DR AMY E E MORRISON (Orcid ID : 0000-0003-3353-1863)

DR LAURA GRAY (Orcid ID : 0000-0002-9284-9321)

PROFESSOR KAMLESH KHUNTI (Orcid ID : 0000-0003-2343-7099)

PROFESSOR MELANIE J DAVIES (Orcid ID : 0000-0002-9987-9371)

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The Microalbuminuria Education Medication and Optimisation (MEMO) study: 4 years follow-up of

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multifactorial intervention in high-risk individuals with type 2 diabetes

W. Crasto¹, A. E. Morrison³, L. J. Gray², E. John², J. Jarvis³, J. Brela³, K. Khunti^{1,3}, J. Troughton³, I. G. Lawrence⁴, P. G. McNally⁴ and M. J. Davies^{1,3}

¹Diabetes Research Centre and ²Department of Health Sciences, University of Leicester, ³Leicester Diabetes Centre and ⁴Department of Diabetes and Endocrinology, University Hospitals of Leicester NHS Trust, Leicester, UK

Correspondence to: Amy E. Morrison. E-mail: amymorrison15@doctors.org.uk

What's new?

- A complex intervention that addresses control of multiple risk factors with structured self-management education in high-risk individuals with type 2 diabetes shows favourable improvements in cardio-metabolic risk compared with usual diabetes care.
- Structured self-management education programmes are vital because they empower individuals to learn more about their own long-term condition, and facilitate skills-based learning and decision support (i.e. provide guidance for implementing evidence-based care).
- A recent systematic review that studied the effects of multifaceted diabetes care in European populations showed that biomedical outcomes improved significantly in people with newly diagnosed diabetes compared with those with prevalent diabetes. Our study adds to this body of evidence and suggests that a comprehensive multifactorial care intervention with structured self-management education is beneficial in people with established type 2 diabetes.

Abstract

Aims The Microalbuminuria Education Medication and Optimisation (MEMO) study, revealed improved cardiovascular risk and glycaemic control with 18 months of intensive

multifactorial intervention in high-risk people with type 2 diabetes, without any increase in severe hypoglycaemia. Our aim was to assess longer-term outcomes at 4-year follow-up in these participants.

Methods Some 189 individuals with type 2 diabetes and microalbuminuria were recruited from a multi-ethnic population in Leicestershire, UK. The intervention group ($n = 95$) received multifactorial intervention with self-management education, and the control group ($n = 94$) received usual care. The primary outcome was change in HbA_{1c}, and secondary outcomes were blood pressure (BP), cholesterol, microalbuminuria, estimated GFR, cardiovascular risk scores and major adverse cardiovascular events.

Results Some 130 participants (68.7%), mean (SD) age 60.8 (10.4) years, duration of diabetes 11.5 (9.7) years, completed 4 years of follow-up. Mean change [95% confidence intervals (CI)] in HbA_{1c} over 4 years was greater with intensive intervention compared with control (-3 mmol/mol, 95% CI $-4.95, -1.11$; -0.4% , 95% CI $-0.67, -0.15$; $P = 0.002$). Significant improvements over the 4 years were also seen in systolic BP (-7.3 mmHg, 95% CI $-11.1, -3.5$; $P < 0.001$), diastolic BP (-2.9 mmHg, 95% CI $-5.4, -0.3$; $P = 0.026$), cholesterol (-0.3 mmol/l, 95% CI $-0.52, -0.12$; $P = 0.002$), and 10-year coronary heart disease (-5.3 , 95% CI $-8.2, -2.3$; $P < 0.001$) and stroke risk (-4.4 , 95% CI $-7.5, -1.3$; $P < 0.001$).

Conclusion Multifactorial intervention with structured diabetes self-management education compared with usual diabetes care has benefits for cardio-metabolic risk factor profile. There was no increase in severe hypoglycaemia and cardiovascular mortality despite intensive glycaemic control, although the study was not powered to assess these outcomes.

Clinical Trial Registration No.: ISRCTN83140074

<H1>Introduction

Microalbuminuria is an easy, accessible marker of an atherogenic milieu and diffuse vascular injury [1]. It is an independent predictor of microvascular and macrovascular complications of type 2 diabetes, which are a major cause of morbidity and mortality in individuals with type 2 diabetes [2–4]. Management of these complications places huge demands on both the individual and healthcare resources, especially as the prevalence of this multimorbid condition continues to rise [5,6]. The constellation of modifiable risk factors including hyperglycaemia, hypertension, hypercholesterolemia, obesity and smoking, which predispose

to vascular disease, are also commonly seen in individuals with type 2 diabetes and microalbuminuria; this suggests that the synergistic effect of simultaneous targeted control of multiple risk factors is key to reducing vascular risk [7,8].

Intensive self-management behaviours in individuals with type 2 diabetes, including adherence to dietary and exercise advice, medication adherence, medication optimization and diabetes self-management, are beneficial to improve cardiovascular outcomes [9,10]. Self-management education is therefore an important determinant in the successful management of this challenging chronic condition [11,12].

In the Steno-2 study, multifactorial intervention in individuals with type 2 diabetes and microalbuminuria significantly reduced microvascular and macrovascular events and cardiovascular mortality [7, 13]. After two decades of follow-up, the study reported 7.9 years of life gained with intensive multifactorial intervention in this high-risk cohort [7].

The Microalbuminuria Education and Medication Optimisation study (MEMO) used a similar design; however, the intervention group received intensive, targeted, multifactorial care with structured self-management education based on the Diabetes Education and Self-Management for Ongoing and Newly Diagnosed (DESMOND) model of self-management education [11,12,14]. Other key differences were that the study recruited high-risk individuals with type 2 diabetes and microalbuminuria from primary care and specialist clinics within a multi-ethnic population in Leicestershire, UK, thus allowing for broad generalization of the study findings in other settings [8]. After 18 months of multifactorial intervention, the study showed greater improvements in metabolic control and cardiovascular risk profile, with lower rates of moderate and no severe hypoglycaemic events despite pursuing tight glycaemic control in the intervention group compared with control.

This article reports long-term effects of the 18-month, intensive multifactorial intervention on glycaemic control, cardio-metabolic risk factor control and cardiovascular outcomes including major adverse cardiovascular events at and over 4 years of follow-up.

<H1>Methods

The design and methods for participant inclusion, randomization, treatment and initial follow-up have been reported previously [8].

<H2>Study participants

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In brief, the MEMO study recruited 189 individuals aged between 25 and 80 years diagnosed with type 2 diabetes (on diet, oral glucose-lowering agents or insulin) and microalbuminuria, referred from both primary care and secondary care (specialist diabetes clinics) [8].

<H2>Study design

The study was a randomized, open-labelled, parallel-group, prospective trial. Individuals were randomized to an intensive intervention group ($n = 95$) or control ($n = 94$) to receive standard care [based on the Leicestershire diabetes guidelines for the management of individuals with type 2 diabetes; adapted National Institute for Health and Care Excellence (NICE) 2008 guidelines for the management of individuals with type 2 diabetes] by their own healthcare provider [15,16]. The original study was powered to assess differences between the treatment groups in change from baseline HbA_{1c} at 18 months.

The intensive, targeted, multifactorial intervention was delivered for 18 months with participants being followed up on a one-to-one basis at 3-monthly intervals. Structured education was based on the DESMOND model of education and was delivered by trained DESMOND educators [11,12]. At the start of the education intervention, all intensive study participants attended a 3-h group education session which was divided into blocks of between eight and ten participants per group, focusing on the importance and relevance of microalbuminuria in type 2 diabetes. The information was provided using easy to understand, non-medical language, with pictorial depictions of the kidneys and blood vessels to demonstrate the role of microalbuminuria, and its impact on renal and cardiovascular systems. Strong emphasis was placed on the importance of controlling modifiable cardiovascular risk factors including HbA_{1c}, blood pressure (BP), cholesterol, smoking and lifestyle risk factors such as diet and exercise. The second phase of the 1-h self-management education sessions were held in a group format delivered by one educator and blocks of six participants per group, focusing on BP, lipid levels, blood glucose, insulin self-management, food maps and weight management. The sessions were individualized allowing participants to choose any preferred initial session they wished to attend followed by participation at multiple sessions.

Individual study visits led by the study physician also focused on educating participants on increasing physical activity, lifestyle changes and medication adherence. Treatment targets for HbA_{1c} ≤ 48 mmol/mol ($\leq 6.5\%$), BP $\leq 130/70$ mmHg, total cholesterol ≤ 3.5 mmol/l and LDL-cholesterol ≤ 2.0 mmol/l (or a 30% reduction below baseline total cholesterol levels)

were individualized and discussed at each visit. Participants in the intervention group were given a BP monitor for ambulatory BP monitoring to record and discuss readings that were outside the target range. A blood glucose meter was provided only to individuals on insulin therapy to aid day-to-day insulin self-management and alert study staff to difficulties in managing hyperglycaemia or hypoglycaemia. Optimization of medications to achieve individualized targets was carried out in a step-wise manner (based on NICE 2008 guidelines for the management of individuals with type 2 diabetes) taking care to avoid adverse events including hypoglycaemia [15]. Hypoglycaemic events (≤ 3.9 mmol/l) were recorded by participants and graded according to severity: Grade 1 (minor hypoglycaemia) was defined as self-measured and self-treated capillary blood glucose > 3.1 mmol/l and ≤ 3.9 mmol/l; Grade 2 (moderate hypoglycaemia) was defined as a self-measured and self-treated blood glucose of ≤ 3.1 mmol/l; and Grade 3 (major hypoglycaemia) was defined as blood glucose of ≤ 3.1 mmol/l or requiring the assistance of another person.

<H2>Assessments and procedures

After 18 months of intensive intervention, informed consent for follow-up was obtained from all participants in both groups to attend follow-up study visits at 2, 3 and 4 years until December 2013, when the last randomized participant completed the planned 4-year follow-up (Fig. 1). Participants who did not attend follow-up visits, despite repeated attempted contact from the study team, were withdrawn from the study at the time point at which they failed to attend review. The study protocol was approved by the Leicestershire Research Ethics Committee.

Blood samples in a fasted state were obtained at follow-up visits and analysed at the biochemical laboratory, University Hospitals of Leicester, Leicester UK. HbA_{1c} was measured using ion-exchange liquid chromatography (G7, Tosoh). Biochemical analyses for creatinine, electrolytes, total and LDL-cholesterol and triglycerides were carried out using an Abbott Aeroset clinical chemistry analyser. Total cholesterol was measured by the cholesterol oxidase method and HDL-cholesterol by a similar method with addition of sequential reagents. LDL-cholesterol was calculated by the Friedewald formula [17]. Serum creatinine was measured by the kinetic Jaffe enzymatic method. The laboratory routinely reports GFR by the modified four-variable MDRD equation for estimating kidney function [18]. Urine albumin to creatinine ratio (UACR) was measured on a spot urine specimen (preferably first void sample) using the Olympus OSR6167 Microalbumin Analyser (sensitivity of 0.46 mg/l).

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At follow-up visits, BP was measured according to a standard protocol with a portable digital sphygmomanometer (Omron M5-I) and an appropriately sized cuff. The mean of two BP readings measured 10 min apart at rest was considered to be representative.

Adverse events, serious adverse events and clinical outcome data were obtained from clinical records (letters from primary care physicians, outpatient specialist clinic letters, hospital discharge reports) or self-report from the participants.

<H2>Statistical methods

Baseline data by intervention group were compared in those who took part in the original trial and those followed up at 18 months and 4 years. This was to assess whether those who were followed up were representative of the original cohort. The treatment groups were compared using linear regression for continuous outcomes at 1, 2, 3 and 4 years adjusted for the baseline value. Missing outcomes were not replaced and we used linear mixed-effects models to assess changes over time. This procedure measures the cumulative effect of the treatment and includes the maximum number of participants, these models are referred to as 'overall' in the tables. An additional model adjusted for medication use was also performed. The percentages of participants achieving the following targets by group were plotted as: (i) $\text{HbA}_{1c} < 48 \text{ mmol/mol}$ (6.5%), (ii) total cholesterol $< 3.5 \text{ mmol/l}$, (iii) systolic BP $< 130 \text{ mmHg}$, and (iv) diastolic BP $< 80 \text{ mmHg}$. Adjustments were not made for multiple testing. All the results presented should be viewed as hypothesis generating and small P -values interpreted taking into account the overall pattern of the results.

The UKPDS risk engine (version 2.0) for 10-year coronary heart disease and stroke risk was downloaded from the website, and used to analyse the data [19]. All data analyses were conducted in Stata (version 15), plots were produced using R for Windows (version 3.4.3). Throughout statistical significance relates to $P < 0.05$.

<H1>Results

One hundred and eighty-nine individuals were eligible and agreed to participate in the MEMO study. Of these participants, 95 were randomized to the control group and 94 to the intervention group. Ninety participants (96%) in the intervention group attended the initial education session, 68 (73%) participants attended at least one education session, 51 (61%) attended more than one educational session, 27 of 46 (58%) attended the initial insulin

management session and at 18 months, and 34 of 57 participants (59%) attended more than five insulin management sessions.

Overall at 18 months, 169 (89.4%) individuals completed the study intervention. At 4-year follow-up, 130 (68.8%) individuals from both arms completed the study follow-up, 60 in the control group ($n = 35$, 36.8% lost to follow-up) and 70 in the intervention group ($n = 24$, 25.5% lost to follow-up). The flow of participants through the study is shown in Fig. 1. Baseline clinical and biochemical characteristics of the cohorts of participants who were randomized, followed up at 18 months and followed up at 4 years are shown in Table 1. Those followed up are broadly representative of those initially randomized.

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<H2>Cardiovascular risk factors

Table 2 shows the biomedical outcomes by treatment group at 1, 2, 3 and 4 years follow-up and overall difference between the two groups over this period.

At 3 and 4 years, the difference in change in HbA_{1c} between the two groups was no longer statistically significant. Taking into account all of the follow-up data in a single analysis (adjusted for baseline values and medication), there was an overall significant improvement in HbA_{1c} in the intervention group compared with control (-3 mmol/mol, -0.4%).

Mean change in systolic and diastolic BP was greater in the intervention group compared with control both at 3 and 4 years follow-up. The overall mean change (adjusted for baseline values and medication) in systolic BP (-7.3 mmHg, 95% CI -11.1 to -3.5 ; $P < 0.001$) and diastolic BP (-2.9 mmHg, 95% CI -5.4 to -0.3 ; $P = 0.03$) was significantly greater in the intervention group compared with the control group.

Significantly lower cholesterol levels were seen in the intervention group compared with the control at every follow-up visit. When adjusted for baseline values and medication, mean change in total cholesterol levels was significantly greater in intervention group compared with control (-0.3 , -0.5 to -0.1 ; $P = 0.002$). A significantly greater improvement in the intervention group was seen in the LDL-cholesterol levels at every point of follow-up. At 4 years, a significant difference in LDL-cholesterol levels between the two groups was seen when adjusting for baseline values and medication (-0.3 , -0.5 to -0.2 ; $P < 0.001$).

At 4-year follow-up, mean change in eGFR was significantly greater in the intervention group compared with control (5.25 ml/min, 95% CI 0.13 , 10.38 ; $P = 0.045$). UACR improved

significantly in the intervention group compared with control at 3 years (-0.54 mg/mol, 95% CI $0.99, -0.09$; $P = 0.02$) although this effect was no longer significant at 4-year follow-up.

Total body weight (kg) and waist circumference (cm) were not significantly different between the groups.

<H2>Modelled cardiovascular risk scores

Mean (95% CI) 10-year UKPDS risk scores for fatal and non-fatal coronary heart disease and stroke, improved significantly with intensive intervention (-5.31 , 95% CI $-8.22, -2.39$; $P < 0.001$) and (-4.41 , 95% CI $-7.50, -1.33$; $P < 0.001$), respectively compared with control.

<H2>Medication use

Table 3 highlights medication regimes in the comparative groups at both baseline and 4-year follow-up. There were no significant differences in medication prescribed for diabetes (oral glucose-lowering agents or insulin use) between study groups whereas use of antihypertensive medications including angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers was significantly higher among intervention participants ($P = 0.01$) and at higher doses ($P = 0.03$). Significantly higher statin doses and aspirin use were seen in the intervention group.

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<H2>Treatment targets

The proportion of participants reaching treatment targets for HbA_{1c} (< 48 mmol/mol; $< 6.5\%$), total cholesterol (< 3.5 mmol/l), systolic BP (< 130 mmHg) and diastolic BP (< 80 mmHg) were recorded at baseline and 1, 2, 3 and 4 years (Fig. 2).

<H2>Adverse events

Hypoglycaemia, mortality, cardiovascular events and other serious adverse event data are given in Table 4. There were significantly more moderate (grade 2) hypoglycaemic events throughout the 4 years of follow-up in the intervention group ($n = 28$, 37.3%) compared with control ($n = 9$, 12.5%) ($P = 0.01$). Numerically, fewer episodes of severe hypoglycaemia (grade 3) were seen in the intervention group ($n = 4$, 5.3%) compared with control ($n = 9$, 12.5%).

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The most commonly occurring vascular events in both groups were angina and lower limb revascularization. Vascular events resulted in more serious adverse events in the intervention group ($n = 5$) than in the control ($n = 1$); comprising acute coronary syndrome, congestive

cardiac failure and cerebrovascular disease. Major adverse cardiovascular events [20] were more commonly seen in the intervention ($n = 9$, 12.6%) compared with control ($n = 5$, 8.5%). There were 11 deaths overall throughout the 4 years of the study (intervention $n = 5$, 7.1%; control $n = 6$, 10%). The majority of these were classified as cardiovascular causes of death ($n = 8$) with equal numbers in each arm of the study.

<H1>Discussion

The 4-year follow-up results of the MEMO multifactorial intervention showed greater improvements in cardiovascular disease risk factor profile including systolic and diastolic BP and hyperlipidaemia in those receiving the intervention compared with standard care. There were significant improvements in glycaemic control (even for individuals on insulin therapy) without increase in severe hypoglycaemia, both during the study intervention and over 4 years of follow-up. Cardiovascular risk scores improved with intensive intervention and despite tight targeted glycaemic targets, there was no increase in cardiovascular or all-cause mortality.

In recent years, the management of type 2 diabetes has moved away from a one-dimensional, biomedical approach to individualized, targeted, multifactorial care with self-management education [15,21]. Structured self-management education programmes are vital because they empower individuals to learn more about their own long-term condition, facilitate skills-based learning and decision support (i.e. provide guidance for implementing evidence-based care) [11]. Furthermore, high-quality, structured diabetes self-management education programmes in type 2 diabetes have shown improved biomedical outcomes with mean HbA_{1c} reductions of $\geq 0.4\%$ (3 mmol/mol), at 4-year follow-up [22-24]. In the MEMO study, group difference at 4-year follow-up was 0.41% in favour of intensive intervention and nearly 30% of participants in the intensive group achieved tight treatment targets of ≤ 48 mmol/mol (6.5%) both during and at the end of the follow-up period [8]. Despite pursuing tight glycaemic targets, there was no significant increase in severe hypoglycaemic events, weight gain or increased use of glucose-lowering medications. Because the MEMO study was a complex intervention, it is not possible to tease out the efficacy of its individual components, although structured education was a core element which may have strengthened the effects of the intervention.

Improvements in metabolic risk factor targets are also associated with improved outcomes [25,26]. In the MEMO structured education programme, intervention participants were

allowed to choose and attend multiple educational sessions on dietary choices, physical activity, weight management, medication optimization, glucose and BP monitoring, and insulin self-management, empowering them to achieve their own desired targets while promoting a patient-centred delivery of care. More than 45% of intensive group participants achieved tight cholesterol targets of ≤ 3.5 mmol/l and BP of $\leq 130/80$ mmHg, although this was matched by similar target achievers in the control group (for BP only). Finally, medication optimization was a key component of the MEMO intensive intervention and nearly 98.5% were taking an angiotensin converting enzyme inhibitor or angiotensin receptor blockers and 88% were taking statin therapy, with nearly 32% on the maximum allowed dose of 80 mg a day without any observed side effects at 4 years follow-up.

The safety of pursuing tight blood glucose targets in individual with type 2 diabetes has been under scrutiny in the past two decades due to attendant risks of cardiovascular and neurological complications [27]. Individualization of treatment particularly for glycaemic control is now embedded in most management guidelines for type 2 diabetes individuals [15,21]. An interesting sub-analysis of the ACCORD study showed that a large proportion of events are preceded by behavioural situations with reduced carbohydrate intake being an important determining factor [28]. Proactive planning with behaviour modification particular for those on insulin therapy is therefore important to prevent severe hypoglycaemic episodes. In the MEMO study, rates of severe hypoglycaemia were lower with intensive intervention despite comparable use of oral glucose-lowering medications and injectable therapies between the intervention and control study groups. Furthermore, all intensive group participants voluntarily accessed education sessions on food maps and insulin self-management, and adding these tools into the educational programme had a beneficial impact on avoidance of adverse events.

Apart from hyperglycaemia, intensive BP control to < 135 mmHg is associated with reductions in microalbuminuria, overt nephropathy and reduces the risk of macrovascular events (death or stroke), albeit with a significant increase in severe adverse events [29]. In the MEMO study, the mean difference in systolic and diastolic BP at baseline and 4 years follow-up was 6.2 and 3.1 mmHg respectively, and was sustained throughout the 4 years of follow-up with no significant increase in medication-related adverse events, suggesting that self-management strategies can offer beneficial improvements on clinical outcomes.

The MEMO study was carried out in a multi-ethnic high-risk population recruited from primary care and specialist clinics, and the design of the study is in keeping with the gold standard of care that should be offered to these individuals who are already at a very high risk of cardiovascular disease. Hence, the findings of this study are generalizable to other high-risk populations. Although structured education has proven value, the MEMO study based on the DESMOND philosophy and principles of structured self-management education and patient empowerment is the first intervention to show that structured education alongside medication optimization offers cardio-metabolic risk factor benefits and long-term reductions in cardiovascular risk. A recent systematic review that studied the effects of multifaceted diabetes care in European populations showed that biomedical outcomes were significantly improved in people with newly diagnosed diabetes compared with those with prevalent diabetes [30]. Our study adds to the body of this evidence and suggests that a comprehensive multifactorial care intervention with structured self-management education is beneficial even in people with established type 2 diabetes.

There are some limitations to this work which must also be considered when interpreting the results. The study was powered to assess difference in change in HbA_{1c} at 18 months between intervention groups. Therefore, the results presented should be viewed as secondary and hypothesis generating rather than hypothesis testing. We have also therefore not adjusted for multiple comparisons and therefore significant findings by chance should also be considered. MEMO is a complex intervention, comprising self-management education and intensive treatment using tight targets for HbA_{1c}, BP and cholesterol. We cannot tease out from these results which components of the intervention lead to the changes seen. Additionally, around one-third of participants did not complete the 4-year follow-up and are not included in the analysis. The level of drop-out was higher in the control group (63.2% vs. 74.5%) and this may have biased the results. The baseline characteristics of those followed up at 4 years are compared with those randomized, and reassuringly those followed up are roughly representative of those who started the study.

<H1>Conclusion

Substantial and sustained improvements in cardio-metabolic risk factors with reduction in cardiovascular and stroke risk in the MEMO study suggest that intensive multifactorial intervention coupled with structured, self-management education programmes may be integral to management because they empower individuals to learn more about their own

long-term condition, facilitate skills-based learning and decision support. Although the study lacked power and was not a primary outcome, severe hypoglycaemia and cardiovascular mortality did not increase despite intensive glycaemic intervention.

Funding sources

Competing interests

WC has received lecture fees and grants from Sanofi-Aventis, Boehringer Ingelheim, Novo Nordisk, Napp Pharmaceuticals, Internis and MSD. KK has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme. He has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim, and Merck Sharp & Dohme. MJD has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen, and as a speaker for Mitsubishi Tanabe Pharma Corporation. She has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi-Aventis and Lilly. The remaining author declare no competing interests.

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FIGURE 1 CONSORT diagram of flow of participants in the Microalbuminuria Education and Medication Optimisation (MEMO) study at 4 years of follow-up.

FIGURE 2 [Author to supply caption.] EMO, ; SU, ; TZD, ; OAD, .

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Table 1. Baseline characteristics at baseline and in those who were followed up at 18 months and 4 years

	Baseline		18 months follow-up		4-year follow-up	
	Control (n = 95)	Intervention (n = 94)	Control (n = 84)	Intervention (n = 85)	Control (n = 60)	Intervention (n = 70)
Age, years (SD)	60.3 (10.7)	62.6 (10.3)	59.8 (10.7)	62.1 (10.1)	60.7 (10.7)	60.8 (10.1)
Men,	72 (75.8)	71 (75.5)	63 (75.0)	65 (76.5)	46 (76.7)	56 (80.0)
White European	61 (64.2)	68 (72.3)	53 (63.1)	61 (71.8)	37 (61.7)	50 (71.4)
South Asian	30 (31.6)	22 (23.4)	28 (33.3)	21 (24.7)	20 (33.3)	18 (25.7)
Duration of diabetes, years mean (SD)	11.9 (9.4)	11.0 (9.3)	11.9 (9.4)	11.0 (9.4)	12.0 (10.2)	11.1 (9.2)
HbA _{1c} , mmol/mol mean (SD)	63 (17)	62 (16)	62 (16)	54 (14)	62 (16)	61 (16)
HbA _{1c} , % mean (SD)	8.0 (1.6)	7.9 (1.4)	7.8 (1.4)	7.1 (1.0)	7.9 (1.5)	7.7 (1.4)
Total cholesterol, mmol/l mean (SD)	4.2 (0.9)	4.2 (0.8)	4.1 (0.9)	3.7 (0.8)	4.1 (1.0)	3.6 (0.6)
LDL-cholesterol, mmol/l mean (SD)	2.2 (0.8)	2.1 (0.6)	2.2 (0.7)	1.7 (0.6)	2.1 (0.8)	1.7 (0.5)
HDL-cholesterol, mmol/l mean (SD)	1.0 (0.3)	1.1 (0.3)	1.1 (0.3)	1.2 (0.3)	1.2 (0.4)	1.1 (0.3)
Triglycerides, mmol/l mean (SD)	2.6 (1.6)	2.3 (1.7)	1.9 (1.0)	1.7 (0.9)	1.9 (1.0)	1.9 (1.1)
Urine albumin to creatinine ratio, mg/mmol l ⁻¹ mean (SD)	18.8 (33.8)	27.0 (62.5)	28.0 (73.3)	35.9 (99.9)	41.2 (121.1)	25.0 (52.3)
Estimated GFR, ml/min 1.73 m ⁻² mean (SD)	70.6 (18.3)	65.9 (14.3)	74.3 (27.0)	69.9 (22.0)	66.0 (20.7)	68.9 (20.1)
Systolic BP, mmHg mean (SD)	136.3 (16.2)	139.2 (16.4)	139.3 (16.8)	129.3 (15.6)	135.5 (19.2)	131.8 (15.6)
Diastolic BP, mmHg mean (SD)	76.9 (11.9)	76.0 (12.2)	76.0 (11.5)	69.9 (11.3)	75.9 (12.5)	72.9 (11.0)
Body weight, kg mean (SD)	93.6 (25.6)	93.9 (20.1)	94.9 (25.3)	94.5 (21.5)	90.5 (25.1)	96.3 (21.7)
Waist circumference, cm						
Men mean (SD)	112.6 (16.2)	112.9 (12.9)	110.1 (14.1)	111.8 (11.7)	109.0 (12.7)	113.8 (11.8)

Women mean (SD)	108.8 (16.4)	107.8 (17.0)	110.3 (15.7)	104.5 (15.1)	110.1 (15.7)	108.5 (16.7)
BMI, kg/m ² mean (SD)	32.8 (7.9)	33.1 (6.8)	33.4 (7.8)	32.8 (6.4)	31.7 (7.4)	33.1 (6.8)
Comorbidities						
Ischemic heart disease	14 (14.7)	24 (25.5)	14 (16.7)	21 (24.7)	11 (18.3)	14 (20.0)
Congestive cardiac failure	7 (7.4)	8 (8.5)	5 (6.0)	6 (7.1)	4 (6.7)	3 (4.3)
Cerebrovascular accident	5 (5.3)	10 (10.6)	5 (6.0)	9 (10.6)	4 (6.7)	7 (10.0)
Peripheral vascular disease	6 (6.3)	4 (4.3)	5 (6.0)	4 (4.7)	2 (3.3)	4 (5.7)
Smokers	14 (14.7)	12 (12.8)	11 (13.1)	12 (14.1)	7 (11.7)	9 (12.9)

Data shown as n (%), unless otherwise stated.

Table 2. Changes in biomedical outcomes at 1, 2, 3 and 4 years, and overall

	N		Change (95% CI)		Difference*	P-value	Difference†	P-value
	Control	Intervention	Control	Intervention				
HbA _{1c} (mmol/mol)								
1 year	82	84	0.37 (−1.77, 2.58)	−2.29 (−3.99, −0.66)	−2.81 (−0.10, −0.37)	0.02	–	–
2 years	67	74	−1.62 (−4.21, 0.96)	−3.54 (−5.98, −1.18)	−2.07 (−4.87, 0.81)	0.16	−1.846 (−4.80, 1.11)	0.23
3 years	61	71	−1.18 (−4.06, 1.70)	−3.25 (−5.83, −0.74)	−2.44 (−5.39, 0.44)	0.10	−0.37 (−3.77, 3.10)	0.17
4 years	60	70	0.59 (−1.77, 2.95)	−1.40 (−4.06, 1.26)	−1.85 (−5.02, 1.33)	0.25	−0.37 (−3.77, 3.10)	0.84
Overall	91	89	–	–	−3.03 [−4.95, −1.11]	0.002	−2.88 (−5.17, 0.59)	0.01
HbA _{1c} (%)								
1 year	82	84	0.05 (−0.24, 0.35)	−0.31 (−0.54, −0.09)	−0.38 (−0.71, −0.05)	0.02	–	–

2 years	67	74	-0.22 (-0.57, 0.13)	-0.48 (-0.81, -0.16)	-0.28 (-0.66, 0.11)	0.16	-0.25 (-0.65, 0.15)	0.23
3 years	61	71	-0.16 (-0.55, 0.23)	-0.44 (-0.79, -0.10)	-0.33 (-0.73, 0.06)	0.10	-0.29 (-0.69, 0.12)	0.17
4 years	60	70	0.08 (-0.24, 0.40)	-0.19 (-0.55, 0.17)	-0.25 (-0.68, 0.18)	0.25	-0.05 (-0.51, 0.42)	0.84
Overall	91	89	–	–	-0.41 (-0.67, -0.15)	0.002	-0.39 (-0.70, -0.08)	0.01
Systolic BP								
1 year	79	79	-0.04 (-4.15, 4.08)	-7.01 (-11.38, -2.65)	-5.57 (-10.51, -0.62)	0.03	–	–
2 years	66	69	1.58 (-3.04, 6.19)	-8.32 (-12.97, -3.67)	-7.95 (-13.21, -2.70)	0.003	-8.51 (-13.83, -3.19)	0.002
3 years	61	70	-0.28 (-5.38, 4.82)	-3.99 (-8.42, 0.45)	-2.09 (-7.80, 3.61)	0.47	-2.79 (-8.72, 3.14)	0.35
4 years	56	67	0.59 (-4.78, 5.95)	-6.69 (-11.28, -2.09)	-4.96 (-10.90, 0.98)	0.10	-5.36 (-11.53, 0.81)	0.09
Overall	87	86	–	–	-6.19 (-9.55, -2.84)	<0.0001	-7.29 (-11.10, -3.49)	< 0.0001
Diastolic BP								
1 year	79	79	-0.32 (-3.04, 2.41)	-3.22 (-6.11, -0.32)	-2.80 (-6.05, 0.45)	0.09	–	–
2 years	66	69	-0.58 (-3.40, 2.25)	-2.88 (-5.68, -0.09)	-2.39 (-5.67, 0.88)	0.15	-2.24 (-5.57, 1.08)	0.18
3 years	61	70	-1.11 (-4.11, 1.88)	-1.26 (-4.27, 1.76)	-0.41 (-4.08, 3.26)	0.83	-0.58 (-4.39, 3.22)	0.76
4 years	56	67	-1.04 (-4.17, 2.10)	-3.11 (-6.12, -0.10)	-2.56 (-6.31, 1.19)	0.18	-1.84 (-5.60, 1.92)	0.33
Overall	87	86	–	–	-3.05 (-5.28, -0.82)	0.01	-2.85 (-5.36, -0.34)	0.03
Total cholesterol								
1 year	82	84	-0.07 (-0.25, 0.11)	-0.50 (-0.70, -0.31)	-0.45 (-0.67, -0.23)	<0.001	–	–
2 years	67	74	-0.17 (-0.42, 0.08)	-0.63 (-0.83, -0.42)	-0.45 (-0.71, -0.19)	0.001	-0.34 (-0.60, -0.08)	0.01

					−0.20)		−0.08)	
3 years	61	70	−0.12 (−0.38, 0.13)	−0.53 (−0.75, −0.30)	−0.42 (−0.68, −0.16)	0.002	−0.34 (−0.62, −0.06)	0.02
4 years	60	68	−0.16 (−0.43, 0.12)	−0.59 (−0.81, −0.37)	−0.48 (−0.75, −0.21)	0.001	−0.40 (−0.69, −0.11)	0.01
Overall	91	89	–	–	−0.40 (−0.57, −0.23)	<0.001	−0.32 (−0.52, −0.12)	0.002
Triglycerides								
1 year	81	82	−0.55 (−0.84, −0.26)	−0.68 (−1.00, −0.36)	−0.23 (−0.49, 0.31)	0.08	–	–
2 years	66	74	−0.73 (−1.08, −0.38)	−0.65 (−1.06, −0.24)	0.06 (−0.23, 0.36)	0.66	0.15 (−0.17, 0.46)	0.37
3 years	61	70	−0.75 (−1.16, −0.34)	−0.77 (−1.15, −0.39)	−0.09 (−0.37, 0.18)	0.50	−0.001 (−0.29, 0.29)	0.99
4 years	60	68	−0.64 (−1.03, −0.24)	−0.53 (−0.93, −0.13)	−0.01 (−0.34, 0.31)	0.93	0.01 (−0.34, 0.35)	0.97
Overall	91	89	–	–	−0.17 (−0.37, 0.04)	0.11	−0.005 (−0.25, 0.24)	0.97
LDL-cholesterol								
1 year	70	76	0.05 (−0.12, 0.23)	−0.36 (−0.53, −0.20)	−0.43 (−0.63, −0.22)	<0.001	–	–
2 years	62	68	−0.04 (−0.30, 0.21)	−0.56 (−0.73, −0.38)	−0.51 (−0.74, −0.28)	<0.001	−0.40 (−0.63, −0.18)	0.001
3 years	54	59	−0.04 (−0.29, 0.20)	−0.32 (−0.49, −0.15)	−0.37 (−0.57, −0.16)	0.001	−0.34 (−0.55, −0.13)	0.002
4 years	52	63	−0.05 (−0.28, 0.18)	−0.49 (−0.68, −0.31)	−0.42 (−0.64, −0.21)	<0.001	−0.36 (−0.58, −0.14)	0.002
Overall	91	89	–	–	−0.38 (−0.53, −0.23)	<0.001	−0.33 (−0.50, −0.17)	<0.001

HDL-cholesterol								
1 year	74	77	0.12 (0.03, 0.22)	0.08 (0.01, 0.15)	-0.02 (-0.14, 0.09)	0.68	–	–
2 years	63	70	0.12 (0.06, 0.17)	0.08 (0.02, 0.14)	-0.02 (-0.10, 0.06)	0.59	-0.05 (-0.13, 0.03)	0.25
3 years	57	61	0.14 (0.08, 0.20)	0.06 (-0.005, 0.13)	-0.07 (-0.16, 0.02)	0.14	-0.06 (-0.16, 0.04)	0.23
4 years	54	64	0.11 (0.07, 0.15)	0.02 (-0.03, 0.07)	-0.09 (-0.16, -0.02)	0.01	-0.09 (-0.16, -0.02)	0.01
Overall	91	89	–	–	-0.03 (-0.07, 0.02)	0.30	-0.04 (-0.09, 0.02)	0.18
Non-HDL-cholesterol								
1 year	74	77	-0.13 (-0.32, 0.06)	-0.56 (-0.76, -0.37)	-0.48 (-0.72, -0.25)	<0.001	–	–
2 years	63	70	-0.23 (-0.48, -0.02)	-0.65 (-0.85, -0.45)	-0.46 (-0.72, -0.21)	<0.001	-0.33 (-0.59, -0.06)	0.02
3 years	57	61	-0.22 (-0.48, 0.03)	-0.47 (-0.68, -0.26)	-0.34 (-0.60, -0.08)	0.01	-0.29 (-0.57, -0.02)	0.04
4 years	54	63	-0.21 (-0.47, 0.04)	-0.60 (-0.81, -0.39)	-0.42 (-0.68, -0.17)	0.001	-0.36 (-0.64, -0.09)	0.01
Overall	91	89			-0.42 (-0.58, -0.26)	<0.001	-0.32 (-0.52, -0.12)	0.001
Estimated GFR								
1 year	82	84	1.72 (-0.83, 4.26)	2.37 (0.16, 4.58)	0.90 (-2.44, 4.24)	0.59	–	–
2 years	67	74	1.49 (-1.70, 4.69)	3.54 (0.95, 6.13)	1.79 (-2.25, 5.83)	0.38	1.78 (-2.45, 6.01)	0.41
3 years	61	69	-1.59 (-4.96, 1.78)	1.13 (-1.65, 3.91)	2.67 (-1.65, 6.98)	0.22	1.03 (-3.39, 5.46)	0.65
4 years	60	70	-4.55 (-8.70, -0.40)	0.91 (-2.27, 4.10)	5.25 (0.13, 10.38)	0.05	4.17 (-1.02, 9.35)	0.11
Overall	91	89	–	–	0.98 (-2.04, 3.99)	0.53	1.40 (-2.11, 4.91)	0.43
Albumin to creatinine ratio (log)								

3 years	44	50	0.48 (0.17, 0.80)	-0.15 (-0.52, 0.22)	-0.54 (-0.99, -0.09)	0.02	-0.45 (-0.90, 0.002)	0.05
4 years	50	52	0.26 (-0.09, 0.60)	0.12 (-0.22, 0.45)	-0.11 (-0.57, 0.35)	0.64	-0.14 (-0.63, 0.35)	0.56
Overall	79	84	-	-	-0.23 (-0.52, 0.06)	0.12	-0.23 (-0.51, 0.06)	0.12
Weight								
1 year	77	78	0.74 (0.06, 1.42)	1.21 (0.14, 2.28)	0.48 (-0.78, 1.74)	0.46	-	-
2 years	64	66	0.92 (-0.23, 2.07)	2.28 (0.85, 3.71)	1.36 (-0.47, 3.19)	0.14	1.44 (-0.60, 3.47)	0.16
3 years	61	66	1.39 (-0.30, 3.08)	2.35 (0.78, 3.93)	0.96 (-1.34, 3.25)	0.41	2.47 (-0.27, 5.20)	0.08
4 years	56	64	1.13 (-0.53, 2.78)	2.26 (0.70, 3.81)	0.93 (-1.32, 3.18)	0.41	1.13 (-1.25, 3.50)	0.35
Overall	87	86	-	-	0.55 (-0.66, 1.76)	0.37	1.35 (-0.29, 2.98)	
Waist circumference								
1 year	72	71	0.01 (-1.26, 1.29)	0.69 (-0.72, 2.10)	0.66 (-1.19, 2.52)	0.48	-	-
2 years	62	62	0.76 (-0.75, 2.27)	1.31 (-0.35, 2.97)	0.55 (-1.63, 2.74)	0.62	0.89 (-1.51, 3.29)	0.46
3 years	56	62	1.50 (-0.10, 3.10)	3.15 (1.60, 4.69)	1.73 (-0.40, 3.86)	0.11	2.81 (0.31, 5.31)	0.03
4 years	51	60	1.67 (-0.07, 3.41)	2.47 (0.79, 4.14)	1.14 (-1.20, 3.48)	0.34	1.85 (-0.65, 4.34)	0.15
Overall	89	92	-	-	0.40 (-0.99, 1.78)	0.58	1.42 (-0.27, 3.13)	0.10
10-year CHD risk score								
1 year	71	73	-3.15 (-5.87, -0.42)	-8.21 (-10.90, -5.51)	-5.73 (-9.36, -2.10)	0.002	-	-
2 years	60	64	-21.44 (-29.31, -13.56)	-25.84 (-33.30, -18.39)	-2.80 (-7.50, 1.91)	0.24	-3.54 (-8.68, 1.60)	0.18
3 years	55	59	-19.28 (-26.97, -11.60)	-26.38 (-34.27, -18.48)	-1.74 (-6.86, 3.38)	0.50	-1.69 (-7.36, 3.99)	0.56
4 years	50	60	-17.90 (-26.10, -9.70)	-22.56 (-31.15, -13.97)	0.54 (-5.29, 6.36)	0.86	-0.69 (-7.02, 5.63)	0.83
Overall	89	92	-	-	-5.31 (-8.22, -2.40)	<0.001	-3.53 (-6.80, -0.26)	0.03

					-2.39)		-0.26)	
10-year fatal CHD score								
1 year	71	73	-2.46 (-4.97, 0.05)	-7.12 (-9.70, -4.55)	-5.26 (-8.65, -1.88)	0.003	-	-
2 years	60	64	-19.78 (-27.66, -11.90)	-24.43 (-31.74, -17.12)	-2.64 (-6.99, 1.70)	0.23	-3.37 (-8.13, 1.39)	0.16
3 years	55	59	-17.48 (-25.15, -9.81)	-25.05 (-32.85, -17.25)	-1.83 (-6.60, 2.94)	0.45	-1.92 (-7.14, 3.30)	0.47
4 years	50	60	-16.37 (-24.42, -8.33)	-22.09 (-30.16, -14.03)	-0.26 (-5.24, 4.72)	0.92	-1.15 (-6.54, 4.25)	0.67
Overall	89	92	-	-	-5.30 (-8.14, -2.45)	<0.001	-3.50 (-6.51, -0.49)	0.02
10-year stroke risk score								
1 year	71	73	-0.99 (-2.11, 0.13)	-2.82 (-4.23, -1.41)	-1.97 (-3.74, -0.20)	0.03	-	-
2 years	60	64	-18.48 (-27.80, -9.17)	-26.00 (-34.00, -18.00)	-2.83 (-7.66, 1.99)	0.25	-3.94 (-9.24, 1.35)	0.14
3 years	55	59	-16.60 (-25.78, -7.43)	-27.31 (-35.98, -18.64)	-2.02 (-7.44, 3.40)	0.46	-3.79 (-9.78, 2.20)	0.21
4 years	50	60	-16.12 (-25.65, -6.60)	-24.79 (-34.06, -15.52)	-0.14 (-6.18, 5.91)	0.97	-0.98 (-7.56, 5.60)	0.77
Overall	89	92			-4.41 (-7.50, -1.33)	0.01	-3.31 (-6.99, 0.37)	0.08
10-year fatal stroke risk score								
1 year	71	73	0.19 (-0.50, 0.87)	-1.46 (-2.39, -0.53)	-1.64 (-2.67, -0.61)	0.002	-	-

2 years	60	64	-2.44 (-4.01, -0.86)	-4.57 (-6.15, -2.99)	-0.82 (-1.71, 0.07)	0.07	-1.06 (-2.07, -0.06)	0.04
3 years	55	59	-2.30 (-3.88, -0.71)	-4.55 (-6.29, -2.81)	-0.39 (-1.44, 0.65)	0.46	-0.62 (-1.81, 0.58)	0.31
4 years	50	60	-2.31 (-4.06, -0.55)	-4.49 (-6.26, -2.73)	-0.40 (-1.53, 0.73)	0.48	-0.49 (-1.73, 0.75)	0.44
Overall	89	92	–	–	-1.36 (-2.09, -0.62)	<0.001	-0.88 (-1.57, -0.18)	0.01

CHD, coronary heart disease.

*Difference adjusted for baseline value for 2, 3 and 4 year data.

†Difference adjusted for baseline value and medication.

‡only collected at baseline, 18 months, 3 and 4 years.

Table 3. Medication use in the MEMO study at baseline and at 4 years follow-up

	Baseline		4-year follow-up	
	Control (n = 95)	Intervention (n = 94)	Control (n = 60)	Intervention (n = 70)
Glucose lowering therapy, n (%)				
Diet alone	7 (7.4)	11 (11.7)	5 (8.3)	2 (2.9)
Metformin	61 (64.2)	53 (56.4)	39 (65.0)	50 (71.4)
Sulphonylureas	21 (22.1)	17 (18.1)	12 (16.7)	13 (18.6)
Glitazones	14 (14.7)	16 (17.0)	9 (15.0)	5 (7.1)
OAD's with insulin	32 (33.7)	22 (23.4)	19 (31.7)	32 (45.7)
Insulin alone	18 (19.0)	24 (25.5)	12 (20.0)	9 (12.9)
Insulin dose, units	99.4 (75.8)	78.5 (53.6)	54.4 (78.8)	61.6 (72.6)
Insulin dose, units per kg	0.97 (0.55)	0.78 (0.50)	1.04 (0.85)	0.97 (0.72)
Antihypertensive therapy, n (%)				
Angiotensin converting enzyme inhibitor or angiotensin II receptor blocker	79 (83.2)	77 (81.9)	49 (81.7)	66 (94.3)
None	11 (11.6)	5 (5.3)	4 (6.7)	1 (1.4)
1 drug	31 (32.6)	25 (26.6)	19 (31.7)	17 (24.3)
2 drugs	18 (19.0)	25 (26.6)	12 (20.0)	24 (34.3)
≥ 3 drugs	35 (36.8)	39 (41.5)	22 (36.7)	28 (35.7)
Lipid-lowering therapy, n (%)				
None	19 (20.0)	12 (12.8)		
Statins	74 (77.9)	77 (81.9)	52 (86.7)	59 (84.3)
Fibrates	0 (0.0)	3 (3.2)	4 (6.7)	3 (4.3)
Aspirin, n (%)	65 (68.4)	80 (85.1)	37 (61.7)	56 (80.0)

Table 4. Mortality, cardiovascular events and other serious adverse events during the four years follow-up in the intervention and the control groups

Events	Intervention	Control
Hypoglycaemic event, n (%)		

Grade 1 (mild, 3.1–3.9 mmol/l)	46 (54.8)	36 (43.4)
Grade 2 (moderate, < 3.1 mmol/l)	28 (37.3)	9 (12.5)
Grade 3 (severe, < 3.1 mmol/l, requiring assistance of another person)	4 (5.3)	9 (12.5)
Vascular events, n (%)		
Angina	3 (4.2)	5 (8.3)
Non-fatal myocardial infarction	–	1 (1.7)
Transient ischemic attack	–	1 (1.7)
Coronary revascularization	1 (1.4)	–
Lower limb revascularization	3 (4.2)	3 (5)
Other reported medical events, n (%)		
Cellulitis, falls, anaemia, vasculitis, NCCP, leg ulcer	31 (44.3)	28 (46.7)
Gastrointestinal	15 (21.4)	5 (8.3)
Respiratory	6 (8.6)	7 (11.7)
Musculoskeletal	2 (2.9)	5 (8.3)
Serious adverse events, n (%)		
Acute coronary syndrome	1 (1.4)	–
Congestive cardiac failure	3 (4.2)	–
Cerebrovascular disease	1 (1.4)	1 (1.7)
Overall major adverse cardiovascular events	9 (12.6)	5 (8.5)
Hypoglycaemia	–	3 (5)
Any other medical condition (SDH, endometrial Ca, lung collapse)	5 (7.1)	8 (13.3)

Death from cardiovascular cause	4 (5.7)	4 (6.7)
All-cause mortality (cardiovascular causes excluded)	1 (1.4)	2 (3.3)

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Figure 1:

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Author/s:

Crasto, W;Morrison, AE;Gray, LJ;John, E;Jarvis, J;Brela, J;Khunti, K;Troughton, J;Lawrence, IG;McNally, PG;Davies, MJ

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