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The development of multimorbidity during 16 years after diagnosis of type 2 diabetes

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Abstract

Objective: The aims of this study were to (1) quantify the development and composition of multimorbidity (MM) during 16 years following the diagnosis of type 2 diabetes and (2) evaluate whether the effectiveness of structured personal diabetes care differed between patients with and without MM. **Research design and methods:** One thousand three hundred eighty-one patients with newly diagnosed type 2 diabetes were randomized to receive either structured personal diabetes care or routine diabetes care. Patients were followed up for 19 years in Danish nationwide registries for the occurrence of outcomes. We analyzed the prevalence and degree of MM based on 10 well-defined disease groups. The effect of structured personal care in diabetes patients with and without MM was analyzed with Cox regression models. **Results:** The proportion of patients with MM increased from 31.6% at diabetes diagnosis to 80.4% after 16 years. The proportion of cardiovascular and gastrointestinal diseases in surviving patients decreased, while, for example, musculoskeletal, eye, and neurological diseases increased. The effect of the intervention was not different between type 2 diabetes patients with or without coexisting chronic disease. **Conclusions:** In general, the proportion of patients with MM increased after diabetes diagnosis, but the composition of chronic disease changed during the 16 years. We found cardiovascular and musculoskeletal disease to be the most prevalent disease groups during all 16 years of follow-up. The post hoc analysis of the intervention showed that its effectiveness was not different among patients who developed MM compared to those who continued to have diabetes alone.

Keywords

Multimorbidity, comorbidity, type 2 diabetes, chronic diseases, patient-centered care, intervention, primary care, general practice, post hoc analysis.

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Introduction

In recent decades, more effective treatments and longer survival have led to a higher proportion of patients living with two or more coexisting chronic diseases, also known as multimorbidity (MM).[1–3] In primary care, more than two-thirds of patients aged 50 years or over have MM,[2] and MM increases with age and relatively low socioeconomic status.[2,4,5] MM is a challenge to the health care system as it is associated with reduced physical function,[6] an experience of fragmented care,[7] increased mortality,[8,9] and increased health-care costs.[3] The most common chronic disease in MM patients is diabetes,[10–12] followed by stroke, cancer, ischemic heart disease, and chronic obstructive pulmonary disease (COPD).[12] For MM patients with diabetes, morbidity and mortality increase with the

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number of additional chronic conditions.[8,13] The treatment of patients with MM is also complicated by conflicting treatment guidelines,[14] and because of changing health needs, it has been proposed to replace disease-oriented care with patient-centered care in MM patients.[15] Since diabetes patients constitute a patient group with high risk of developing MM, it is important to identify the composition of diseases developed after diabetes diagnosis. Furthermore, few studies have focused on the development of MM in a longitudinal setting.[16,17]

Objectives

The Diabetes Care in General Practice (DCGP) study included a large population-based sample of patients newly diagnosed with type 2 diabetes, and the study tested the effectiveness of structured personal diabetes care in a randomized design.[18] The aim of the present study was to answer three research questions:

1. How many of the newly diagnosed type 2 diabetes patients developed MM during 16 years after diabetes diagnosis, according to a clinically relevant definition?
2. How was the composition of MM over time among type 2 diabetes patients?
3. Did the intervention of structured personal care have a statistically significant different effect on the seven predefined outcomes in patients with and without MM?

Research design and methods

The DCGP study was an open, cluster-randomized, controlled trial of the effect of structured personal diabetes care versus routine care with 474 general practitioners (GPs), who volunteered to participate (ClinicalTrials.gov NCT01074762). A detailed description of the DCGP study design has previously been reported by Hansen et al.[18] The Copenhagen and Frederiksberg Research Ethics Committee approved the DCGP study.

Patients

The participating GPs were asked to include all patients on their practice lists who were aged 40 years or over and newly diagnosed with type 2 diabetes during 2 years in 1989–1991, but 71 intervention doctors volunteered to recruit patients for a further year (Figure 1). Following recruitment, diabetes diagnosis was confirmed by a single fasting whole-blood/plasma glucose concentration ($\geq$7.0/8.0 mmol/l) measured at a major laboratory. The protocol-based exclusion criteria were life-threatening somatic disease, severe psychiatric disease, or unwillingness to participate (Figure 1). As previously reported, the randomization was balanced.[18] Of the 1381 patients in the final study population, 1369 (99.1%) patients were of Western European descent. Based on whether insulin treatment was started and continued within 180 days after diabetes diagnosis, approximately 97.5% of the patients were considered to have type 2 diabetes.[19]

Intervention

The intervention began when a patient was included in the study from March 1, 1989 to February 28, 1992, and it was terminated for all patients on September 26, 1995. The intervention patients were offered follow-up every 3 months and annual screening for diabetes complications. The consultations focused on risk factor control (glycemia, blood pressure, and lipid profile) and lifestyle changes (diet, weight reduction, smoking cessation, and increased physical activity).[19] Together the patient and the doctor defined attainable goals for control of important risk factors, and at each quarterly follow-up consultation, they were asked to compare achievements with goals and to consider adjusting goal or treatment accordingly. Further details about the intervention have previously been described.[18]

Clinical and registry-based follow-up

To examine objectives 1 and 2, we used registry-based follow-up on all newly diagnosed type 2 diabetes patients. Both intervention and control group were included in these analyses.

A clinical follow-up examination was completed for 970 (93.4%) of 1039 surviving patients (Figure 1) 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.

A description of all variables and definitions has previously been published.[18]

The following Danish registries provided information about MM and the predefined outcomes of the trial: (1) Information on vital and emigration status of all patients were ascertained through the Danish Civil Registration System (CRS) using the unique personal identification number assigned to all residents living in Denmark, which enables unambiguous linkage between study populations and all Danish national registries.[20] All surviving patients were censored on December 31, 2008, using CRS. (2) The Danish Register of Causes of Death supplied information about underlying and possible contributory causes of death.[21] In four patients, the cause of death was not recorded. (3) Information on cancer diagnoses was from The Danish Cancer Registry.[22] (4) The Danish National Patient Register gave information on hospital contacts in Denmark, for example, discharge diagnoses and surgical procedures performed.[23] (5) Psychiatric diagnoses, however, were from the Danish Psychiatric Central Research Register of patients treated at psychiatric departments.[24]

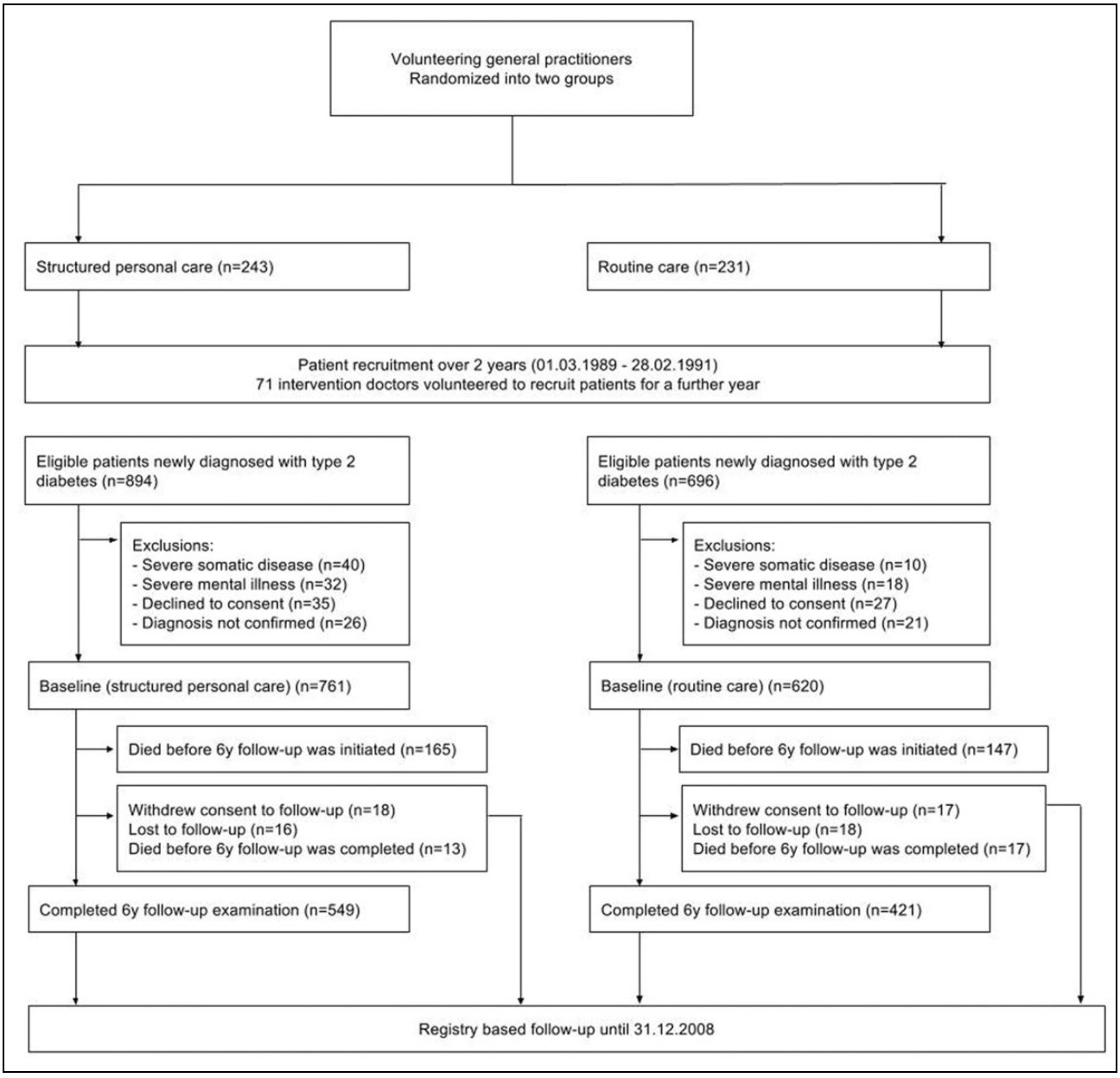

Figure 1. Patient flow.

MM was defined as having diabetes and at least one other chronic condition from 1 of 10 different diagnosis groups: lung, musculoskeletal, thyroid, mental illness, cancer, neurological, gastrointestinal, cardiovascular, chronic kidney, and eye disease. Each group contained preselected diagnosis and procedure codes, coded as International Classification of Diseases, 10th edition (ICD-10) and the earlier version 8th edition (ICD-8)[25] and Nordic Classification of Surgical Procedures.[26] If patients had more than one diagnosis within a diagnosis group, we counted this as only one comorbidity when estimating the degree of MM. Some of the outcomes contained diagnoses that were also included in the definition of MM. If the patient shifted status from diabetes alone to MM due to the occurrence of an outcome, the change in status was registered after the occurrence of the outcome. We only included the first occurrence of an outcome in the analyses. All later incident cases of the same outcome were not included. At diabetes diagnosis, MM was estimated by looking 10 years back in time, except for psychiatric diagnoses that were used without any time limit. The diagnoses were selected based on the following criteria: chronic condition, high prevalence in the general population, relevance for primary care, condition associated with reduced life expectancy, condition of a certain severity, and/or associated with a considerable disease burden for patients (Online Supplemental Material, Table S1). The predefined outcomes of the randomized trial were all-cause mortality, diabetes-related death, "any

diabetes-related endpoint", myocardial infarction, stroke, peripheral vascular disease, and microvascular disease[18] (Online Supplemental Material, Table S2).

Statistical analysis

For objectives 1 and 2, only data from up to 16 years after diabetes diagnosis were used in the analyses as the inclusion phase lasted for 3 years. For objective 3, the full data set with up to 19 years of follow-up was used, and we investigated the incidence of the predefined outcomes in Cox regression models where the diagnosis of MM was a time-varying covariate. This means that the same patient could have contributed to both the diabetes mellitus and the MM group when analyzing outcomes. The Cox model was fit by maximizing the partial likelihood and the baseline survivor function computed using the Breslow estimate. Hazard ratios (HRs) for the intervention effect were calculated for patients with and without MM, respectively, and 95% confidence intervals (CIs) and p values were determined using a sandwich estimator for the variance to account for clustering of patients within practices.[27] The assessments of the intervention effects were adjusted for the following variables at diagnosis: age, sex, cohabitation status, education, body mass index, hypertension, diagnostic fasting plasma glucose, total cholesterols, physical activity, and smoking. Patients with missing values in one or more variables were omitted from the analyses where these variables were included. Incidence rates for each outcome were calculated as the number of patients experiencing the corresponding outcome divided by the person time at risk, that is, from diagnosis to the first occurrence of the outcome, death, or end of follow-up. Patients with any occurrence of an outcome before diabetes diagnosis were excluded from the analyses pertaining to that outcome. Analyses were done in SAS (version 9.4). The level of statistical significance was $p < 5\%$.

Results

At diabetes diagnosis, 31.6% of the patients had MM. The proportion of MM patients increased after diagnosis to 80.4% after 16 years. During the same period, the proportion of patients with diagnoses from two or more disease groups besides diabetes increased from 8.1% to 47.6%. The emergence of still higher degrees of MM in surviving patients during the 16 years after diabetes diagnosis is illustrated in Figure 2.

Compared to patients with diabetes alone, patients with MM were older and more often lived alone (Table 1). Furthermore, they were less physically active and more likely to suffer from hypertension and to report relatively low self-rated health.

During the first 16 years after the diagnosis of type 2 diabetes, the most prevalent chronic conditions in surviving patients were cardiovascular and musculoskeletal diseases

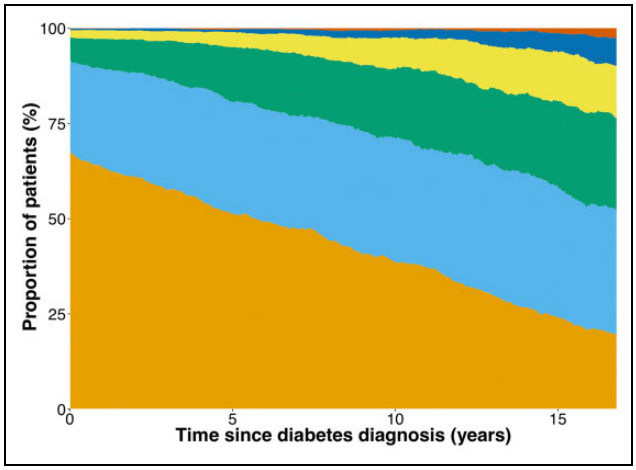

Figure 2. The development of MM during 16 years after diabetes diagnosis. Orange: diabetes only; light blue: diabetes + one chronic disease; green: diabetes + two chronic diseases; yellow: diabetes + three chronic diseases; blue: diabetes + four chronic diseases; red: diabetes + five chronic diseases. MM: multimorbidity.

(Figure 3). While the prevalence of cardiovascular diseases declined, it increased for musculoskeletal diseases. Prevalence of both neurological diseases and eye diseases increased during follow-up and were eventually the third and fourth most common disease group among the MM diabetes patients.

For each of the seven predefined outcomes, the incidence rate was greater among patients with MM than among patients with diabetes alone during the 19 years of follow-up (Table 2). In the main trial, the intervention reduced the risk of myocardial infarction and "any diabetes-related endpoint",[18] while in the present post hoc analysis, the intervention only reduced the incidence of "any diabetes-related endpoint"—and only in patients with MM (Table 2). The effectiveness of the intervention, however, did not show a statistically significant difference between patients with and without MM for any outcome, and there was no clear trend as to whether the intervention effect was relatively larger or smaller among MM patients compared to patients with diabetes only.

The intervention did not influence the emergence of MM in a multivariable adjusted Cox model (structured care vs. routine care: adjusted HR, 0.87; 95% CI, 0.75–1.01; $p = 0.059$).

Conclusions

This study found increasing prevalence and changing composition of MM during the first 16 years after the diagnosis of type 2 diabetes. Furthermore, structured personal diabetes care reduced the incidence of the aggregate outcome, "any diabetes-related endpoint," by 28% among patients with MM. There were no statistically significant differences in the intervention effect between patients with and

Table 1. Characteristics of patients with and without MM at diabetes diagnosis and 6 years later.[a]

		At diabetes diagnosis			Six years after diabetes diagnosis	
	N (DM alone/MM)	DM alone	MM	*N* (DM alone/MM)	DM alone	MM
Sociodemographic						
Age (years)	964/417	64.1 (54.0–72.7)	67.3 (59.4–75.2)	490/480	66.4 (57.3–74.9)	71.4 (62.8–79.0)
Male gender	964/417	509 (52.8)	224 (53.7)	541/528[d]	279 (51.6)	271 (51.33)
Live alone[b]	942/407	283 (30.0)	151 (37.1)	467/443	145 (31.1)	178 (40.2)
Basic school education	916/395	708 (77.3)	325 (82.3)	523/499[d]	388 (74.2)	404 (81.0)
Clinical						
Body mass index (kg/m^2)	958/414	29.0 (26.0–32.7)	29.3 (26.3–32.6)	483/464	28.4 (25.7–31.8)	28.3 (25.1–32.1)
Hypertension (yes)	964/417	683 (70.9)	343 (82.3)	490/480	330 (67.4)	379 (79.0)
Systolic blood pressure (mmHg)	959/415	150 (130–160)	150 (130–160)	487/474	150 (135–160)	148.5 (130–160)
Diastolic blood pressure (mmHg)	959/415	85 (80–90)	80 (80–90)	487/474	85 (80–90)	80 (76–90)
Biochemical						
Hemoglobin A1c (%)[c]	827/309	10.2 (8.8–11.8)	9.9 (8.4–11.6)	483/470	8.7 (7.9–9.9)	8.5 (7.6–9.7)
Hemoglobin A1c (mmol/mol)	827/309	88 (73–105)	85 (68–103)	483/470	72 (63–85)	69 (60–83)
Fasting plasma glucose	964/417	13.9 (10.8–17.2)	13.2 (10.3–16.6)	378/348	8.5 (6.9–10.9)	8.3 (6.5–13.9)
Total cholesterol (mmol/l)	945/405	6.2 (5.4–7.1)	6.2 (5.4–7.2)	483/469	6.0 (5.3–6.8)	6.0 (5.2–6.9)
Fasting triglycerides (mmol/l)	943/403	1.9 (1.4–2.9)	2.1 (1.5–3.0)	442/417	1.7 (1.2–2.5)	1.9 (1.4–2.8)
Serum creatinine (μmol/l)	946/405	88 (79–98)	93 (82–107)	483/469	87 (79–99)	94 (81–109)
Urinary albumin	928/390			468/439		
Normal		539 (58.1)	221 (56.7)		300 (64.1)	247 (56.3)
Microalbuminuria		345 (37.2)	148 (38.0)		158 (33.8)	158 (36.0)
Proteinuria		44 (4.7)	21 (5.3)		10 (2.1)	34 (7.7)
Behavioral[b]						
Sedentary physical activity (yes)	939/406	225 (24.0)	147 (36.2)	465/436	99 (21.3)	172 (39.5)
Current smoking (yes)	940/406	348 (37.0)	124 (30.5)	461/442	145 (31.5)	133 (30.1)
Patient attitudes[b]						
Self-rated health	943/407	943 (100)	407 (100)	468/441	468 (100)	441 (100)
Excellent		133 (14.1)	26 (6.4)		113 (24.2)	58 (13.2)
Good		360 (38.2)	88 (21.6)		218 (46.6)	148 (33.6)
Fair		375 (39.8)	230 (56.5)		127 (27.1)	200 (45.4)
Poor/very poor		75 (8.0)	63 (15.5)		10 (2.1)	35 (7.9)
Process of care[b]						
Number of consultations last year				489/480	6 (4–9)	7 (5–11.5)
Number of diabetes-related consultations				489/480	4 (3–6)	4 (3–6)

DM: diabetes mellitus; MM: multimorbidity; IQR: interquartile range.
[a]Values are medians (IQR) or numbers (percentages of group).
[b]Data from questionnaires to patients (behavioral) or their general practitioners (process of care).
[c]The diagnostic value is limited to measurements from within 45 days of diabetes diagnosis. Reference range: 5.4–7.4%.
[d]For these variables, the totals refer to the number of patients alive when the 6-year examination was initiated.

without MM for this or any of the other six predefined outcomes.

Research in MM is in its infancy, and there is no agreement on how it is defined. It is acknowledged, however, that the diseases included in the definition of MM should be the most prevalent and those with a high burden of disease.[28,29] In line with this view, we chose a relatively simple definition of MM that would be easy to implement in clinical practice using 10 diagnoses groups of chronic diseases. Each group contained preselected clinically linked diagnoses with similarities in pathophysiological risk profile and treatment.[30] Our definition was partly based on previous recommendations on defining MM.[28,31]

In the definitions of MM, the most common disease constituting MM was found to be diabetes, followed by stroke, cancer, ischemic heart disease, and COPD.[12] In a study examining chronic comorbidity clusters in patients with type 2 diabetes, the most common diseases were

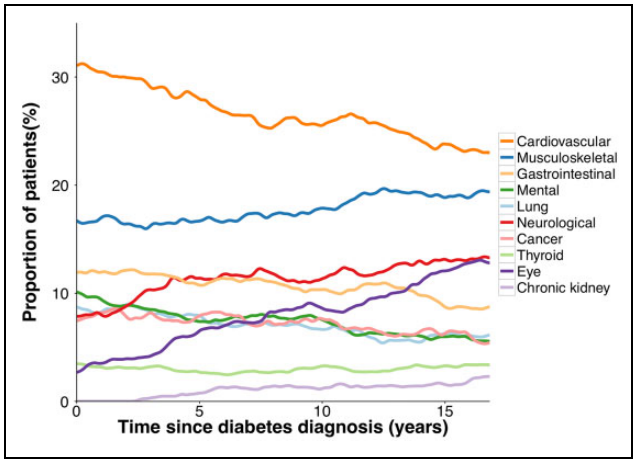

Figure 3. The prevalence of 10 disease groups during 16 years after diabetes diagnosis.

cardiovascular and musculoskeletal diseases, just as we found in the present study.[32]

In accordance with clinical experience, we found that the degree of MM increased markedly after the diagnosis of type 2 diabetes; the prevalence of MM, defined as having at least one chronic disease besides diabetes, increased from 31.6% at diagnosis to 80.4% during the first 16 years after diabetes diagnosis. Because of the large variation in definitions of MM in the existing literature, these results could not be compared with the results from other studies.[8,10–12,28] While the observed increase in the prevalence of eye diseases after diabetes diagnosis was expected,[33] the decrease in cardiovascular disease was probably a result of selective survival. One of our interesting findings was the relatively high proportion of multimorbid diabetes patients having musculoskeletal disease. In the present study, kidney disease was rare, but in our definition of MM, with preselected chronic diagnoses, we only included severe chronic kidney diseases, which generated hospital contacts.

We found that MM was associated with relatively high age, living alone, sedentary lifestyle, and relatively low self-rated health. These observations were in accordance with previous MM research.[1–5,34–37]

This study meets a previously expressed need for examining the effectiveness of a patient-centered approach in the management of patients with diabetes and coexisting chronic morbidities.[32] In a recent post hoc analysis of the DCGP study, we found an especially pronounced effect of structured personal care among patients with a severe psychiatric disease.[38] Although the diabetes patients with MM in the DCGP study were also at high risk of developing serious outcomes (Table 2), the effect of the same intervention did not differ between patients with or without coexisting chronic disease. The DCGP study implemented self-management in the shape of collaborative goal setting, self-efficacy strategies, and a close doctor–patient relationship—a strategy that is being increasingly recognized as a key component for improving the health status of people with multiple chronic conditions.[39] A recently updated Cochrane review[40] on interventions for patients with MM also concluded that interventions targeting the management of specific risk factors or focused areas of increased difficulty were more likely to be effective. Lately, methods have been developed for managing patients with MM in primary care: like the DCGP study, these methods involve realistic goal setting based on the prioritization of health problems, taking the patient's preferences into account,[41,42] and there is a great need for further intervention research within this area.

Strengths and limitations

The results from this post hoc analysis of the DCGP trial should be interpreted as observational since these analyses were not mentioned in the original study protocol. Even though the GPs volunteered to participate in the study, we believe that the patients included in the DCGP study were not different from patients having doctors not willing to participate, because the GPs were recruited from all over Denmark, making the study sample representative for the patients with newly diagnosed type 2 diabetes in Denmark at the time the study was conducted.[19] Further strengths were the relatively large sample of newly diagnosed patients, the long follow-up, and the availability of many confounders for the multivariate adjustments.

The five major Danish national registries used to ascertain both outcomes and the development of MM in the present analyses are believed to have high completeness and accuracy (Online Supplemental Material, Tables S1 and S2).[20–24] Previous studies on Australian hospital administrative data on discharge diagnoses showed a significant underreporting of comorbidities.[43] The Danish National Patient Register contains diagnoses and procedure codes from both inpatient and outpatient wards and is not limited to discharge diagnoses; however, it has served as a basis for payment to the public hospitals since 2000, and since this study also extracted data before this period, it is a possible limitation that the completeness has not been as accurate before the year of 2000.

This way of defining MM disregarded diagnoses made in general practice alone, such as minor psychiatric disorders, moderate asthma, and all levels of kidney disease, which would not get treated or registered in accordance with contacts in the secondary sector. On the other hand, it could be regarded as a strength that our definition of MM rested on diagnoses from secondary care, as this implied relatively high severity of the diseases that we included in our analyses. Since we included both inpatient and outpatient hospital wards, an actual hospitalization was not required. Even though we made a thorough preselection and included a high number of prevalent and serious diagnoses, it is a limitation that some rare but important diagnoses could have been overlooked resulting in some severely ill persons not being considered as such. However,

Table 2. Mortality and diabetes-related outcomes for diabetes patients with and without MM during 19 years of follow-up.

	Structured personal care			Routine care					
	Number of events	Person years	Absolute risk Events per 1000 patient years (95% CI)	Number of events	Person years	Absolute risk Events per 1000 patient years (95% CI)	HR[b] for structured care versus routine care (95% CI)[c]	*P* value[d]	Interaction *P* value[e]
All-cause mortality									
DM alone	54	4081	13.2 (9.9–17.3)	53	3188	16.6 (12.5–21.8)	0.80 (0.55–1.18)	0.27	0.39
MM[a]	476	4776	99.7 (90.9–109.0)	400	3940	101.5 (91.8–112.0)	0.96 (0.83–1.11)	0.59	
Diabetes-related deaths									
DM alone	30	4081	7.4 (5.0–10.5)	28	3188	8.8 (5.8–12.7)	0.89 (0.50–1.58)	0.69	0.78
MM	305	4776	63.9 (56.9–71.4)	257	3940	65.2 (57.5–73.7)	0.97 (0.81–1.16)	0.73	
"Any diabetes-related end point"									
DM alone	214	3845	55.7 (48.4–63.6)	191	3027	63.1 (54.5–72.7)	0.88 (0.71–1.09)	0.25	0.20
MM	382	2139	178.6 (161.2–197.5)	344	1596	215.5 (193.3–239.6)	0.72 (0.58–0.89)	0.0022	
Myocardial infarction									
DM alone	53	4044	13.1 (9.8–17.2)	54	3158	17.1 (12.8–22.3)	0.75 (0.48–1.17)	0.21	0.77
MM	205	3969	51.6 (44.8–59.2)	192	3105	61.8 (53.4–71.2)	0.81 (0.65–1.02)	0.068	
Stroke									
DM alone	50	4036	12.4 (9.2–16.3)	42	3130	13.4 (9.7–18.2)	0.98 (0.64–1.52)	0.94	0.72
MM	151	3981	37.9 (32.1–44.5)	144	3273	44.0 (37.1–51.8)	0.90 (0.68–1.17)	0.42	
Peripheral vascular disease									
DM alone	8	4048	2.0 (0.8–3.9)	8	3151	2.5 (1.1–5.0)	1.04 (0.36–3.06)	0.94	0.73
MM	32	4702	6.8 (4.7–9.6)	31	3870	8.0 (5.4–11.4)	0.84 (0.47–1.52)	0.57	
Microvascular disease									
DM alone	31	4074	7.6 (5.2–10.8)	30	3188	9.4 (6.3–13.4)	0.78 (0.46–1.33)	0.36	0.46
MM	96	4388	21.9 (17.7–26.7)	82	3562	23.0 (18.3–28.6)	0.97 (0.67–1.40)	0.87	

DM: diabetes mellitus; MM: multimorbidity; CI: confidence interval; HR: hazard ratio.

[a]MM is defined as DM + 1 or more morbidities (see Online Supplemental Material, Table S1).

[b]The HR is calculated in a Cox proportional hazard regression model where the degree of MM is a time-varying covariate. The corresponding 95% CI and *p* values are determined using a sandwich estimator for the variance to account for clustering of patients within practices.

[c]Adjusted for age, sex, and clustering, as well as for the following variables at diagnosis: live alone, basic school education, body mass index, hypertension, diagnostic fasting plasma glucose, total cholesterol, sedentary physical activity, and current smoking.

[d]Tests the effect of randomization within patient groups with and without MM.

[e]Tests whether the effect of randomization is different between patient groups with and without MM.

when defining MM, a limited number of preselected diagnoses are widely used.[4,10,12,44]

In conclusion, 80% of patients with type 2 diabetes had MM 16 years after diabetes diagnosis. Cardiovascular and musculoskeletal diseases were the most prevalent morbidities. While musculoskeletal, neurological, eye, and chronic kidney diseases increased after diabetes diagnosis, the prevalence of cardiovascular, gastrointestinal, mental illness, cancer, and lung diseases decreased. The risk of all outcomes was significantly greater for patients with MM compared to patients having diabetes only. The intervention of structured personal diabetes care, however, lowered the risk of the aggregate outcome, "any diabetes-related endpoint", but this result was not obtained for the remaining outcomes and the intervention effect was not different between patients with and without MM. High-risk patients with MM, however, did seem at least as susceptible to interventions as type 2 diabetes patients without comorbidities.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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