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ARTICLE

The impact of gender on the long-term morbidity and mortality of patients with type 2 diabetes receiving structured personal care: a 13 year follow-up study

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Abstract
Aims/hypothesis The aim of this study was to assess gender differences in mortality and morbidity during 13 follow-up years after 6 years of structured personal care in patients with type 2 diabetes mellitus.
Methods In the Diabetes Care in General Practice (DCGP) multicentre, cluster-randomised, controlled trial (ClinicalTrials.gov registration no. NCT01074762), 1,381 patients newly diagnosed with type 2 diabetes were randomised to receive 6 years of either structured personal care or routine care. The intervention included regular follow-up, individualised goal setting and continuing medical education of general practitioners participating in the intervention. Patients were re-examined at the end of intervention. This observational analysis followed 970 patients for 13 years thereafter using national registries. Outcomes were all-cause mortality, incidence of diabetes-related death, any diabetes-related endpoint, myocardial infarction, stroke, peripheral vascular disease and microvascular disease.
Results In women, but not men, a lower HR for structured personal care vs routine care emerged for any diabetes-related endpoint (0.65, p=0.004, adjusted; 73.4 vs 107.7 events per 1,000 patient-years), diabetes-related death (0.70, p=0.031; 34.6 vs 45.7), all-cause mortality (0.74, p=0.028; 55.5 vs 68.5) and stroke (0.59, p=0.038; 15.6 vs 28.9). This effect was different between men and women for diabetes-related death (interaction p=0.015) and all-cause mortality (interaction p=0.005).
Conclusions/interpretation Compared with routine care, structured personal diabetes care reduced all-cause mortality and diabetes-related death in women but not in men. This gender difference was also observed for any diabetes-related outcome and stroke but was not statistically significant after extensive multivariate adjustment. These observational results from a post hoc analysis of a randomised controlled trial cannot be explained by intermediate outcomes like HbA_{1c} alone, but involves complex social and cultural issues of gender. There is a need to rethink treatment schemes for both men and women to gain benefit from intensified treatment efforts.

Keywords Gender · General practice · Intervention · Mortality · Myocardial infarction · Primary care · Sex · Stroke · Type 2 diabetes mellitus

Abbreviations

CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DCGP	Diabetes Care in General Practice
GP	General practitioner
MI	Myocardial infarction

Introduction

Men generally have a lower life expectancy than women [1] and people with type 2 diabetes are at increased risk of

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premature death, especially from cardiovascular disease (CVD), compared with people without diabetes [2, 3]. The relative protection against CVD and death observed in women vs men is reversed in patients with diabetes [4]. Women with diabetes have a proportionally greater risk of cardiovascular death and stroke than men with diabetes [2, 4]. Control of blood glucose [5], blood pressure [6] and cholesterol [7] may decrease the risk of diabetic complications. Gender-based behaviour change and attitudes towards diabetes are common observations. Women tend to diet more [8–10], use the healthcare system more often [11] and more often report that diabetes has a negative impact on their lives [12], but they exercise less than men [9, 10, 13]. Despite these known gender differences in diabetes-related behaviour and diabetes outcomes there is only limited evidence on the impact of gender on the effectiveness of diabetes interventions. However, it has been suggested that the health service should be concerned with inequalities between men and women in the management of patients at risk of coronary heart disease [14].

In the pragmatic, open, multicentre, randomised controlled trial Diabetes Care in General Practice (DCGP) (ClinicalTrials.gov registration no. NCT01074762), the intervention of structured personal care reduced the incidence of any diabetes-related outcome and myocardial infarction (MI) in patients newly diagnosed with type 2 diabetes [15]. However, the observed effect of structured personal care on reducing HbA_{1c} measured 6 years after diagnosis was present only in women [13]. With evidence of gender differences in disease outcomes, behaviours and attitudes in people with type 2 diabetes, it is relevant to investigate the impact of gender on intervention outcomes in diabetes trials. Hence, at the end of 6 years of structured diabetes intervention, we assessed gender differences in mortality and cardiovascular and microvascular complications over a follow-up period of 13 years, using registry data.

Methods

Study population The DCGP study was a pragmatic, open, controlled trial in which general practices were randomised to provide structured personal care or routine care [16]. In the DCGP study, 474 Danish general practitioners (GPs) treated 1,381 patients with diabetes newly diagnosed based on specific diagnostic criteria (Fig. 1) [16]. Among these patients, 1,369 (99.1%) were of western European descent. Based on onset of insulin treatment, approximately 97.5% of the patients were considered to have type 2 diabetes. The present study population comprises the 970 patients who survived and were re-examined at the end of 6 years of intervention. Of these, 478 were women, and 492 were men. The study was approved by the Research Ethics Committee of Copenhagen

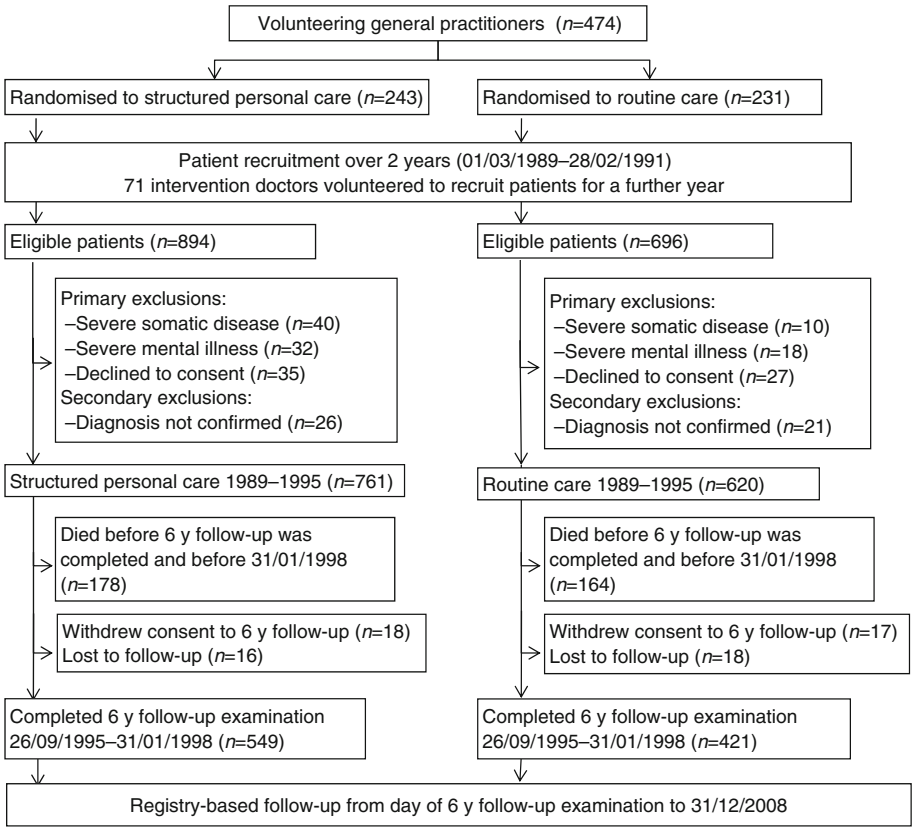

Fig. 1 Patient flow through trial. y, year

and Frederiksberg (V.100.869/87) and oral consent was given by all patients.

Intervention In Denmark, routine care for type 2 diabetes is usually provided in the primary care setting and costs are covered by a tax-based health insurance system. In the intervention group, follow-up every 3 months and annual screening for diabetes complications were supported by a questionnaire sent to GPs 1 month before the next expected consultation. GPs were asked to work with patients to define the best possible goals for controlling important risk factors, with an emphasis placed on glycaemic control [16]. At each quarterly consultation, GPs were asked to evaluate patients' achievements in light of the goals set.

GPs were introduced to possible solutions to therapeutic problems through six annual half-day seminars, annual descriptive feedback reports on individual patients and folders and leaflets for doctors and for patients. Generally, the importance of diet was stressed and doctors were recommended to postpone, if possible, the start of glucose-lowering drugs until at least 3 months after diabetes diagnosis to observe the effect of any weight loss. GPs were encouraged to recommend increased physical exercise and simple dietary rules [16]. In cases of persistent hyperglycaemia, hypertension and/or dyslipidaemia, pharmacological treatment was recommended. No individual patient-specific advice on treatment was given to GPs, who were allowed to deviate from the recommendations in an effort to individualise treatment. None of the intervention procedures were explicitly based on the sex of the patient. Patients were never approached by the study centre.

GPs in the routine care group were free to choose any treatment and to change it over time [16]. The practices providing routine care were not contacted by the study coordinating centre during the trial after patient inclusion had stopped. In September 1995, the intervention was terminated and the 6 year examination was initiated. No further attempt was made to maintain patients in the randomised groups or to influence their therapy.

Clinical follow-up The clinical 6 year follow-up examination was completed for 970 (93.4%) of 1,039 surviving patients after a median (interquartile range) of 5.57 (4.96–6.16) years in the structured personal care group and 5.85 (5.30–6.45) years in the routine care group. At this follow-up examination, GPs recorded body weight, blood pressure, glucose-lowering medication, number of consultations the preceding year and whether a patient had ever been treated at a diabetes clinic. In questionnaires, patients gave information about whether they lived alone, smoking habits and leisure-time physical activity. Analysis of fasting blood samples and freshly voided morning urine samples was centralised. The fraction of HbA_{1c} was determined using the same ion-exchange HPLC method throughout the study. The reference interval was 5.4–7.4% (36–57 mmol/mol). This method was later compared with a newer Diabetes Control and Complications Trial (DCCT)-aligned HPLC method. The reference range may cautiously be converted to 4.8–6.7% (29–50 mmol/mol) if the DCGP analytical method had been DCCT-aligned [16]. A description of other variables and definitions has previously been published [16]. Hypertension was defined as systolic/diastolic blood pressure ≥160/90 mmHg and/or the use of antihypertensive and/or diuretic drugs. Microalbuminuria was defined as urinary albumin concentration ≥15 to <200 mg/l and proteinuria as ≥200 mg/l.

At 6 year follow-up, GPs answered questions about patient motivation for best possible control and treatment, patient attitudes to study participation, influence of patient's own efforts on the course of diabetes treatment, a realistic goal for fasting whole-blood glucose and the GP's opinion on whether knowledge that the patient was participating in a study influenced consultations. Patients answered five questions concerning altered habits, food habits, home glucose monitoring, attitudes towards diabetes and social support. All questions were based on a literature review and interviews with people who have type 2 diabetes. Experienced GPs and sociologists reviewed the questions, which were revised after pilot testing.

Registry-based follow-up After the end of intervention, patients were followed up for 13 years using Danish registries. The vital and emigration status of all patients were certified through the Danish Civil Registration System [17], in which everyone living in Denmark is registered with a permanent and unique personal identification number allowing linkage between study populations and all national registries. Surviving patients were censored on 31 December 2008. The Danish Register of Causes of Death contains information about underlying and possible contributory causes of death [18]. In four cases the cause of death was not recorded in this registry. The Danish National Patient Register includes information on almost all contacts with hospitals in Denmark [19] (e.g. discharge diagnosis[es] and surgical procedures performed). The seven outcomes used in the registry-based follow-up were made with reference to those in the UK Prospective Diabetes Study (UKPDS) [20]: any diabetes-related endpoint, diabetes-related deaths, all-cause mortality, MI, stroke, peripheral vascular disease and microvascular disease.

Statistical analysis The incidences of death and other outcomes were analysed univariably with logrank tests and multivariably in Cox regression models. In the latter, 95% CIs and p values were determined using a sandwich estimator for the variance to account for clustering of patients within practices [19]. Patients with missing values for one or more variables were omitted from the analyses where these variables were included. Absolute risks for each outcome were calculated as the number of patients experiencing the corresponding outcome divided by the sum of the risk times

(i.e. from the start of the 6 year follow-up examination to the first occurrence of the outcome, death or end of follow-up). Patients with any occurrence of an outcome preceding the 6 year follow-up were excluded from the analyses pertaining to that outcome. Two multivariate models are presented: one model adjusting for age, diabetes duration and clustering and one model with additional adjustment for BMI, hypertension, HbA_{1c}, total cholesterol, sedentary physical activity, current smoking and receipt of glucose-lowering medication. Whether the effect of randomisation differed between gender groups was tested by the interaction of patient sex and randomisation group in a joint model for men and women. Analyses were done in SAS v9.2 (SAS Institute, Cary, NC, USA). The level of statistical significance was $p<0.05$.

Results

After 6 years of intervention no gender-specific differences in the effect of the intervention on intermediate outcomes was seen, except for HbA_{1c} (Table 1). In the intervention and control group, respectively, HbA_{1c} concentration was 8.6% (70 mmol/mol) and 9.4% (79 mmol/mol) in women and 8.8% (73 mmol/mol) and 9.0% (75 mmol/mol) in men (interaction $p=0.003$). There was no difference between men and women in the effect of intervention on referral to a diabetes clinic, although since diabetes diagnosis, fewer women had been referred in the structured personal care group than in the routine care group (17.3% vs 31.3%, $p=0.003$).

The intervention did not have a statistically significant effect on patients' attitudes. While men in the intervention group tended to feel that they had less social support than the men in the control group, the possible effect of the intervention went in the opposite direction for women (Table 2). This tendency is in line with the observation that, when considering the influence of a patient's own efforts on treatment course, the intervention GPs considered that the men's efforts were at a lower level than that of the control GPs' male patients. Again, the intervention had an effect in the opposite direction for women (interaction $p=0.011$, Table 2). In both randomisation arms, women were considered to comply better with dietary advice than men.

During 13 years of follow-up, no statistically significant reductions in outcomes were observed for men when comparing the structured personal intervention group with the routine care group (Table 3). In women, however, a lower HR (95% CI) and absolute risk for personal structured vs routine care emerged for any diabetes-related endpoint (0.65 [0.48, 0.87], $p=0.004$, adjusted for age, diabetes duration, clustering, physical activity, smoking and clinical variables; 73.4 vs 107.7 events per 1,000 patient-years), diabetes-related death (0.70 [0.50, 0.96], $p=0.031$; 34.6 vs 45.7), all-cause mortality (0.74 [0.57, 0.97], $p=0.028$; 55.5 vs 68.5) and stroke (0.59 [0.36, 0.97], $p=0.038$; 15.6 vs 28.9). This effect differed between men and women for diabetes-related death (interaction $p=0.015$, Table 3) and all-cause mortality (interaction $p=0.005$). Hence, survival for women who received structured care improved whereas there was a tendency towards a poorer survival for men following structured care (Fig. 2).

Discussion

During 13 years of follow-up after the completion of 6 years of structured personal diabetes care, women experienced lower all-cause mortality and lower incidences of diabetes-related death, any diabetes-related endpoint, and stroke compared with women in the control group. Such effects were not seen in men. The gender difference was statistically significant for all-cause mortality and diabetes-related death.

Gender perspective The structured personal care intervention provided focused treatment strategies for lowering blood glucose, blood pressure and cholesterol but the intervention did not take a patient's gender into consideration in any way. The intervention, however, lowered HbA_{1c} in women but not men (Table 1). The HbA_{1c} level has been shown to have a graded positive association with risk of stroke in women [21] and mortality increases with HbA_{1c} in type 2 diabetes [22]. The lowering of HbA_{1c} could therefore contribute to explaining the positive outcome for women. However, the difference in mortality outcome persisted after adjustment for HbA_{1c}. Turnbull et al, in a meta-analysis, found that treatment allocation to more intensive glucose control reduced the risk of major cardiovascular events but not all-cause or cardiovascular mortality [23]. Intensive multifactorial therapy in high-risk patients with type 2 diabetes and well-established microalbuminuria, however, has previously been shown to reduce death from any cause and cardiovascular death [24].

Gender differences in diabetes outcomes are well documented. However, we are not aware of other studies assessing the impact of gender on endpoints in structured diabetes interventions. A large meta-analysis found women with diabetes to be at more than 40% higher risk of incident coronary heart disease than men with diabetes [25]. Moreover, a relatively higher increase in mortality [3, 26], fatal CVD [4, 27] and stroke [3, 28] has been found among women diagnosed with diabetes compared with men. However, one meta-analysis found that the excessive relative risk of CVD in women with type 2 diabetes was absent when adjusting for classical CVD risk factors [29]. With our gender-based results showing improved morbidity and mortality outcomes for women receiving structured personal care, but without any obvious explanation from improved intermediate outcomes (except for HbA_{1c}, for which we adjust), we need to discuss how gender really matters in diabetes and diabetes care.

Table 1 Characteristics of patients at end of intervention

Characteristic	Men (*n*=492)				Women (*n*=478)				Interaction *p* value[b]
	n (routine/structured)	Routine care	Structured personal care	*p* value[a]	*n* (routine/structured)	Routine care	Structured personal care	*p* value[a]	
Sociodemographic									
Age, years	220/272	67.1±10.8	66.7±10.5	0.85	201/277	70.0±10.7	70.1±11.1	0.89	0.87
Diabetes duration, years	220/272	5.9±0.7	5.5±0.9	<0.0001	201/277	6.0±0.9	5.6±0.9	<0.0001	0.43
Live alone	213/246	44 (20.7)	64 (26.0)	0.31	189/259	96 (50.8)	116 (44.8)	0.44	0.34
Clinical									
BMI, kg/m^2	219/265	28.3±4.1	28.8±4.5	0.008	191/272	29.4±5.8	29.0±5.5	0.46	0.24
Hypertension	220/272	155 (70.5)	182 (66.9)	0.31	201/277	157 (78.1)	215 (77.6)	0.34	0.88
Biochemical									
HbA_{1c}, %[c]	218/269	9.0±1.6	8.8±1.7	0.30	196/270	9.4±1.9	8.6±1.3	<0.0001	0.003
HbA_{1c}, mmol/mol		75	73			79	70		
Total cholesterol, mmol/l	218/268	6.0±1.2	5.8±1.5	0.013	196/270	6.5±1.2	6.3±1.2	0.46	0.52
Fasting triacylglycerol, mmol/l	187/251	2.3±1.8	2.3±3.0	0.29	169/252	2.3±1.2	2.0±1.3	0.22	0.71
Serum creatinine, μmol/l	218/268	102±28	105±67	0.33	196/270	90±29	89±25	0.51	0.22
Urinary albumin	206/258			0.51	188/255			0.47	0.97
Normal: <15 mg/l		110 (53.4)	139 (53.9)			119 (63.3)	179 (70.2)		
Microalbuminuria: ≥15 to <200 mg/l		83 (40.3)	101 (39.2)			60 (31.9)	72 (28.2)		
Proteinuria: ≥200 mg/l		13 (6.3)	18 (7.0)			9 (4.8)	4 (1.6)		
Behavioural									
Sedentary (leisure-time) physical activity[d]	212/243	54 (25.5)	57 (23.5)	0.29	187/256	72 (38.5)	85 (33.2)	0.20	0.70
Current smoker[d]	209/246	73 (34.9)	104 (42.3)	0.68	188/257	43 (22.9)	58 (22.6)	0.99	0.91
Process of care									
Consultations/year[d]	220/272	6.7±4.6	8.0±7.7	0.061	200/277	8.0±6.4	8.4±5.0	0.45	0.15
Diabetes-related consultations/year[d]	220/272	4.3±3.4	5.0±3.7	0.17	200/277	4.5±3.6	5.2±3.1	0.085	0.95
Ever treated at a diabetes clinic[d]	220/272	48 (21.8)	44 (16.2)	0.13	201/277	63 (31.3)	48 (17.3)	0.003	0.29
Glucose-lowering therapy[d]	220/272			0.59	201/277			0.83	0.47
Diet only		73 (33.2)	81 (29.9)			58 (28.9)	78 (28.2)		
Oral glucose-lowering medicine		122 (55.5)	161 (59.4)			109 (54.2)	165 (59.6)		
Insulin		25 (11.4)	29 (10.7)			34 (16.9)	34 (12.3)		

Values are means (SD) or *n* (% of randomisation group)

The *p* values are from multivariate generalised linear models (ordinary linear regression for continuous variables, logistic regression for binary variables and Poisson regression for count variables with log[diabetes duration] as offset) where the effect of structured care vs routine care is adjusted for age and diabetes duration. Clustering with GPs is accounted for by the use of generalised estimating equations

[a] Tests effect of randomisation within gender groups

[b] Tests whether the effect of randomisation differs between gender groups

[c] Reference range: 5.4–7.4%

[d] Data from questionnaires to patients (behavioural) or their GPs (process of care)

Table 2 Attitudes and opinions of patients and GPs at end of intervention

Attitude/opinion	Men (*n*=492)				Women (*n*=478)				Interaction *p* value[b]
	n (routine/structured)	Routine care	Structured personal care	*p* value[a]	*n* (routine/structured)	Routine care	Structured personal care	*p* value[a]	
Information from patient questionnaires									
Altered habits after diagnosis	209/241			0.23	187/258			0.37	0.10
Yes		121 (57.9)	155 (64.3)			123 (65.8)	156 (60.5)		
Yes, but very little		42 (20.1)	43 (17.8)			34 (18.2)	55 (21.3)		
No		46 (22.0)	43 (17.8)			30 (16.0)	47 (18.2)		
Food habits	210/241			0.13	188/258			0.44	0.13
Diabetes diet		48 (22.9)	72 (29.9)			76 (40.4)	99 (38.4)		
Full diet without sugar		118 (56.2)	127 (52.7)			91 (48.4)	128 (49.6)		
Diet as for non-diabetic individuals		44 (20.9)	42 (17.4)			21 (11.2)	31 (12.0)		
Performs home blood or urinary glucose monitoring	205/243	58 (28.3)	79 (32.5)	0.50	188/256	56 (29.8)	61 (23.8)	0.28	0.062
Attitudes towards diabetes	207/240			0.64	185/256			0.17	0.24
The illness is unproblematic		101 (48.8)	115 (47.9)			95 (51.4)	152 (59.4)		
Work/worked with the illness		88 (42.5)	103 (42.9)			66 (35.7)	79 (30.9)		
It is a strain		18 (8.7)	22 (9.2)			24 (13.0)	25 (9.8)		
Social support	204/239			0.029	183/251			0.36	0.053
Full support		161 (78.9)	173 (72.4)			94 (51.4)	142 (56.6)		
Handle it by oneself		30 (14.7)	45 (18.8)			57 (31.2)	71 (28.3)		
Feels alone/misunderstood		13 (6.4)	21 (8.8)			32 (17.5)	38 (15.1)		
For the patient in question, the GP's opinion									
Patient's motivation for best possible control and treatment over past year	220/271			0.16	199/276			0.13	0.98
Very good		65 (29.6)	58 (21.4)			53 (26.6)	56 (20.3)		
Good		69 (31.4)	92 (34.0)			60 (30.2)	106 (38.4)		
Fair		52 (23.6)	74 (27.3)			49 (24.6)	73 (26.5)		
Poor		34 (15.4)	47 (17.4)			37 (18.6)	41 (14.9)		
Patient's attitude to study participation	216/266			<0.0001	194/272			<0.0001	0.45
Happy with the attention		48 (22.2)	138 (51.9)			43 (22.2)	136 (50.0)		
No special importance		159 (73.6)	102 (38.4)			138 (71.1)	115 (42.3)		
Irritated or bothered		9 (4.2)	26 (9.8)			13 (6.7)	21 (7.7)		
The influence of patient's own efforts on treatment course	219/271			0.003	198/276			0.58	0.011
Good		144 (65.8)	148 (54.6)			117 (59.1)	171 (62.0)		
None in particular		36 (16.4)	51 (18.8)			29 (14.7)	49 (17.8)		
Bad		39 (17.8)	72 (26.6)			52 (26.3)	56 (20.3)		
Realistic goal for fasting whole-blood glucose	213/270			0.048	195/276			0.009	0.35
≤7 mmol/l		58 (27.2)	92 (34.1)			51 (26.2)	98 (35.5)		

Table 2 (continued)

Attitude/opinion	Men (*n*=492)				Women (*n*=478)				Interaction *p* value[b]
	n (routine/structured)	Routine care	Structured personal care	*p* value[a]	*n* (routine/structured)	Routine care	Structured personal care	*p* value[a]	
>7 to 8 mmol/l		51 (23.9)	65 (24.1)			37 (19.0)	74 (26.8)		
>8 to 9 mmol/l		29 (13.6)	48 (17.8)			32 (16.4)	35 (12.7)		
>9 mmol/l		75 (35.2)	65 (24.1)			75 (38.4)	69 (25.0)		
Use of fact that patient was participating in study during consultations	218/268			<0.0001	196/277			<0.0001	0.29
Used vigorously		2 (0.9)	41 (15.3)			4 (2.0)	36 (13.0)		
Used moderately		17 (7.8)	123 (45.9)			17 (8.7)	120 (43.3)		
Only mentioned when necessary		199 (91.3)	104 (38.8)			175 (89.3)	121 (43.7)		

Values are given as *n* (% of randomisation group)

The *p* values are multivariate (multinomial) logistic regression models where the effect of structured care vs routine care is adjusted for age and diabetes duration. Clustering with GP is accounted for by the use of generalised estimating equations

[a] Tests effect of randomisation within gender group

[b] Tests whether the effect of randomisation differs between genders

Table 3 Outcomes from registry-based monitoring for 13 years after intervention was terminated

Outcome	No. of patients without outcome at end of intervention (routine/structured)	No. (%) of patients with outcome			Absolute risk (events per 1,000 patient-years)			HR (95% CI)[a] for structured care vs routine care						
		Routine care	Structured personal care	*p* value[b]	Routine care	Structured personal care	*p* value[c]	Adjusted for age, diabetes duration and clustering	*p* value[d]	Interaction *p* value[e]	Additionally adjusted for physical activity, smoking and clinical variables[f]	*p* value[d]	Interaction *p* value[e]	*n*
Any diabetes-related endpoint														
6–19 years men	138/183	87 (63.0)	104 (56.8)	0.29	87.4	77.1	0.38	0.89 (0.65, 1.21)	0.45	0.13	0.90 (0.67, 1.22)	0.50	0.13	319
6–19 years women	144/195	104 (72.2)	117 (60.0)	0.018	107.7	73.4	0.002	0.65 (0.49, 0.87)	0.003		0.65 (0.48, 0.87)	0.004		332
Diabetes-related deaths														
6–19 years men	219/271	84 (38.4)	110 (40.6)	0.64	43.8	49.3	0.42	1.20 (0.90, 1.60)	0.22	0.009	1.09 (0.81, 1.47)	0.56	0.015	444
6–19 years women	200/276	82 (41.0)	91 (33.0)	0.061	45.7	34.6	0.064	0.72 (0.54, 0.96)	0.026		0.70 (0.50, 0.96)	0.031		434
All-cause mortality														
6–19 years men	220/272	136 (61.8)	179 (65.8)	0.40	70.9	80.3	0.28	1.21 (0.96, 1.52)	0.10	0.003	1.11 (0.88, 1.40)	0.36	0.005	446
6–19 years women	201/277	123 (61.2)	146 (52.7)	0.061	68.5	55.5	0.083	0.78 (0.62, 0.99)	0.043		0.74 (0.57, 0.97)	0.028		435
MI														
6–19 years men	193/241	64 (33.2)	70 (29.1)	0.35	41.0	35.7	0.43	0.95 (0.68, 1.32)	0.75	0.27	1.00 (0.69, 1.44)	0.99	0.27	395
6–19 years women	183/257	58 (31.7)	61 (23.7)	0.06	35.5	25.3	0.063	0.72 (0.49, 1.05)	0.090		0.71 (0.45, 1.12)	0.14		406
Stroke														
6–19 years men	198/245	43 (21.7)	49 (20.0)	0.67	26.3	25.1	0.83	1.04 (0.67, 1.61)	0.86	0.021	0.78 (0.48, 1.28)	0.32	0.31	443
6–19 years women	190/253	46 (24.2)	37 (14.6)	0.008	28.9	15.6	0.004	0.51 (0.33, 0.78)	0.002		0.59 (0.36, 0.97)	0.038		443
Peripheral vascular disease														
6–19 years men	216/269	12 (5.6)	17 (6.3)	0.76	6.4	7.9	0.58	1.12 (0.49, 2.54)	0.79	0.085	1.10 (0.49, 2.46)	0.82	0.51	479
6–19 years women	198/275	9 (4.6)	6 (2.2)	0.14	5.1	2.3	0.11	0.37 (0.13, 1.06)	0.064		0.67 (0.20, 2.27)	0.52		461
Microvascular disease														
6–19 years men	211/261	28 (13.3)	31 (11.9)	0.66	16.0	15.0	0.78	0.95 (0.57, 1.60)	0.85	0.37	0.98 (0.57, 1.67)	0.94	0.62	467
6–19 years women	196/270	29 (14.8)	31 (11.5)	0.30	17.8	12.5	0.15	0.74 (0.42, 1.30)	0.29		0.90 (0.47, 1.70)	0.74		454

[a] HR is calculated in a Cox proportional hazard regression model. The corresponding 95% CIs and *p* values are determined using a sandwich estimator for the variance to account for clustering of patients within practices

[b] *p* value from a Rao–Scott χ^2 test: a Pearson χ^2 test adjusted for clustering of patients with GPs

[c] *p* value from a logrank test

[d] Tests the effect of randomisation within gender groups

[e] Tests whether the effect of randomisation differs between gender groups

[f] Besides age, diabetes duration and clustering, this model also adjusted for BMI, hypertension, HbA_{1c}, total cholesterol, sedentary physical activity, current smoking and receipt of glucose-lowering medication

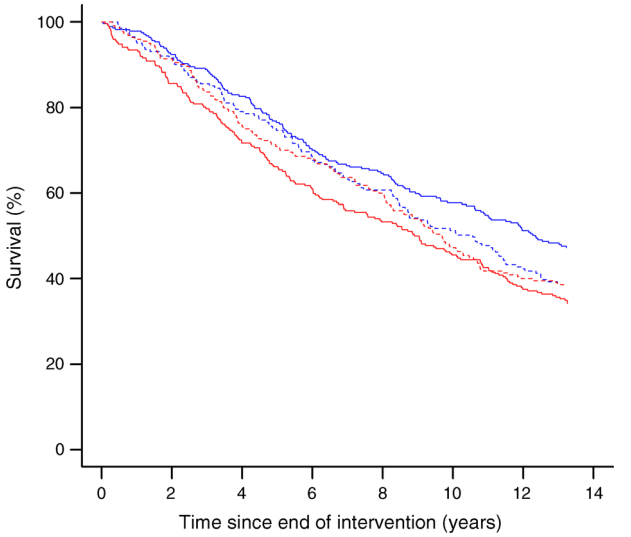

Fig. 2 Survival after end of intervention according to randomisation arm and gender. Solid blue line, structured care, women; solid red line, structured care, men; dotted blue line, routine care, women; dotted red line, routine care, men

In medical research, gender issues are usually presented as cross-sectional measures of difference, indicating a dichotomous and essentialist understanding of men and women. However, to explain the impact of gender on our study outcome, a more complex conceptual and theoretical framework is needed [30]. In this discussion, we shall regard gender in the context of social and cultural interaction ('doing gender') beyond an inborn property [30]. Taksdal and Widerberg have presented a framework assessing gender as 'biology', 'identity', 'symbol' and 'structure' [31]. We shall apply this framework to discuss potential hypotheses for the impact of gender, reflected by the difference in the intervention effect on all-cause mortality between men and women in our study.

In medicine, gender in terms of 'biology' (usually reported as 'sex') has traditionally been regarded as most relevant. Generally, women lose their female cardiovascular protection when suffering from type 2 diabetes [26]. This has been explained by epigenetic changes prompting more unfavourable presentation of oestrogen receptors associated with higher oxidative stress, pro-inflammatory profile and increased atherosclerotic plaque formation [32].

Gender in terms of 'identity' is linked with how people think, feel and behave when they incorporate masculinity and femininity and perform masculine or feminine roles. Women disclose their diabetes status and integrate management more readily into their lives, whereas men are more reluctant to talk about their diabetes and are less observant of self-management practices [8]. Women find it more stressful to accommodate their own needs and health concerns into daily life since they often see themselves as caretakers and givers rather than receivers [33]. We previously reported a more adaptive attitude towards treatment among women, and this could lead to better treatment adherence and disease outcomes [13]. Women report poorer social support compared with men [34], possibly linked to a poorer self-perceived quality of life [35]. This, together with health status, is related to increased mortality [36]. Hence, the structured diabetes intervention might have provided disease-related support and attention, which improved disease behaviour and self-perceived quality of life, leading to positive long-term outcomes for women.

Gender in terms of 'symbol' pertains to cultural images of masculinity and femininity—which is necessary to be considered a real man or a real woman [37]. Negotiating work and healthcare have been identified as barriers to disease self-management and acceptance of disease [38]. Men have been found to be less worried about long-term outcomes and to be more troubled by limitations to their personal freedom following diabetes diagnosis [34]. Men expect less benefit from self-management [34] and rely more on self-directed learning [8]. This may contribute to the poorer outcome among men in the structured diabetes intervention.

Gender in terms of 'structure' deals with work, economy, power and privileges. In most societies men are better educated, have higher positions in society, are more financially independent and take greater control of decision making than women. Several studies have shown that men with diabetes and CVD are more likely than women with comparable conditions to receive more intensive medical treatments such as statins, antihypertensive drugs and acetylsalicylates [26, 39], which would be expected to lead to better treatment outcomes. As we provided a focused, structured and personalised intervention for both men and women, quality of care could be assumed to be similar in both groups. Therefore, a possible treatment bias might have been levelled out, adding to improved outcomes among women.

Structured personal diabetes care could provide women with significant attention and support and thus provide an incentive to treatment adherence. Women accept disease and implement disease management more easily [13], which might affect long-term outcomes. Masculinity may be challenged by diabetes, demanding daily consideration and lifestyle changes [34]. The structured approach could conflict with men's tendency to trust self-directed learning instead of self-management.

Strengths and weaknesses of the study This is a post hoc analysis of a randomised controlled trial and the results should be interpreted as observational. The detailed information on possible confounders, however, allowed for extensive adjustment of HRs.

The outcomes of this study were drawn from the Danish national registries. The Danish Register of Causes of Death covers the entire population of Denmark [18] and the Danish National Patient Registry has covered discharges from Danish

hospitals since 1977 [19]. From 1995 onwards this registry has also covered outpatients, but contacts with the few and small private specialised hospitals were not included in the registry until 2007. The private hospitals may be considered relatively unimportant in the present analyses, as hardly any of the outcomes of interest are treated there.

Vital status was confirmed for all our study participants. The cause-specific mortality, in our study diabetes-related deaths, relies on the validity of the diagnoses in the national registries. These methodological considerations, however, are not relevant for the outcome of all-cause mortality. The validity has not been established for all the non-fatal outcomes. In one study, the predictive value of MI as primary diagnosis or underlying cause of death was 93.6% and the sensitivity was 77.6% in comparison with definite or possible MI [40]. For a stroke diagnosis the predictive value was 81–86% in the Danish National Patient Register when evaluated in an audit of patient records [41].

In the nationwide DCGP study, time-dependent changes in definitions of diseases and in registration and coding practices are unlikely to cause differential misclassification according to treatment allocation. This assumption of non-differential misclassification is supported by the fact that the diagnoses in the registries are almost entirely provided by GPs unaware of patients' randomisation status.

There are several arguments to support the generalisability of the present results to the wider population of patients with type 2 diabetes: the study sample was population-based; patients were included with no upper age limit; the setting was general practice where most patients with type 2 diabetes are treated; the elements of the intervention resemble standard procedures in general practice and a relatively high number of general practices participated. Due to our application of individualised treatment goals it is, however, uncertain whether patients subjected to treatment-to-target will show the same gender difference.

Clinical implications We present a post hoc observational analysis of a randomised trial comparing structured personal diabetes care with routine diabetes care. Of seven predefined outcomes, the intervention reduced all-cause mortality, diabetes-related death, any diabetes-related outcome and stroke in women, but not in men, and this gender difference was statistically significant for all-cause mortality and diabetes-related death. After 6 years of intervention, HbA_{1c} was only lowered in women, but the improvements in outcomes for women were preserved after adjustment for HbA_{1c}. Hence, we propose that the improved outcomes in women may be explained by complex social and cultural issues of gender. There is a need to further explore the gender-specific effects of major intervention trials in order to rethink the way we provide medical care to both men and women, so that both men and women benefit from intensified treatment efforts.

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Contribution statement NdFO developed the research question and wrote the protocol for this follow-up study together with the other authors. NdFO was responsible for the original study design, randomisation, intervention delivery and data collection and obtained funding. VS performed the statistical analyses. All authors made substantial contributions to the analysis and interpretation of data. KM contributed with gender theory. The paper was written by MØK, LH, ABSN and NdFO and the other authors revised it critically for important intellectual content. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final version of the manuscript. NdFO is guarantor.

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