (12.5)
2 agents	142 (50.9)
3 agents	81 (29.0)
≥4 agents	10 (3.6)
Outcome variables	
HbA1c, %, mean (SD)	8.9 (1.2)
HbA1c, mmol/mol, mean (SD)	74 (13)
Glycaemic variability, CV, %, mean (SD)	30.0 (8.3)
High glycaemic variability (CV≥36%), n (%)	57 (20.4)
Time-in-range, %, mean (SD)	41.1 (25.6)
Time-above-range, % mean (SD)	56.6 (27.2)

Time-below-range, % mean (SD)	2.3 (5.9)
Predictor variable	
Number of chronic conditions, n(%)	
T2D only	30 (10.8)
T2D + 1 chronic condition	70 (25.1)
T2D + 2 chronic condition	68 (24.4)
T2D + 3 chronic condition	42 (15.1)
T2D + ≥4 chronic conditions	69 (24.7)

1 T2D, type 2 diabetes; SD, standard deviation; IRSD, Index of Relative Socioeconomic Disadvantage;
2 IQR, inter-quartile range

3

4 The prevalence of individual LTCs included in our multimorbidity counts are shown in Table 2. Of the
5 279 study participants, 192 (68.8%) people had at least one concordant condition and 183 (65.6%)
6 had at least one discordant condition in addition to T2D. Hypertension (57.4%) was the most
7 prevalent concordant condition followed by coronary heart disease (22.6%). Painful conditions
8 (29.8%) was the most prevalent discordant condition followed by depression (19.0%).

9

10 **Table 2. Prevalence of individual multimorbid conditions in participants with type 2 diabetes**

Presence of chronic conditions concordant with type 2 diabetes, n (%)	N=279
At least 1 chronic condition concordant with diabetes	192 (68.8)
Hypertension	160 (57.4)
Coronary heart disease	63 (22.6)
Peripheral vascular disease	8 (2.9)
Chronic kidney disease	17 (6.1)
Stroke/TIA	9 (3.2)
Diabetic retinopathy	28 (10.0)
Diabetic neuropathy	28 (10.0)
Atrial fibrillation	12 (4.3)
Presence of chronic conditions discordant with type 2 diabetes, n (%)	N=279
At least 1 chronic condition discordant with diabetes	183 (65.6)
Depression	53 (19.0)
Painful conditions	83 (29.8)
Asthma	39 (14.0)
GORD	39 (14.0)
Thyroid disorders	14 (5.0)
Rheumatoid arthritis and other connective tissue disorders	6 (2.2)
COPD	12 (4.3)
Anxiety	13 (4.7)
Irritable bowel syndrome	1 (0.4)
Cancer	7 (2.5)
Alcohol problems	0 (0)
Other psychoactive substance misuse	0 (0)
Treated constipation	0 (0)
Diverticular disease	16 (5.7)

Prostate disorders	6 (2.2)
Glaucoma	5 (1.8)
Epilepsy	0 (0)
Dementia	0 (0)
Schizophrenia/bipolar disorder	4 (1.4)
Psoriasis/eczema	21 (7.5)
Inflammatory bowel disease	1 (0.4)
Migraine	4 (1.4)
Chronic sinusitis	1 (0.4)
Anorexia/bulimia	0 (0)
Bronchiectasis	0 (0)
Parkinson's disease	1 (0.4)
Multiple sclerosis	0 (0)
Viral hepatitis	1 (0.4)
Chronic liver disease	4 (1.4)

1 T2D, type 2 diabetes; TIA, transient ischaemic attack; COPD, chronic obstructive pulmonary disease;
2 GORD, gastroesophageal reflux disease

3
4

5 The mean difference in HbA1c, CV and TIR between participants with different multimorbidity
6 counts are presented in Tables 3, 4 and 5, respectively. The reference group was people with T2D
7 and no other LTCs. For all increasing counts of multimorbidity (total, concordant and discordant)
8 there were no statistically significant associations with HbA1c, GV nor TIR.

9
10

Table 3. Multivariable linear regression model: Relationship between HbA1c (%) and multimorbidity in participants with type 2 diabetes.

Predictor variables	Non-adjusted			Adjusted		
	β (SE)	95% CI	P	β (SE)	95% CI	p
Categories of diabetes and multimorbidities						
Diabetes only (reference)						
Diabetes plus 1 chronic condition	-0.31 (0.26)	-0.84, 0.21	0.240	-0.27 (0.29)	-0.83, 0.29	0.345
Diabetes plus 2 chronic conditions	-0.15 (0.27)	-0.68, 0.38	0.575	-0.22 (0.29)	-0.79, 0.35	0.450
Diabetes plus 3 chronic conditions	-0.00 (0.29)	-0.58, 0.57	0.996	0.06 (0.32)	-0.56, 0.68	0.844
Diabetes plus ≥ 4 chronic conditions	-0.20 (0.27)	-0.73, 0.32	0.460	-0.20 (0.30)	-0.78, 0.38	0.504
Categories of diabetes and concordant conditions						
Diabetes only (reference)						
Diabetes plus 1 concordant condition	-0.18 (0.18)	-0.52, 0.17	0.317	-0.10 (0.19)	-0.47, 0.26	0.578
Diabetes plus 2 concordant conditions	-0.04 (0.22)	-0.46, 0.39	0.865	-0.04 (0.24)	-0.50, 0.43	0.880
Diabetes plus 3 concordant conditions	0.04 (0.29)	-0.54, 0.60	0.915	0.21(0.31)	-0.39, 0.83	0.488
Diabetes plus ≥ 4 concordant conditions	-0.06 (0.39)	-0.83, 0.71	0.884	-0.01 (0.42)	-0.83, 0.80	0.979
Categories of diabetes and discordant conditions						
Diabetes only (reference)						
Diabetes plus 1 discordant condition	0.14 (0.18)	-0.21, 0.50	0.433	0.13 (0.19)	-0.26, 0.51	0.517
Diabetes plus 2 discordant conditions	0.26 (0.20)	-0.13, 0.66	0.183	0.21 (0.21)	-0.20, 0.61	0.320
Diabetes plus 3 discordant conditions	-0.14 (0.27)	-0.68, 0.40	0.611	-0.20 (0.29)	-0.78, 0.37	0.488
Diabetes plus ≥ 4 discordant conditions	0.03 (0.35)	-0.65, 0.72	0.927	0.11 (0.38)	-0.63, 0.87	0.761

SE: Standard error

Adjusting for age, gender, socioeconomic status, BMI, smoking status, insulin use, and number of non-insulin hypoglycaemic medication. All co-variates were treated as fixed effects and the general practice as a random effect to allow for the correlation of HbA1c within each practice.

Table 4. Multivariable linear regression model: Relationship between glycaemic variability (CV) and multimorbidity in participants with type 2 diabetes.

Predictor variables	Non-adjusted			Adjusted		
	β (SE)	95% CI	P	β (SE)	95% CI	p
Categories of diabetes and multimorbidities						
Diabetes only (reference)						
Diabetes plus 1 chronic condition	2.52 (1.76)	-0.94, 5.97	0.154	0.09 (1.75)	-3.34, 3.52	0.959
Diabetes plus 2 chronic conditions	4.44 (1.78)	0.96, 7.93	0.012	1.70 (1.78)	-1.78, 5.18	0.338
Diabetes plus 3 chronic conditions	1.97 (1.94)	-0.83, 5.78	0.309	-1.20 (1.93)	-4.99, 2.58	0.533
Diabetes plus ≥ 4 chronic conditions	3.93 (1.81)	0.39, 7.48	0.029	-0.45 (1.87)	-4.11, 3.21	0.808
Categories of diabetes and concordant conditions						
Diabetes only (reference)						
Diabetes plus 1 concordant condition	2.92 (1.14)	0.70, 5.15	0.010	1.34 (1.11)	-0.85, 5.53	0.230
Diabetes plus 2 concordant conditions	4.84 (1.39)	2.11, 7.56	0.001	2.57 (1.42)	-0.20, 5.36	0.070
Diabetes plus 3 concordant conditions	0.49 (1.88)	-3.19, 4.17	0.794	-1.43 (1.86)	-5.08, 2.22	0.442
Diabetes plus ≥ 4 concordant conditions	5.53 (2.57)	0.50, 10.55	0.031	-0.98 (2.65)	-6.18, 4.21	0.711
Categories of diabetes and discordant conditions						
Diabetes only (reference)						
Diabetes plus 1 discordant condition	-0.34 (1.23)	-2.75, 2.07	0.782	-1.33 (1.17)	-3.63, 0.97	0.258
Diabetes plus 2 discordant conditions	-0.61 (1.38)	-3.31, 2.09	0.657	-1.84 (1.29)	-4.37, 0.68	0.153
Diabetes plus 3 discordant conditions	0.39 (1.83)	-3.20, 3.98	0.832	-1.10 (1.77)	-4.57, 2.37	0.536
Diabetes plus ≥ 4 discordant conditions	-1.45 (2.35)	-6.06, 3.15	0.536	-2.31 (2.33)	-6.86, 2.25	0.322

SE: Standard error

Adjusting for age, gender, socioeconomic status, BMI, smoking status, insulin use, and number of non-insulin hypoglycaemic medication. All co-variables were treated as fixed effects and the general practice as a random effect to allow for the correlation of GV within each practice.

Table 5. Multivariable linear regression model: Relationship between percentage time-in-range and multimorbidity in participants with type 2 diabetes.

Predictor variables	Non-adjusted			Adjusted		
	β (SE)	95% CI	P	β (SE)	95% CI	p
Categories of diabetes and multimorbidities						
Diabetes only (reference)						
Diabetes plus 1 chronic condition	3.09 (5.58)	-7.84, 14.04	0.579	0.92 (5.96)	-10.77, 12.61	0.877
Diabetes plus 2 chronic conditions	-5.84 (5.63)	-16.85, 5.17	0.299	-6.75 (6.04)	-18.58, 5.09	0.264
Diabetes plus 3 chronic conditions	-2.46 (6.13)	-14.47, 9.55	0.688	-6.51 (6.56)	-19.37, 6.36	0.322
Diabetes plus ≥ 4 chronic conditions	-2.93 (5.66)	-14.01, 8.16	0.605	-4.96 (6.28)	-17.26, 7.34	0.430
Categories of diabetes and concordant conditions						
Diabetes only (reference)						
Diabetes plus 1 concordant condition	1.71 (3.69)	-5.51, 8.94	0.642	0.77 (3.84)	-6.76, 8.30	0.841
Diabetes plus 2 concordant conditions	-6.02 (4.49)	-14.82, 2.78	0.180	-7.95 (4.85)	-17.47, 1.56	0.101
Diabetes plus 3 concordant conditions	-0.66 (6.09)	-12.60, 11.28	0.914	-3.73 (6.43)	-16.34, 8.86	0.561
Diabetes plus ≥ 4 concordant conditions	4.89 (8.24)	-11.27, 21.04	0.553	2.64 (8.71)	-14.43, 19.72	0.762
Categories of diabetes and discordant conditions						
Diabetes only (reference)						
Diabetes plus 1 discordant condition	-1.92 (3.81)	-9.39, 5.54	0.615	-2.30 (3.98)	-10.11, 5.50	0.563
Diabetes plus 2 discordant conditions	-8.59 (4.19)	-16.81, -0.37	0.040	-7.87 (4.24)	-16.18, 0.43	0.063
Diabetes plus 3 discordant conditions	5.85 (5.70)	-5.33, 17.03	0.305	8.40 (5.98)	-3.32, 20.11	0.160
Diabetes plus ≥ 4 discordant conditions	-8.65 (7.28)	-22.92, 5.61	0.234	-9.52 (7.82)	-24.86, 5.82	0.224

SE: Standard error

Adjusting for age, gender, socioeconomic status, BMI, smoking status, insulin use, and number of non-insulin hypoglycaemic medication. All co-variables were treated as fixed effects and the general practice as a random effect to allow for the correlation of TIR within each practice.

1 4. DISCUSSION

2 In this study, we examined associations between multimorbidity and measures of glycaemia in 279
3 people with T2D in Australian general practice using data from the GP-OSMOTIC trial collected at the
4 time of patient enrolment. The majority of people with T2D in this cohort (89.2%) were living with
5 multimorbidity. We used CGM data to derive GV and TIR in this cohort. Our findings suggest that
6 there was no significant relationship between multimorbidity (total, concordant and discordant) and
7 various measures of glycaemia, including HbA1c, GV (using CV), and TIR, reflecting glucose control
8 over 3-months to several weeks respectively.

9

10 Uncertainty exists about the association between multimorbidity and HbA1c in people with T2D (18).
11 We did not find significant relationships between multimorbidity and a single concurrent measure of
12 HbA1c, nor CGM related measures of glycaemia in this cohort. Our findings may be linked to the
13 higher health care utilisation (29) and better quality of care (30) seen in people with other LTCs.
14 Higher health care utilisation may result in more opportunities for clinical interventions leading to
15 better glycaemic management. We did not explore health utilisation, nor did we evaluate HbA1c
16 measures over the longer term.

17

18 Evidence suggests associations between higher GV and micro- and macrovascular complications (13,
19 14) including the development of diabetes peripheral neuropathy (31), and the development of
20 cardiovascular diseases (32). Lower TIR has been linked to the development of diabetic retinopathy
21 and diabetic nephropathy (15). There is good evidence of a relationship between higher GV, lower
22 TIR and complications of T2D, yet we did not find any significant associations between concordant
23 LTCs (which include some important complications of T2D), GV and TIR.

24

25 To the best of our knowledge, this is the first study to explore the effect of the total burden of
26 disease reflected in multimorbidity on GV and TIR in people with T2D. The prevalence of
27 multimorbidity and individual LTCs in this study align with the prevalence numbers found in studies
28 of community cohorts of people with T2D in the UK and Taiwan (4). This suggests that a strength of
29 this study is that we could capture multimorbidity and LTCs similar to the general population of
30 people with T2D despite using a specialised RCT T2D cohort in general practice. There are some
31 limitations to note for our study. This was a cross-sectional analysis of a relatively small sample size
32 using baseline data from the GP-OSMOTIC trial, which was powered to detect differences in HbA1c
33 between the intervention and control groups. Therefore, there may be insufficient statistical power
34 to observe differences in GV and TIR across different multimorbidity categories. We therefore did

1 not explore the effects of individual LTCs on glycaemic measures. Information on LTCs for this cohort
2 was only collected at baseline and we were unable to model for changes in multimorbidity.
3 Therefore, a limitation of our study is that we were unable to consider the temporality and duration
4 of the conditions in addition to diabetes. Another limitation is that the study only included people
5 attending general practice. It is possible that people attending general practice, as opposed to those
6 receiving care from specialists, may have a lower GV as we observed the mean (SD) CV was 30.0
7 (8.3)% which was below the consensus cut-off of 36% defining high GV (11). As a result, we do not
8 know if our results apply to the population that experience higher levels of GV. Therefore, those
9 with worse GV, who may be seeing specialists and attending hospital clinics may not be represented.
10 However, this cohort of people with T2D had HbA1c levels significantly above the recommended
11 target. Although the mean CV of this cohort was not high as determined by the consensus cut-off,
12 the mean (SD) TIR of 41.1 (25.6)% was relatively low. The higher levels of HbA1c and low TIR in this
13 cohort may be linked to why we did not observe significant differences in our outcomes between the
14 different categories of multimorbidity. Detecting a difference in our outcomes might have been
15 more likely in a cohort with a greater spread of HbA1c, CV and TIR.

16

17 There is an association between multimorbidity and increased mortality in people with T2D (4, 18).
18 We explored multimorbidity's effects on measures of blood glucose as a way to help us understand
19 the underlying mechanisms to the increased mortality seen in those with LTCs. Our findings suggest
20 that future studies should explore factors other than glycaemic measures, that could contribute to
21 the increased mortality that has been observed elsewhere. Future research involving larger patient
22 populations to examine how clinicians and people with T2D utilise CGM and interpret CGM outputs
23 to approach glycaemic targets and make treatment decisions in the context of multimorbidity are
24 warranted.

25

26 **CONCLUSION**

27 In 279 well characterised people with T2D in Australian general practice, we found no significant
28 associations between multimorbidity counts, HbA1c, GV and TIR. This study, together with recent
29 publications on this topic (4, 18), suggest that out of target glycaemic levels do not explain the
30 increased mortality seen in those with T2D and multimorbidity. Future studies should try to identify
31 which factors, other than glycaemic measures, contribute to the increased mortality in those with
32 T2D and multimorbidity.

33

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15

ACKNOWLEDGEMENTS

Source of funding

The GP-OSMOTIC trial was supported by a Project Grant from the National Health and Medical Research Council (NHMRC) of Australia (ID APP1104241). Additional funding was provided by Sanofi Australia. In-kind support (Flash Libre Pro reader devices, sensors, and software) was provided by Abbott Diabetes Care. JC was supported by a NHMRC postgraduate scholarship (ID APP1168372). AJ was supported by a NHMRC Practitioner Fellowship and was a Sydney Medical School Foundation Fellow. JMN was supported by a Next Generation Clinical Researchers Program – TRIP Fellowship Funded from the Medical Research Future Fund.

Declaration of competing interest

No competing financial interests exist.

1

2 REFERENCES

- 3 1. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of
4 multimorbidity and implications for health care, research, and medical education: a cross-sectional
5 study. *Lancet*. 2012;380(9836):37-43.
- 6 2. Smith SM, Ferede A, O'Dowd T. Multimorbidity in younger deprived patients: an exploratory
7 study of research and service implications in general practice. *BMC family practice*. 2008;9:6.
- 8 3. Australian Bureau of Statistics. National Health Survey: First Result, 2014-15. 2015.
- 9 4. Chiang JI, Hanlon P, Li TC, Jani BD, Manski-Nankervis JA, Furler J, et al. Multimorbidity,
10 mortality, and HbA1c in type 2 diabetes: A cohort study with UK and Taiwanese cohorts. *PLoS Med*.
11 2020;17(5):e1003094.
- 12 5. Mair FS, May CR. Thinking about the burden of treatment. *Bmj*. 2014;349:g6680.
- 13 6. Harris MF, Dennis S, Pillay M. Multimorbidity: Negotiating priorities and making progress.
14 *AFP*. 2013;42(12):850-4.
- 15 7. Piette JD, Kerr EA. The impact of comorbid chronic conditions on diabetes care. *Diabetes*
16 *care*. 2006;29(3):725-31.
- 17 8. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas
18 or insulin compared with conventional treatment and risk of complications in patients with type 2
19 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):837-
20 53.
- 21 9. Cox D, Gonder-Frederick L, McCall A, Kovatchev B, Clarke W. The effects of glucose
22 fluctuation on cognitive function and QOL: the functional costs of hypoglycaemia and
23 hyperglycaemia among adults with type 1 or type 2 diabetes. *Int J Clin Pract Suppl*. 2002(129):20-6.
- 24 10. Need for Regulatory Change to Incorporate Beyond A1C Glycemic Metrics. *Diabetes care*.
25 2018;41(6):e92.
- 26 11. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International
27 Consensus on Use of Continuous Glucose Monitoring. *Diabetes care*. 2017;40(12):1631-40.
- 28 12. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical Targets for
29 Continuous Glucose Monitoring Data Interpretation: Recommendations From the International
30 Consensus on Time in Range. *Diabetes care*. 2019:dci190028.
- 31 13. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, et al. Activation of oxidative stress by
32 acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2
33 diabetes. *Jama*. 2006;295(14):1681-7.
- 34 14. Nalysnyk L, Hernandez-Medina M, Krishnarajah G. Glycaemic variability and complications in
35 patients with diabetes mellitus: evidence from a systematic review of the literature. *Diabetes Obes*
36 *Metab*. 2010;12(4):288-98.
- 37 15. Beck RW, Bergenstal RM, Riddlesworth TD, Kollman C, Li Z, Brown AS, et al. Validation of
38 Time in Range as an Outcome Measure for Diabetes Clinical Trials. *Diabetes care*. 2019;42(3):400.
- 39 16. Guo Q, Zang P, Xu S, Song W, Zhang Z, Liu C, et al. Time in Range, as a Novel Metric of
40 Glycemic Control, Is Reversely Associated with Presence of Diabetic Cardiovascular Autonomic
41 Neuropathy Independent of HbA1c in Chinese Type 2 Diabetes. *J Diabetes Res*. 2020;2020:5817074-.
- 42 17. Lu J, Ma X, Zhou J, Zhang L, Mo Y, Ying L, et al. Association of Time in Range, as Assessed by
43 Continuous Glucose Monitoring, With Diabetic Retinopathy in Type 2 Diabetes. *Diabetes Care*.
44 2018;41(11):2370-6.
- 45 18. Chiang JI, Jani BD, Mair FS, Nicholl BI, Furler J, O'Neal D, et al. Associations between
46 multimorbidity, all-cause mortality and glycaemia in people with type 2 diabetes: A systematic
47 review. *PLoS One*. 2018;13(12):e0209585.
- 48 19. Chiang JI, Furler J, Mair FS, Jani B, Nicholl BI, Jenkins A, et al. Impact of multimorbidity count
49 on all-cause mortality and glycaemic outcomes in people with type 2 diabetes: a systematic review
50 protocol. *BMJ open*. 2018;8(4).

- 1 20. Jani BD, Hanlon P, Nicholl BI, McQueenie R, Gallacher KI, Lee D, et al. Relationship between
2 multimorbidity, demographic factors and mortality: findings from the UK Biobank cohort. *BMC Med.*
3 2019;17(1):74.
- 4 21. Furler J, O'Neal D, Speight J, Blackberry I, Manski-Nankervis JA, Thuraisingam S, et al. Use of
5 professional-mode flash glucose monitoring, at 3-month intervals, in adults with type 2 diabetes in
6 general practice (GP-OSMOTIC): a pragmatic, open-label, 12-month, randomised controlled trial.
7 *Lancet Diabetes Endocrinol.* 2020;8(1):17-26.
- 8 22. Furler J, O'Neal DN, Speight J, Blackberry I, Manski-Nankervis JA, Thuraisingam S, et al. GP-
9 OSMOTIC trial protocol: an individually randomised controlled trial to determine the effect of
10 retrospective continuous glucose monitoring (r-CGM) on HbA1c in adults with type 2 diabetes in
11 general practice. *BMJ Open.* 2018;8(7):e021435.
- 12 23. Thuraisingam S, Chondros P, Catchpool M, Dalziel K, Manski-Nankervis JA, Speight J, et al.
13 Update on the General Practice Optimising Structured Monitoring to Improve Clinical Outcomes in
14 Type 2 Diabetes (GP-OSMOTIC) trial: statistical analysis plan for a multi-centre randomised
15 controlled trial. *Trials.* 2019;20(1):93.
- 16 24. Cheung NW, Conn JJ, d'Emden MC, Gunton JE, Jenkins AJ, Ross GP, et al. Position statement
17 of the Australian Diabetes Society: individualisation of glycated haemoglobin targets for adults with
18 diabetes mellitus. *Medical Journal of Australia.* 2009;191(6):339-44.
- 19 25. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data
20 capture (REDCap)--a metadata-driven methodology and workflow process for providing translational
21 research informatics support. *Journal of biomedical informatics.* 2009;42(2):377-81.
- 22 26. Hill NR, Oliver NS, Choudhary P, Levy JC, Hindmarsh P, Matthews DR. Normal reference
23 range for mean tissue glucose and glycemic variability derived from continuous glucose monitoring
24 for subjects without diabetes in different ethnic groups. *Diabetes technology & therapeutics.*
25 2011;13(9):921-8.
- 26 27. Freestyle Libre Flash Glucose Monitoring System User's Manual [Available from:
27 https://freestyleserver.com/Payloads/IFU/2017_oct/ART28697-409_rev-A_Web.pdf.
28
- 28 28. Australian Bureau of Statistics (ABS). Census of population and housing: Socio-economic
29 indexes for areas (SEIFA), Australia, 2011: Australian Bureau of Statistics; 2013 [Available from:
30 <http://www.abs.gov.au/ausstats/abs@.nsf/DetailsPage/2033.0.55.0012011?OpenDocument>.
31
- 31 29. Luijckx H, Schermer T, Bor H, van Weel C, Lagro-Janssen T, Biermans M, et al. Prevalence and
32 incidence density rates of chronic comorbidity in type 2 diabetes patients: an exploratory cohort
33 study. *BMC Medicine.* 2012;10(1):128.
- 34 30. Higashi T, Wenger NS, Adams JL, Fung C, Roland M, McGlynn EA, et al. Relationship between
35 number of medical conditions and quality of care. *The New England journal of medicine.*
36 2007;356(24):2496-504.
- 37 31. Xu F, Zhao L-h, Su J-b, Chen T, Wang X-q, Chen J-f, et al. The relationship between glycemic
38 variability and diabetic peripheral neuropathy in type 2 diabetes with well-controlled HbA1c.
39 *Diabetology & Metabolic Syndrome.* 2014;6(1):139.
- 40 32. Tang X, Li S, Wang Y, Wang M, Yin Q, Mu P, et al. Glycemic variability evaluated by
41 continuous glucose monitoring system is associated with the 10-y cardiovascular risk of diabetic
42 patients with well-controlled HbA1c. *Clin Chim Acta.* 2016;461:146-50.

43

44