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Effectiveness of chronic care models for the management of type 2 diabetes mellitus in Europe: a systematic review and meta-analysis

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ABSTRACT

Objectives: Patient-centred multifaceted care programs are considered to represent optimal chronic care. Our aim was to review the effectiveness of European chronic care programs for type 2 diabetes mellitus (characterized by integrative care and a multi-component framework for enhancing healthcare delivery), compared with routine diabetes care.

Design: Systematic review and meta-analysis.

Data sources: Medline, Embase, Central, and Cinahl from January 2000 to July 2015.

Eligibility criteria: Randomized controlled trials focussing on (i) adults with type 2 diabetes, (ii) multifaceted diabetes care interventions specifically designed for type 2 diabetes and delivered in primary or secondary care, targeting patient, physician, and health care organization, and (iii) usual diabetes care as the control intervention.

Data extraction: Study characteristics, data on baseline demographics and changes in patient outcomes, including HbA1c, blood pressure, and cholesterol level.

Data analysis: Weighted mean differences in change in HbA1c and total cholesterol levels between intervention and control patients (95% confidence interval) were estimated using a random-effects model.

Results: Seven cluster randomized controlled trials were included for review (9,529 patients). One year of multifaceted care improved HbA1c levels in patients with screen-detected and newly diagnosed diabetes, but not in patients with prevalent diabetes, compared to usual diabetes care. Across all seven included trials the weighted mean difference in HbA1c change was -0·07% (95% confidence interval: -0·10 to -0·04) (-0·8 mmol/mol (95% confidence interval:-1·1 to -0·4)); I^2=21%. The findings for total cholesterol, LDL-cholesterol and blood pressure were similar to HbA1c, albeit statistical heterogeneity between the studies was considerably larger.

Conclusions: Effects of European multifaceted diabetes care patient outcomes are only small. Improvements are somewhat larger for screen-detected and newly diagnosed diabetes patients than for patients with prevalent diabetes.

Strengths and limitations of this study

- This is the first systematic review providing a comprehensive overview of studies that have evaluated the effectiveness of multifaceted diabetes care programs addressing all their components together, rather than separately.
- The focus in this systematic review was on European multifaceted diabetes care programs only, to meet the need for efficient and established programs to providing optimal chronic care due to the burden of increasing diabetes prevalence in Europe.
- There is an important lack of studies which evaluate the effectiveness of implementing of all Chronic Care Model-components simultaneously.
- Overall, the studies included in this systematic review provided insufficient details to fully understand the intensity of the intervention, and there was only little overlap in the wide range of outcome measures were evaluated.

INTRODUCTION

Chronic disease management relies on the assumption that providing optimal chronic care requires changes of both patients and professionals with regard to behaviour, culture, and communication.[1 2] Indeed, with aging of the population and the growing prevalence of chronic diseases, initiatives to improving quality of chronic care require more than evidence about effective diagnostic procedures and treatments in comparison to acute disorders.[3] Aimed at describing essential elements for improving outcomes in care of chronic diseases, the Chronic Care Model (CCM) was developed in the mid-1990s and was further refined in 1997.[2 4 5] This primary care-based model is based on the assumption that improvements in care require an approach that incorporates patients, health care providers, and system level interventions.[4 6] The CCM comprises six interrelated components deemed essential for providing high-quality care to patients with chronic disease: (i) health care organization (i.e. providing leadership for securing resources and removing barriers to care), (ii) self-management support (i.e. facilitating skills-based learning and patient empowerment), (iii) decision support (i.e. providing guidance for implementing evidence-based care), (iv) delivery system design (i.e. coordinating care processes), (v) clinical information systems (i.e. tracking progress through reporting outcomes to patients and providers, and (vi) community resources and policies (i.e. sustaining care by using community-based resources and public health policy).[7]

The current literature indicates a widespread application of the CCM to multiple illnesses and various studies have provided a rigorous evaluation of its individual components.[5 8-14] In general, these studies have reported positive effects on patient outcomes and processes of care. The reported effect sizes, however, are relatively small and many outcomes are flawed by a considerable level of statistical heterogeneity.[10 13-25]

An aspect that complicates the assessment of effectiveness of chronic care programs is their inherent multi-component nature.[14 20 25] While some authors found that the total number of CCM elements incorporated in the interventions did not influence patient outcomes,[9 10] others

concluded that interventions containing more than one CCM component were more successful at improving the quality of care than single-component interventions.[11 24 26 27] To date, no summative reviews have evaluated to which extent the complete CCM – thus all six components combined in interventions – improves diabetes care.

As such, the aim of the current review was to systematically identify studies of diabetes care assessing the effect of interventions addressing all six components of the CCM, in order to describe the effects of these models on biochemical and patient-reported outcomes in older patients with type 2 diabetes compared to routine diabetes care.

METHODS

Our systematic review was based on a protocol with input from experts in diabetes care, statistical methods, and primary care, composed according to the PRISMA-P guidelines.[28]

Data sources and searches

We identified studies by searching MEDLINE, Embase, CINAHL and CENTRAL from 2000 until July 2015. Search syntaxes were developed in consultation with the Cochrane Metabolic And Endocrine Disorders Group by adapting and combining published search strategies from previous systematic reviews on chronic (diabetes) care management.[10 12] Given that the CCM – and its terminology – had been introduced in the late 1990s, we restricted the search to publications from January 2000 onwards. In addition, reference lists of eligible studies and systematic reviews on multifaceted diabetes care were searched by hand to identify additional studies. The full MEDLINE search strategy is available in the online supplementary file S1.

Study selection

One reviewer (BB) identified potentially relevant studies for inclusion by screening title and abstract of all citations that resulted from our literature search. Two reviewers (BB and WR) then screened the full text of these articles. Only (cluster) randomized controlled trials were considered eligible for inclusion. Non-randomized studies were excluded, as were studies written in a language other than English. Trials eligible for inclusion had to comply with the following inclusion criteria.

Type of participants: individuals, regardless of gender and ethnicity, diagnosed with type 2 diabetes, and with or without comorbidities.

Type of intervention: previous systematic reviews on multifaceted chronic care have reported that randomized-controlled-trial-interventions are generally described poorly and incomprehensively, which complicates mapping the individual elements of the intervention to the six CCM components. To avoid mapping difficulties, we have reformulated the following inclusion criteria for the interventions: The intervention had to be described as a multifaceted chronic care model or program that (i) was designed specifically for individuals with type 2 diabetes, (ii) was based on guidelines, (iii) provided multi-disciplinary care, (iv) addressed patient empowerment, (v) provided quality management (e.g. patient registry systems, recording of process measurements and adherence to guidelines, achievement of treatment goals), (vi) was delivered in primary or secondary care, and (vii) had a minimum duration of six months. The control intervention had to be defined as usual diabetes care as recommended in that particular country (e.g. regular follow-up with the required health professional and a full diabetes annual review).

Type of outcome measures: we considered three categories of outcome measures: (i) biochemical outcomes, such as HbA1c, triglyceride and cholesterol levels, (ii) patient-reported outcomes, including diabetes-related quality of life and patient empowerment, and (iii) diabetes complications, such as retinopathy, nephropathy, neuropathy, cardiovascular disease, and mortality.

Any disagreements between the two reviewers regarding the in- or exclusion of studies were resolved by consensus.

Data extraction and quality assessment

Using a standard structured data abstraction form, one reviewer (BB) performed the data extraction which was confirmed by a second reviewer (WR). The extracted data included study design, length of intervention/follow-up, sample size, in- and exclusion criteria, mean or median age of the included sample, percentage males, study setting (i.e., primary or

secondary care), intervention details, and mean differences in change for various outcomes. When important information or outcome data were missing, trial authors of the included studies were contacted. When unavailable, the particular data were not included in the analyses.

The standard Cochrane EPOC Risk of Bias Tool was used to assess risk of bias for each of the selected studies.[29] Since all included studies were cluster-randomized controlled trials, additional attention was given to potential sources of bias specific to cluster-randomized trials: (i) recruitment bias: did recruitment of diabetes patients take place before or after randomization of the clusters?, (ii) did the intervention and control group differ in baseline characteristics?, (iii) did any of the clusters drop out during follow-up?, (iv) was clustering accounted for in the statistical analyses? If a certain domain could not be classified as “high” or “low” risk of bias due to inadequate reporting, it was deemed “unclear” risk of bias.

Data synthesis and analysis

Due to heterogeneity of the study populations and duration of the interventions, and due to the small overlap in outcomes of the individual trials, an extensive meta-analysis and meta-regression of the reported outcome variables was not possible. The available data only allowed to statistically pool the results for HbA1c concentrations and total cholesterol levels. Review Manager (RevMan 5.2.0; the Cochrane Collaboration) was used to compute the weighted mean difference in change in HbA1c and total cholesterol between intervention and control groups. To incorporate both between- and within-study variance we used a random effects model for estimating the weighted mean differences in change between intervention and control group across the included trials.[30] Mean differences were pooled separately for the different types of diabetes patients (prevalent, screen-detected, and newly diagnosed), and subsequently for all seven trials. The consistency of the findings across the studies was assessed using forest plots. We evaluated statistical heterogeneity by calculating the I^2

statistic, a measure independent of the number of studies and effect size metric.[31] All outcomes variables other than HbA1c and total cholesterol, we analysed descriptively.

RESULTS

Figure 1 summarises the identification of relevant studies and the numbers of excluded and included studies. The search of the electronic databases identified 9,464 abstracts of studies published between January 2000 and July 2015. After excluding duplicate citations (n=1,227) and studies unrelated to the current review´s topic (n=7,801), we considered 436 articles for full-text review. Another 424 studies failed to meet our explicit inclusion criteria, including 128 systematic reviews on chronic diabetes management from which the reference lists were subsequently searched for additional relevant studies. In total, eleven articles met our inclusion criteria and were included in the current review.[32-42]

<insert figure 1 here>

Study Characteristics

The 11 included articles[32-42] reported on eight unique cluster randomized controlled trial,[32 34 38-40 42-44] carried out between 1989 and 2011. All trials had recruited either general practitioners or physician practices which represented the cluster level (level of randomization). In one study,[44] however, first-level clusters were formed by district (characterized as urban, rural and mixed) and second-level clusters by the physicians. The total number of patients with type 2 diabetes enrolled by the physicians amounted to 9,529, of whom 8,921 (94%) had been included in the analyses.

The objective of each trial was the structured multifaceted management of diabetes, and the interventions were aimed at improving the patients´ cardiovascular risk profile[43 44] and metabolic control,[32 34 38 39 42 43] and assessing the effect of multifaceted care on the occurrence of cardiovascular events,[34 38 39 42] overall mortality,[40] and risk factors for clinical complications.[40] Interventions focused on all aspects of the CCM including more regular and frequent consultations, annual screening for diabetes complications, patient

education/advice, guideline-based clinical treatment and physician education, regular/annual feedback reports to physicians, referrals, record keeping, formation of multidisciplinary (primary care provider) teams, delegation of routine diabetes tasks to a trained practice nurse, patient and physician reminders, and patient-physician communication and decision-making. The interventions were largely delivered by general practitioners and physicians, yet specialized nurses or practice nurses were also involved in the intervention-program as part of the practice team and to (partly) replace the physician in providing diabetes care.[32 34 38 39 42 43]

Two main aspects differed among the eight trials: the type of diabetes patient enrolled and the duration of the intervention. Three trials[32 43 44] had included patients with prevalent diabetes and intervened for one year. The average diabetes duration in these studies ranged from 5.8 to 9.5 years. One trial[40] had enrolled patients with newly diagnosed type 2 diabetes and assessed outcome measures after six years of intervention. Finally, there were four trials[34 38 39 42] that first had initiated a diabetes screening program and subsequently had recruited those with screen-detected diabetes to participate in the intervention study. Follow-up measurements were assessed at one year and at five years. The five-year data of these four studies were not published by the individual trials, yet were pooled in the Addition-Europe study.[45] We included the Addition-Europe study as the ninth trial in this review. Furthermore, Addition-Denmark[39] and Addition-Cambridge[34] had not published their one-year data in sequel to their study protocols. Hence, we had to exclude these two trials from this review, bringing the total number of included studies back to seven. Table 1 presents an overview of the study characteristics and findings of these seven studies. Online supplementary tables S1a and S1b present the baseline patient characteristics for the trials that recruited patients with prevalent diabetes[32 43 44] and for the trials that recruited patients with screen-detected[38 42 45] and newly diagnosed diabetes,[40] respectively.

Table 1: Characteristics of the included cluster randomized controlled trials

Study	Comparison	Effect on endpoints*	Notes
Cleveringa 2008[32]	Patient consultation by a practice nurse + use of a computerized decision support system + guideline-based care + physician support by practice nurse + interdisciplinary care by a specialist team + individualised treatment advice + patient education + physician feedback + recall system + regular patient consultations by practice nurse + physician feedback *vs* routine diabetes care	**Clinical parameters** Systolic blood pressure (+,i) Diastolic blood pressure (+,i) 10-year CHD risk (+, i) **Biochemical parameters** HbA1c (0) Total cholesterol (+, i) HDL-cholesterol (0) LDL-cholesterol (+, i) **Processes of care** HbA1c below target value§ (+,i) Systolic blood pressure below target value§ (+,i) Total cholesterol below target value§ (+,i) LDL-cholesterol below target value§ (+,i) All treatment targets reached§ (+,i)	At baseline, patients in the intervention group had higher HDL-cholesterol levels, were more often smoker and more often had a history of CHD. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between intervention and control were adjusted for cluster structure.
Sönnichsen 2008[44]	Physician education +guideline-based care + patient education + use of a clinical information system tool + interdisciplinary care by a specialist team + patient reminders + physician reminders + goal setting + shared decision making patient and physician + regular consultations *vs* routine diabetes care	**Clinical parameters** Systolic blood pressure (0) Diastolic blood pressure (0) **Biochemical parameters** HbA1c (0) Total cholesterol (+, i) HDL-cholesterol (0) LDL-cholesterol (0) Triglycerides (0) Creatinine (0) Body mass index (+, i) **Processes of care** To the guidelines adherent: -number of eye examinations§ (+, i) -number of foot examinations§ (+, i) -provision of patient education§ (+, i) -regular HbA1c checks§ (+, i)	At baseline, patients in the intervention group had a higher BMI and higher cholesterol levels than patients in the control group. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between intervention and control were adjusted for cluster structure and baseline values.
Frei 2010[43]	Specialist team involving a practice nurse + practice nurse education + physician education + physician support by practice nurse + regular independent patient consultations by practice nurse + use of a clinical information system tool + guideline-based care + physician feedback + patient information leaflets + self-management support for patient + patient treatment groups *vs* routine diabetes care	**Clinical parameters** Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (0) **Biochemical parameters** HbA1c (0) Total cholesterol (0) HDL-cholesterol (0) LDL-cholesterol (+, i) Fasting blood glucose (0) **Processes of care** Number GP visits§ (0) Change in antidiabetic therapy (0) Change in antihypertensive therapy (0) Change in lipid-lowering therapy (0) **Other**	There were no baseline differences in patient characteristics between intervention and control group. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. There was no evidence for a statistically significant clustering effect.

Webb 2010[42]	Structured patient education + lifestyle advice and self-management with ongoing (bimonthly) professional support + individualized management + guideline-based care + shared decision making patient and health care professional + annual screening for diabetic complications + care delivered by a specialist team (specialty doctor, diabetes nurse educator, and a dietician) + patient reminders + physician reminders *vs* routine diabetes care	**Clinical parameters** Systolic blood pressure (+, i) Diastolic blood pressure (+, i) 5-year CHD risk (+, i) 5-year CVD risk (+, i) Weight (+, i) Body mass index (+, i) Waist circumference (0) **Biochemical parameters** HbA1c (+, i) Total cholesterol (+, i) LDL-cholesterol (+, i) HDL-cholesterol (0) Triglycerides (0) **Processes of care** Use of anti-hypertensive drugs[§] (+, i) Use of lipid-lowering drugs[§] (+, i) Use of anti-platelet therapy[§] (+, i) Use of metformin[§] (0) Use of sulphonylurea[§] (0) **Other** Health-related quality of life (0) Hypoglycaemia[§] (+, i)	At baseline, more patients in the intervention group were taking anti-hypertensive medication when entering the study and had higher total and LDL-cholesterol levels. Statistical analyses were conducted by intention-to-treat. It was not reported whether or not data were missing and how missing data were handled. Comparisons between intervention and control were adjusted for cluster structure and baseline values (except quality of life which had not been measured at baseline).
Janssen 2009[38]	Physician education + diabetes nurse education + lifestyle advice + guideline based care + physician support by diabetes nurse + evaluation and feed-back sessions diabetes nurse + frequent patient consultations with diabetes nurse + shared decision making patient, physician and diabetes nurse + physician reminders + patient reminders *vs* routine diabetes care	**Clinical parameters** Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (+, i) **Biochemical parameters** HbA1c (+, i) Total cholesterol (+, i) LDL-cholesterol (+, i) HDL-cholesterol (0) Fasting blood glucose (+, i) Triglycerides (0) **Other** Health-related quality of life (0) Hypoglycaemia[§] (0)	There were no baseline differences in patient characteristics between intervention and control group. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between intervention and control group were adjusted for age, sex, baseline values, and clustering at practice level.
Griffin 2011[45]	This study combined the data after five years of a multifaceted care intervention from the i) Addition-Denmark study (Lauritzen et al [39]), ii) the Addition-Netherlands study (Janssen et al [38]), iii) the Addition-Cambridge study (Echouffo et al [34]), and iv) the Addition-Leicester study (Webb et al [42]) in a meta-analysis.	**Clinical parameters** Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (0) Weight (0) Waist circumference (0) CVD mortality (0) All-cause mortality (0) Myocardial infarction (0) Stroke (0) Revascularization (0) **Biochemical parameters** HbA1c (+, i) Total cholesterol (+, i) LDL-cholesterol (+, i) HDL-cholesterol (0) Triglycerides (0) Creatinine (+, c) **Processes of care** Health-related quality of life (0) Meeting target values for: HbA1c (+, i) blood pressure (+, i)	Baseline characteristics were well matched between intervention and control group. In Denmark however, more patients were identified in practices assigned to the intervention arm then in those assigned to control arm. And in the intervention group, more patients had a history of ischemic heart disease. Statistical analyses were conducted by intention-to-treat and patients with missing outcome values were excluded from the analyses. Those with missing outcome baseline values were included according to the missing indicator method.

		total cholesterol (+, i) **Other** Hypoglycaemia§ (0) Use of any glucose-lowering drugs (+, i) Change in any anti-hypertensive drugs (+, i) Change in any cholesterol-lowering drugs (+, i)	Comparisons between intervention and control were adjusted for cluster structure and baseline values.
Olivarius 2001[40]	Patient follow-up every three months + annual screening for diabetes complications + shared decision making patient and physician + physician feedback + goal setting + clinical guidelines + physician education + patient leaflets and folders + lifestyle advise + protocol based care + physician recall system *vs* routine diabetes care	**Clinical parameters** Systolic blood pressure (+, i) Diastolic blood pressure (0) Weight (0) **Biochemical parameters** HbA1c (+, i) Total cholesterol (+, i) Fasting blood glucose (+, i) Triglycerides (0) Creatinine (0) **Processes of care** Number of consultations§ (+, i) Number of referrals to diabetes clinic§ (-, i) Number of hospital admissions§ (0) Use of metformin§ (+, i) Use of other glucose-lowering drugs§ (0) Use of anti-hypertensive drugs§ (0) Use of lipid-lowering drugs§ (0) **Other** Overall mortality§ (0) Severe hypoglycaemia§ (0) Diabetic retinopathy§ (0) Non-fatal myocardial infarction§ (0) Non-fatal stroke§ (0) Peripheral neuropathy§ (0) Microalbuminuria§ (0) Angina pectoris§ (0) Intermittent claudication§ (0)	At baseline, more patients in the intervention group were excluded because of severe somatic disease than in the control group. Furthermore, occupation and smoking habits differed between the two groups. Statistical analyses were conducted by intention-to-treat. It was not reported whether or not data were missing and missing data were handled. Comparisons between intervention and control group were adjusted for baseline values, duration of diabetes, age, sex, occupation, smoking habits, and clustering at physician level.

T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; CVD, cardiovascular (heart) disease; GP, General Practitioner;
* +=positive effect; 0=no effect; -=negative effect; i=favoring intervention group; u=favoring control (usual care) group. The effects of the intervention are represented by the difference in change from baseline to follow-up between intervention and control group. § The effect of the intervention is represented by a difference in proportions of patients at follow-up between intervention and control group.

Data quality assessment

Figure 2 summarizes the risk of bias for the trials included in this review. Whereas the Addition-Denmark[39] and the Addition-Cambridge[34] trials had not published one-year data, they did provide five-year data for the Addition-Europe meta-analysis[45] and were thus included in the risk of bias assessment. However, since not having published actual trial data, we could not assess the domains of incomplete outcome data, selective reporting, and other bias, which resulted in the occurrence of blanks in Figure 2.

<insert figure 2 here>

Seven trials had at least one domain judged as unclear risk of bias. Five trials had at least one domain judged as high risk of bias. Only one study[43] had explicitly described that their physicians were unaware of being allocated to the intervention or control group when recruiting eligible patients. For the remaining studies prior knowledge of treatment allocation cannot be ruled out (recruitment bias). Furthermore, the Addition studies[34 38 39 42] were the only trials in which patients remained unaware of group assignment throughout the study.

In four studies[34 38 39 42] outcome assessment was performed completely blinded for patient allocation. In one study[44] only laboratory outcomes were assessed blinded, whereas clinical outcomes were obtained by contacting the general practitioner, introducing possible bias. No substantial baseline differences between the intervention and control groups existed with regard to the outcomes of interest.

Diabetes outcomes

HbA1c levels

All studies assessed HbA1c values at follow-up. For six[32 38 42-46] of the seven study populations glycaemic control at baseline was moderate to good, as expressed by mean HbA1c concentrations ranging from 7·0% to 7·8% (53 to 62 mmol/mol) (Table S1a and S1b). The three trials with prevalent type 2 diabetes patients[32 43 44] observed no statistically significant difference in change in HbA1c levels between the intervention and control group after one year of intervention (Figure 3). There was no statistical heterogeneity between these three trials (I^2 = 0%) and the weighted mean difference in change between intervention and control groups was -0·06% (95% CI -0·13 to 0·01) (-0·7 mmol/mol (95% CI -1·4 to 0·1)), in favour of the intervention group. Using a similarly short intervention period, yet studying patients with screen-detected type 2 diabetes, the Addition-Leicester trial[42] observed a

significant difference in change in HbA1c between the two trial arms of -0·20% (95%CI -0·31 to -0·08) (-2·2 mmol/mol (95% CI -3·4 to -0·9)). Whereas the Addition-Netherlands authors[38] did not report the actual difference in HbA1c change between the two groups, they stated in their paper that the improvement in HbA1c was significantly better in the intervention group, compared to the control group. The pooled five-year data from all four Addition-trials[45] showed a somewhat smaller, yet significantly greater improvement in HbA1c concentration in intervention patients, compared to control patients (-0·08% (95% CI -0·14 to -0·02)) (-0·9 mmol/mol (95% CI -1·5 to -0·2)) (Figure 3). Finally, the effect of multifaceted care in Danish patients with newly diagnosed diabetes[40] after six years of intervention was comparable to that in screen-detected patients after five years of intervention[45] (-0·06% (-0·08 to -0·03)) (-0·7 mmol/mol (95% CI -0·9 to -0·3)).

Pooling all seven trials, multifaceted care improved HbA1c concentration with -0·07% (-0·10, -0·04) (-0·8 mmol/mol (95% CI -1·1 to -0·4)) (Figure 3). Statistical heterogeneity across the seven trials was small to moderate (I^2 = 21%).

<insert figure 3 here>

Cholesterol levels

Figure 4 presents the mean differences in change in total cholesterol levels for all seven trials. Of the three trials that studied prevalent diabetes patients, only the Dutch trial[32] observed multifaceted care to significantly improve total cholesterol concentrations. In the remaining two studies,[43 44] cholesterol remained unchanged after one year of intervention. Statistical heterogeneity across the three studies was low (I^2=12%) and their weighted mean difference in change between intervention and control groups amounted to -0·14 mmol/l (95%CI -0·22 to -0·07). As for HbA1c, the effect of multifaceted care on cholesterol seemed larger in screen-detected patients than in patients with prevalent diabetes. After one year of intervention, Addition-Leicester[42] found a mean difference in change between the

intervention and control group of -0·56 mmol/l (95%CI -0·87 to -0·25). The pooled five-year data from all four Addition trials also showed a significantly greater improvement in total cholesterol levels in intervention patients, compared to control patients (-0·27 mmol/l (95%CI -0·34 to -0·19)). Finally, in Danish patients with newly-diagnosed diabetes,[40] six years of multifaceted care had caused cholesterol levels to improve (-0·15 mmol/l (-0·29 to -0·02)).

Pooling all trials, the effect of multifaceted care on improvement of total cholesterol resulted in a weighted difference in change between intervention and control patients of -0·20 mmol/l (95%CI -0·28 to -0·11); I^2=64%.

In addition to improvements in total cholesterol levels, HDL-cholesterol levels appeared to be unaffected by multifaceted care in patients with prevalent diabetes.[32 43 44] LDL-cholesterol levels on the other hand, did improve. Both the Dutch[32] and the Swiss[47] study found significantly better improvements in LDL-cholesterol for the intervention group, when compared to the control group. The Addition-Netherlands[38] and Addition-Leicester[42] studies observed that multifaceted care significantly improved LDL-cholesterol levels after one year, while HDL-cholesterol remained largely unchanged. Similar results were reported for five years of intervention by the Addition-Europe study.[45] The Danish study[40] with newly diagnosed diabetes patients had not measured HDL and LDL-cholesterol levels.

<insert figure 4 here>

Blood pressure

Two[32 43] out of the three trials with patients with prevalent diabetes reported a difference in change in diastolic and systolic blood pressure, both being in favour of the intervention group. Better improvements in blood pressure were also seen in intervention patients with screen-detected diabetes, compared to control patients.[38 42 45] Improvements after one year of intervention[42] were larger than those after five years of intervention.[45] In patients with

newly diagnosed diabetes[40] six years of multifaceted care significantly improved systolic, but not diastolic, blood pressure when compared to usual diabetes care. Similar to HbA1c and total cholesterol, the results for blood pressure were stronger for patients with screen-detected and newly diagnosed diabetes than for those with prevalent, long-standing diabetes.

Body mass index

With regard to the studies on prevalent diabetes, only the Austrian study[44] found a significant difference in change in BMI between the intervention group and control group after one year of intervention. In screen-detected diabetes patients[38 42] multifaceted care resulted in a significantly higher reduction in BMI, compared to usual diabetes care. Furthermore, Addition-Leicester[42] reported a higher reduction in both BMI and body weight (kg) for the intervention group compared to the control group, but observed no difference in reduction of waist circumference. After an intervention duration of five years, the pooled reduction in BMI, weight, and waist circumference in screen-detected diabetes was significantly higher in the intervention group compared to the control group[45]. The Danish trial[40] with newly diagnosed diabetes patients observed no difference in weight change after six years of intervention. BMI had not been measured.

Processes of care

Only three studies assessed processes of care or process quality measures.[32 44 45] The Dutch study[32] with prevalent diabetes patients observed that multifaceted care resulted in significantly more patients reaching treatment targets (18·9%), than usual diabetes care (13·4%) (treatment targets were defined as HbA1c ≤7% (53 mmol/mol), systolic blood pressure ≤140 mmHg, total cholesterol ≤4·5 mmol/l and LDL-cholesterol ≤2·5 mmol/l).

Process quality measures at one year, defined as the percentage of patients receiving guideline-adherent foot-, eye-, and HbA1c-examinations, were reported by the Austrian study with prevalent diabetes patients[44] to be significantly higher in the intervention group. The pooled five-year results from the four Addition studies[45] showed that in both trial arms more patients had values below target thresholds for HbA1c (<7% (53 mmol/mol)), blood pressure (≤135/85 mmHg) and cholesterol level (<4·5 mmol/l), yet proportions were higher in the intervention group than in the control group.

Other outcomes

(See online supplementary results S3).

DISCUSSION

This review assessed the effectiveness of chronic disease management models for type 2 diabetes on the improvement of patient outcomes, in Europe. In general, the effects of multifaceted care on patient outcomes were rather small and their magnitude seemed to differ according to the type of diabetes patient being studied. Our analysis suggested that in comparison to usual diabetes care, multifaceted care improves HbA1c levels for patients with screen-detected diabetes and patients with newly diagnosed diabetes, but not for patients with prevalent type 2 diabetes. Similar findings were observed for total cholesterol, LDL-cholesterol, BMI and body weight. The resulting improvements in blood pressure seemed less strongly related to the type of diabetes patient studied. Other outcomes, such as fasting glucose levels, triglycerides, hypoglycaemia, and cardiovascular risk, had been reported inconsequently and results widely varied across the included trials.

The few cluster randomized controlled trials that we identified from the literature were relatively heterogeneous with regard to the individual components of the implemented intervention, duration of the intervention, type of diabetes patient, analytical methodology, and reported outcomes. For each trial, methodological quality was acceptable and there were very low rates of dropout among the enrolled patients. Still, details on the randomization procedure was frequently missing as well as information concerning concealment of allocation from general practitioners and physicians in advance to recruitment of eligible patients. Given the current literature, it is not possible to draw an unequivocal conclusion about the effectiveness of chronic multifaceted care on diabetes patient outcomes.

Overall, previous systematic reviews have reported that an integrated approach to diabetes care may improve some processes of health care. Improvements have been described for frequency of retinopathy screening,[20 48 49] screening for peripheral polyneuropathy and foot lesions,[20 48 49] proteinuria measurements,[49] and the monitoring of lipid and HbA1c.[49] Further

improvements have been observed for clinical outcomes, including HbA1c,[19 20 23 48] blood pressure,[10 20] and blood lipid levels,[10 19] and there also seems to be an economic benefit of integrated diabetes care.[50]. Still, others have found no impact on outcome measures and processes of care[18 25 49] and have disputed the clinical relevance of statistically significant findings.[19]

The novelty of the current systematic review is that it provides a comprehensive overview of diabetes-care trials that have evaluated the effectiveness of the all the six components of the CCM combined, instead of one or more components. Overall, we found there is an important lack of studies which evaluate the implementation of all six CCM-components simultaneously. In current literature, findings on the issue of whether multifaceted chronic care is to be preferred over single-faceted care are conflicting.[9-12 24-26 51] However, improving the management of a complex disease like diabetes is a challenging goal which, we believe, may not be achieved by targeting single care aspects only. Another novel aspect of the current review is the focus on state-of-the-art diabetes management in Europe only. The reason for this more narrow view is the enormous burden that type 2 diabetes represents in Europe, both in individual and in societal terms.[46] The prevalence of diabetes is expected to increase from 59.8 million adults in 2015 to 71.1 million in 2040.[52]

As reflected by recent guidelines for the management of patients with type 2 diabetes,[53] health care providers have increasingly focused at improving and controlling cardiovascular risk factors to improve patient outcomes, including hyperglycaemia, overweight or obesity, elevated blood pressure, and dyslipidemia. Results from the Steno-2 trial support the view that even in high-risk patients with type 2 diabetes multifaceted care has the potential to reduce the risk of complications and mortality.[54] Randomizing 160 patients with type 2 diabetes and persistent microalbuminuria to an intensive multifactorial treatment and conventional therapy, the authors found that the multifactorial treatment was associated with a lower risk of cardiovascular events after 13·3 years of follow-up, as well as with a lower risk of death from cardiovascular disease, compared to conventional treatment . And while the

CCM has been proposed as a tool to improve the quality of diabetes care and, subsequently, patient outcomes, the current review indicates that at least the existing programs have not been as successful in this respect as intended. The challenge thus remains to translate results from landmark studies like Steno-2, into primary care, where the majority of type 2 diabetes patients are being treated.

There are some limitations of our work that need to be considered. First, many studies provided insufficient details in their methods section to fully understand the intensity of (specific components of) the intervention. This complicated our appraisal of whether all components of the CCM were covered. In addition, the different interventions that the trials have used to represent a given component of the CCM have possibly resulted in some heterogeneity across the trials. Second, whereas the aim of the current review was to investigate the effectiveness of chronic care models in Europe, the trials available for this review only represented the Western part of Europe. Countries with the highest prevalence of diabetes lie in Eastern Europe, i.e. Turkey, Montenegro, Macedonia, and Serbia.[46] The top-three countries in Western Europe with the highest diabetes prevalence are Germany, Spain, and Italy,[46] none of which were represented in this review. And third, the procedure of selecting relevant studies for the current review was largely performed by only one person. However, two reviewers subsequently screened the full text of all potentially relevant papers such that the final decision on inclusion was based on two opinions.

In conclusion, the available scientific evidence regarding the effectiveness of multifaceted chronic care programs for type 2 diabetes in older patients in Europe is low. In general, the current findings support the concept of the chronic care model, yet the improvements in patient outcomes and processes of care are only small. The effect of the intervention seems, at least partly, to depend on the type of diabetes patient, which could suggest effect modification by disease duration and/or disease severity. While key aspect of type 2 diabetes can be improved by a multifactorial intervention, it is not yet clear if these improvements will subsequently lower diabetes-related complications, such as cardiovascular disease and

overall mortality. In addition, there is a lack of knowledge on effective methods to address important pragmatic questions about improvement of care, for example, which specific mechanism or procedure of a chronic care model works, for which patients, and under which circumstances?[55] Another aspect that could offer more insight into the effectiveness of chronic care programs is the degree in which they change social behaviour. This implies that more attention should be spent in trials to factors like adherence to treatment strategies, level of self-management skills, and patients´ knowledge about their disease. These traits need to be positively affected before an improvement in clinical measures can even occur,[1] yet studies reveal little on person-centred factors.

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Contributors

BWCB designed the review by writing the review protocol, identified studies for inclusion, extracted and interpreted the data, and drafted and revised the article. KM contributed to the review protocol and to the discussion. He further revised the draft paper for intellectual

content. JW was involved in conception of the review and he contributed to the review protocol, to interpretation of the data and to the discussion. Furthermore, JW revised the draft paper for intellectual content. CL contributed to the review protocol and to the discussion, and she revised the draft paper for intellectual content. PS conceived and initiated the review, contributed to the review protocol and he contributed to the interpretation of the data, to the discussion and to revision of the draft paper. MR was involved in conception of the review and he revised the draft paper for intellectual content. WR contributed to the review protocol, identified studies for inclusion, extracted and interpreted the data and revised the draft paper for intellectual content. All authors approved the final completed article.

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ONLINE SUPPLEMENTARY INFORMATION

S1 Text. Search strategy Medline

S2 Table 1a. Baseline patient characteristics of the included cluster randomized controlled trials studying patients with prevalent diabetes

S2 Table 1b. Baseline patient characteristics of the European cluster randomized controlled trials studying patients with screen-detected and newly diagnosed diabetes

S3 Text. Results

FIGURES TITLES AND LEGENDS

Figure 1: Flow chart summarizing the identification of studies included for review.

Figure 2: Risk of bias graph.

Review authors' judgments about each risk of bias item presented as percentages across all included studies. Studies included are Cleveringa et al. (2008)[32]; Sönnichsen et al. (2008)[44]; Frei et al. (2010)[43]; Olivarius et al. (2001)[40]; Janssen et al. (2009)[38]; Webb et al. (2010)[42]; Lauritzen et al. (2000)[39]; and Echouffo et al. (2009)[34]. The studies from Lauritzen and Echouffo are included in the risk of bias assessment since their 5-year follow-up data were included in the Addition-Europe meta-analysis by Griffin et al.[45]. The blanks in the figure represent the absent one-year data from the studies by Lauritzen and Echouffo. The information on these two studies in the Addition-Europe publication was too sparse to resolve this missing information.

Figure 3: Mean difference in change (95% confidence interval) in HbA1c levels (%) after multifaceted care between intervention and control groups. Results are stratified by type of diabetes patient.

IV, intervention; CI, confidence interval; df, degrees of freedom

[a] All studies had an intervention duration of one year. [b] The methodology for calculating the difference in change between intervention and control group that Cleveringa et al.[32] have used (subtracting the total cholesterol change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the total cholesterol change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa et al.,[32] we have recalculated their cholesterol results according to the methodology used by all other studies. [c] The study of Webb et al.[42] had an

intervention duration of one year and the study of Griffin et al.[45] had a duration of five years. [d] This study combined the 5-year intervention data from all four Addition studies, including the five-year data from Webb et al.[42] [e] This study had an intervention duration of six years.

Figure 4: Mean difference in change (95% confidence interval) in total cholesterol levels (mmol/l) after multifaceted care between intervention and control groups. Results are stratified by type of diabetes patient.

IV=Intervention; CI=Confidence interval

[a] All studies had an intervention duration of one year. [b] The methodology for calculating the difference in change between intervention and control group that Cleveringa et al.[32] have used (subtracting the total cholesterol change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the total cholesterol change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa et al.,[32] we have recalculated their cholesterol results according to the methodology used by all other studies. [c] The study of Webb et al.[42] had an intervention duration of one year and the study of Griffin et al.[45] had a duration of five years. [d] This study combined the 5-year intervention data from all four Addition studies, including the five-year data from Webb et al.[42] [e] This study had an intervention duration of six years.

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Figure 1

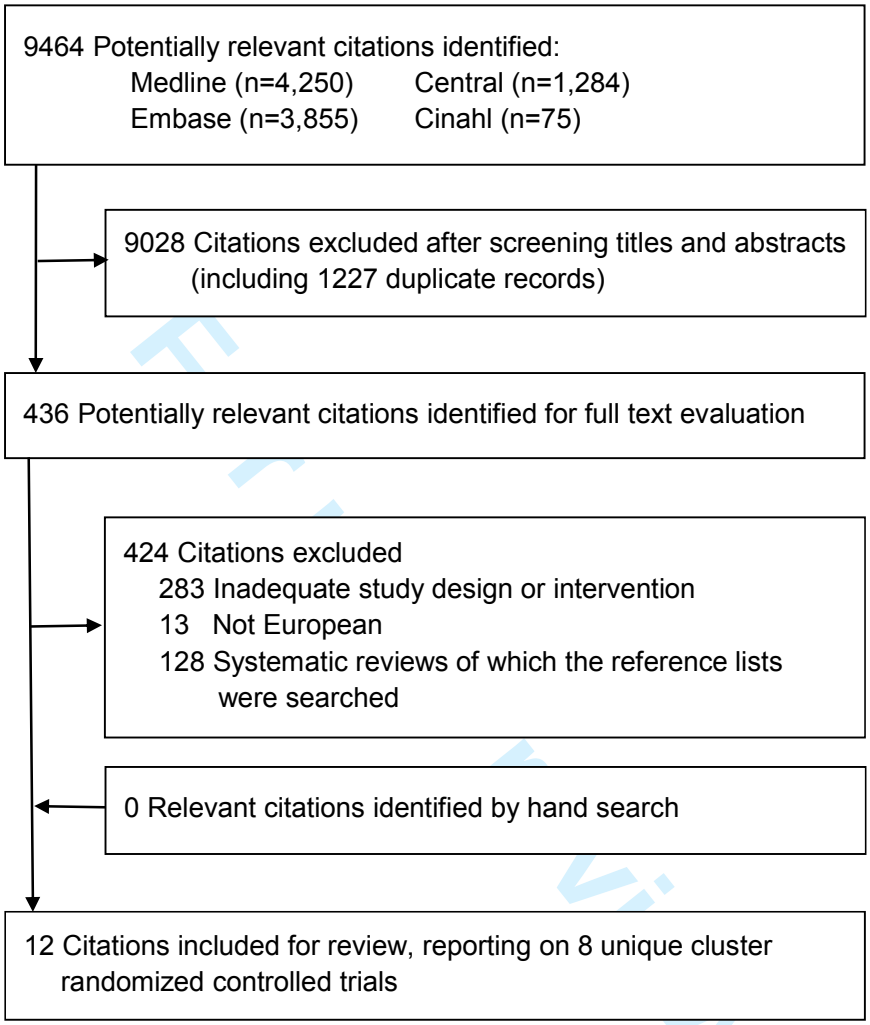

Figure 1: Flow chart summarizing the identification of studies included for review

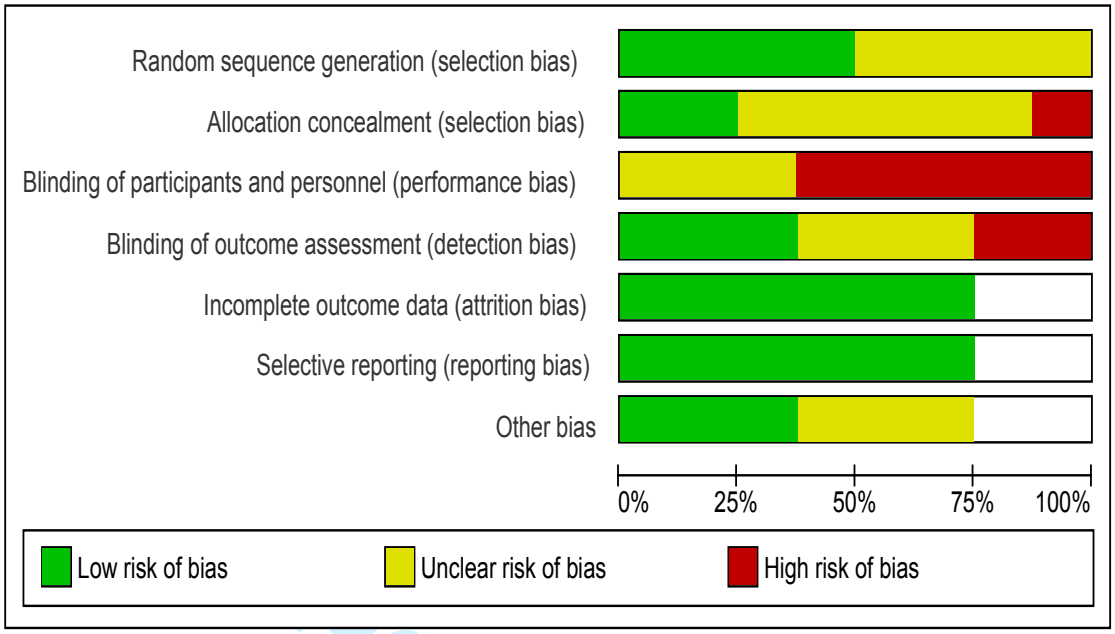

Figure 2: Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies. Studies included are Cleveringa *et al*. (2008)[32]; Sönnichsen *et al.* (2008)[44]; Frei *et al.* (2010)[43]; Olivarius *et al.* (2001)[40]; Janssen *et al.* (2009)[38]; Webb *et al.* (2010)[42]; Lauritzen *et al.* (2000)[39]; and Echouffo *et al.* (2009)[34]. The studies from Lauritzen and Echouffo are included in the risk of bias assessment since their 5-year follow-up data were included in the Addition-Europe meta-analysis by Griffin *et al*.[45]. The blanks in the figure represent the absent one-year data from the studies by Lauritzen and Echouffo. The information on these two studies in the Addition-Europe publication was too sparse to resolve this missing information.

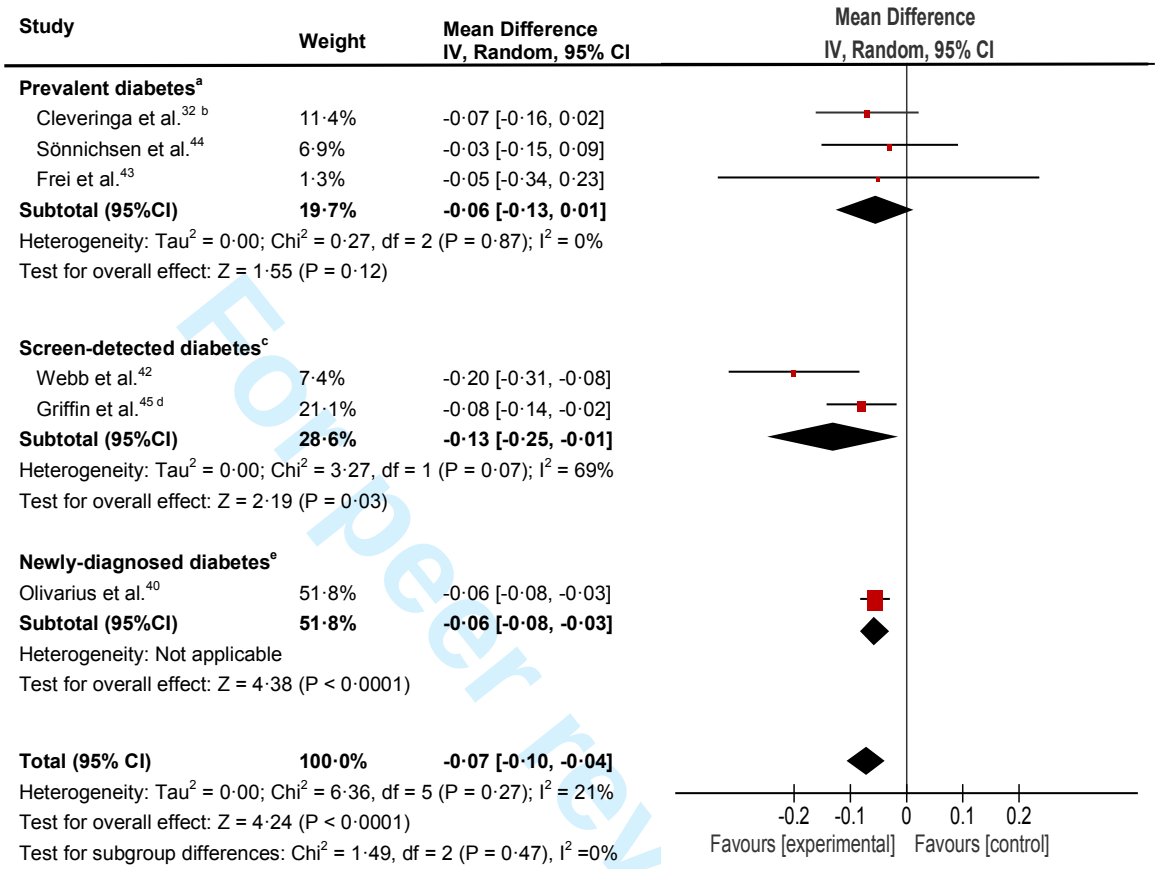

Figure 3: Mean difference in change (95% confidence interval) in HbA1c levels (%) after multifaceted care between intervention and control groups. Results are stratified by type of diabetes patient.

IV, intervention; CI, confidence interval; df, degrees of freedom

[a] All studies had an intervention duration of one year. [b] The methodology for calculating the difference in change between intervention and control group that Cleveringa et al.[32] have used (subtracting the total cholesterol change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the total cholesterol change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa et al.[32], we have recalculated their cholesterol results according to

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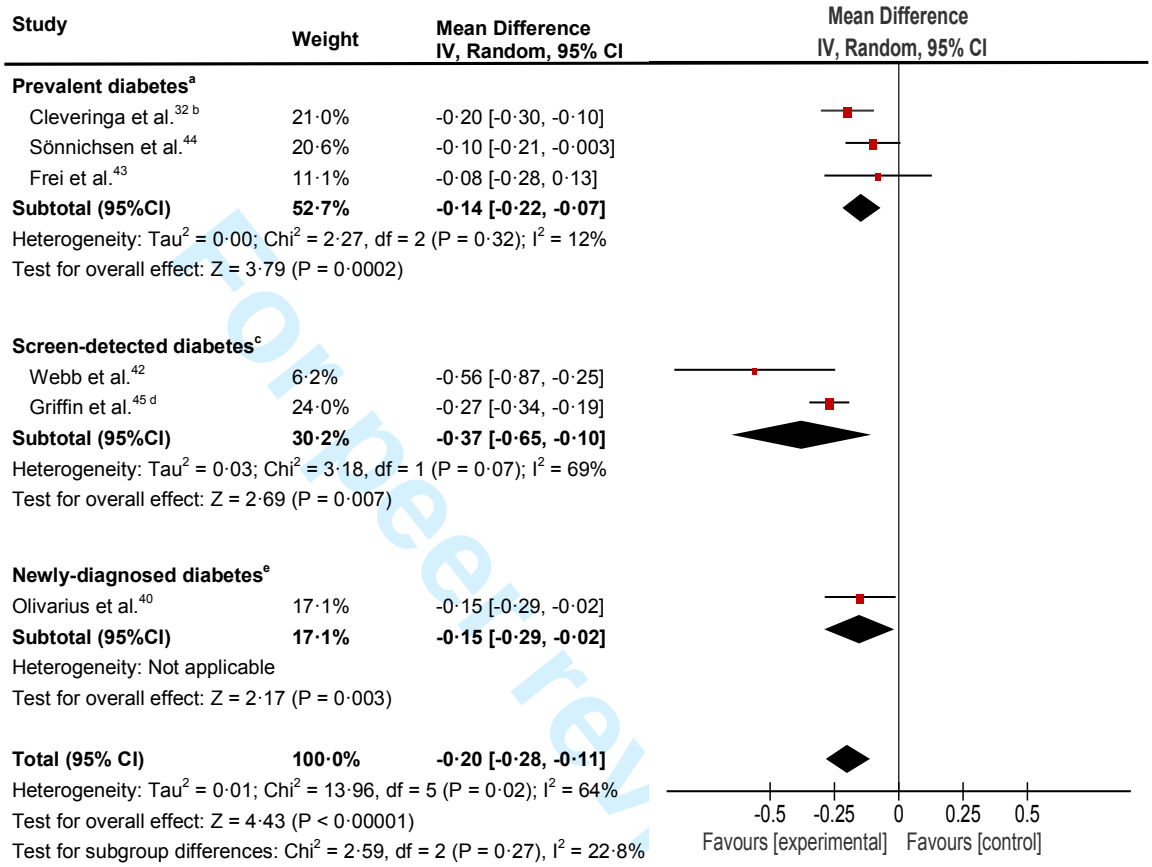

Figure 4: Mean difference in change (95% confidence interval) in total cholesterol levels (mmol/l) after multifaceted care between intervention and control groups. Results are stratified by type of diabetes patient.

IV=Intervention; CI=Confidence interval

[a] All studies had an intervention duration of one year. [b] The methodology for calculating the difference in change between intervention and control group that Cleveringa et al.[32] have used (subtracting the total cholesterol change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the total cholesterol change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings

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Appendix S1: Search strategy Medline

1 Patient Education as Topic/

2 exp Self Care/

3 Self Efficacy/

4 ((patient* or consumer* or client*) adj3 (educat* or train* or teach* or instruct* or skill*)).tw.

5 (self care or self management or self efficacy or self monitoring).tw.

6 patient participation/

7 empowerment.tw.

8 (self adj (monitor* or manag* or care)).tw.

9 motivation/

10 (patient* adj2 (activation or psychosocial support or social support)).tw.

11 (collaborative decision making* or shared decision making*).tw.

12 or/1-11 (230620)

13 exp Education, Continuing/

14 Pamphlets/

15 Advance Directives/

16 (leaflet? or booklet? or poster or posters).tw.

17 ((written or printed or oral) adj information).tw.

18 Guideline Adherence/

19 (education* adj2 (program* or intervention* or meeting* or session* or strateg* or workshop* or visit*)).tw.

20 (behavio?r* adj2 intervention*).tw.

21 (education* adj1 (method? or material?)).tw.

22 ((opinion or education$ or influential) adj1 leader?).tw.

23 facilitator?.tw.

24 academic detailing.tw.

25 consensus conference?.tw.

26 (guideline? adj2 (introduc* or issu* or impact or effect* or disseminat* or distribut*)).tw.

27 ((effect* or impact or evaluat* or introduc* or compar*) adj2 training program*).tw.

28 practice guidelines as topic/

29 telemedicine/

30 ((effect? or impact or evaluat* or introduce* or compar*) adj2 (care program* or (prevent* adj program*))).tw.

31 guidelines as topic/

32 ((patient* or practice) adj guideline?).tw.

33 or/13-32

34 exp Patient Care planning/

35 Nurse clinicians/

36 Ambulatory Care/

37 Office Visits/

38 (nurse adj (clinician? or practitioner?)).tw.

39 (team? adj2 (care or treatment or assessment or consultation)).tw.

40 (integrat* adj2 (care or service?)).tw.

41 (care adj2 (coordinat* or program* or continuity)).tw.

42 (case adj1 management).tw.

43 outreach.tw.

44 disease management.tw.

45 disease management/

46 patient care team/

47 exp ambulatory care facilities/

48 nurse practitioners/

49 ((share* or step*) adj care).tw.

50 community matron*.tw.

51 or/34-50

52 Reminder Systems/

53 Medical Records/

54 Medical Records Systems, Computerized/

55 (register? or registry or registries).tw.

56 reminder?.tw.

57 (recall adj2 system*).tw.

58 (prompter? or prompting).tw.

59 chart review*.tw.

60 ((effect? or impact or records or chart?) adj2 audit).tw.

61 (information adj2 (management or system?)).tw.

62 hospital information systems/

63 ambulatory care information systems/

64 management information systems/

65 decision support systems, clinical/

66 ((introduce$ or impact or effect? or implement$ or computer$) adj2 protocol?).tw.

67 Feedback/ or feedback.tw.

68 (feedback adj1 (loop? or control? or regula* or mechanism? or inhib* or system? or circuit? or sensory or visual or audio* or auditory)).tw.

69 67 not 68

70 or/52-66,69

71 Reimbursement, incentive/

72 exp Reimbursement mechanisms/

73 Capitation Fee/

74 Physician Incentive Plans/

75 "Salaries and Fringe Benefits"/

76 Physician's Practice Patterns/

77 (quality adj (improvement or management or assurance)).tw.

78 ((continuous or total) adj quality).tw.

79 quality of health care/

80 quality assurance, health care/

81 total quality management/

82 quality improvement/

83 quality indicators, health care/

84 program evaluation/

85 technology assessment, biomedical/

86 exp Standard of care/

87 or/71-86

88 exp Diabetes Mellitus, Type 2/

89 exp Diabetes Complications/

90 (obes* adj3 diabet*).tw.

91 (MODY or NIDDM or T2DM or T2D).tw.

92 (non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend*).tw.

93 ((typ? 2 or typ? II or typ?2 or typ?II) adj3 diabet*).tw.

94 ((adult* or matur* or late or slow or stabl*) adj3 diabet*).tw.

95 or/88-94

96 exp Diabetes Insipidus/

97 diabet* insipidus.tw.

98 or/96-97

99 95 not 98

100 infan*.tw.

101 (newborn* or new born*).tw.

102 (perinat* or neonat*).tw.

103 (baby* or babies).tw.

104 toddler*.tw.

105 (boy or boys or boyhood).tw.

106 girl*.tw.

107 kid?.tw.

108 (child* or schoolchild*).tw.

109 adolescen*.tw.

110 juvenil*.tw.

111 youth*.tw.

112 teen*.tw.

113 pubescen*.tw.

114 Pediatrics/

115 p?ediatric*.tw.

116 school?.tw.

117 or/100-116

118	exp africa/
119	exp americas/
120	exp asia/
121	exp oceania/
122	or/118-121
123	randomized controlled trial.pt.
124	controlled clinical trial.pt.
125	randomized.ab.
126	placebo.ab.
127	drug therapy.fs.
128	randomly.ab.
129	trial.ab.
130	groups.ab.
131	exp animals/ not humans/
132	or/123-130
133	132 not 131
134	or/12,33,51,70,87
135	134 and 99 and 133
136	135 not 117 not 122
137	limit 136 to (english language and yr="2000 -Current")

Appendix S2: Table 1a

Table S1a: Baseline patient characteristics of the included cluster randomized controlled trials studying patients with prevalent diabetes

	Cleveringa *et al*[1] *		Sönnichsen *et a*[2] †		Frei *et al*[3] ‡	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
N	1699	1692	649	840	162	164
Follow up duration (years)	1	1	1	1	1	1
Type of diabetes patients	Prevalent diabetes		Prevalent diabetes		Prevalent diabetes	
Country	Netherlands		Austria		Switzerland	
Baseline characteristics						
Age (years)	65·2 ± 11·3	65·0 ± 11·0	65·4 ± 10·4	65·5 ± 10·4	65·7 ± 10·4	68·3 ± 10·6
Sex (% men)	48·2	49·8	51·0	53·1	54	60
Ethnicity (% Caucasian)	97·7	97·6	-	-	-	-
Diabetes duration (years)	5·8 ± 5·7	5·4 ± 5·8	7·0 ± 6·5		9·5 ± 7·4	10·3 ± 7·8
Current smoking (% yes)	**22·6**	**16·6**	13·4		14	9
Clinical parameters						
Body mass index (kg/m^2)	30·0 ± 5·3	30·2 ± 5·3	**30·4 ± 5·1**	**29·7 ± 4·9**	30·5 ± 5·3	30·7 ± 5·9
Systolic blood pressure (mmHg)	149 ± 22	149 ± 21	141 ± 19	139 ± 17	140·3 ± 18·4	137·8 ± 16·8
Diastolic blood pressure (mmHg)	83 ± 11	82 ± 11	83 ± 11	82 ± 10	83·1 ± 10·4	78·7 ± 10·2
5-year UKPDS CHD risk (%)	-	-	-	-	-	-
10-year UKDPS CHD risk (%)	22·5 ± 16·5	21·7 ± 15·8	-	-	-	-

Biochemical parameters						
HbA1c (%)	7·1 ± 1·3	7·0 ± 1·1	7·46 ± 1·53	7·34 ± 1·31	7·8 ± 1·5	7·6 ± 1·1
Total cholesterol (mmol/l)	5·0 ± 1·0	4·9 ± 1·1	**5·15 ± 1·14**	**5·02 ± 1·09**	5·0 ± 1·2	4·7 ± 1·1
HDL-cholesterol (mmol/l)	**1·36 ± 0·36**	**1·32 ± 0·35**	1·35 ± 0·39	1·32 ± 0·36	1·2 ± 0·3	1·3 ± 0·4
LDL-cholesterol (mmol/l)	2·8 ± 0·92	2·8 ± 0·95	2·87 ± 0·96	2·87 ± 0·91	2·8 ± 1·1	2·5 ± 1·1
Fasting glucose (mmol/l)	8·0 ± 2·4	7·8 ± 2·2	-	-	8·4 ± 2·5	7·7 ± 2·2
Creatinine (µmol/l)	87·5 ± 27·7	85·9 ± 22·5	84·9 ± 30·9	84·9 ± 34·5	-	-
Triglycerides (mmol/l)	1·8 ± 1·1	1·8 ± 1·3	2·14 ± 1·82	2·00 ± 1·73	-	-
Urinary albumin (mg/l)	-	-	-	-		
Diabetes complications and comorbidities						
History of myocardial infarction (%)	**47·1**	**63·3**	8·4		-	-
History of stroke (%)			7·0		-	-
Diabetic retinopathy (%)	2·9	3·3	-	-	9·3	8·1
Peripheral neuropathy (%)	-	-	-	-	18·6	13·4

Values are mean ± sd, or percentages. Bold font indicates that the particular baseline characteristic differed statistically significantly between intervention and control group.

* The information on BMI, fasting glucose, creatinine, triglycerides, and retinopathy was obtained through contacting the authors.

† The information on diabetes duration, smoking, history of myocardial infarction, and history of stroke was obtained from the publication describing baseline characteristics of the total study population and stratified by sex (Flamm *et al*. 2011).

‡ Peripheral neuropathy is represented by "*pathological foot status*" and diabetic retinopathy is represented by "*annual eye exam: pathological*".

Appendix S2: Table 1b

Table S1b: Baseline patient characteristics of the included cluster randomized controlled trials studying patients with screen-detected and newly diagnosed diabetes

	Webb *et al*[6]		Janssen *et al*[5]		Griffin *et al*[9]		Olivarius *et al*[4]	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
N	146	199	255	243	1678	1379	649	614
Follow up duration (years)	1	1	1	1	5	5	6	6
Type of diabetes patients	Screen-detected diabetes		Screen-detected diabetes		Screen-detected diabetes		Newly-diagnosed diabetes	
Country	United Kingdom		Netherlands		United Kingdom, Netherlands, Denmark		Denmark	
Baseline characteristics								
Age (years)	59·4 ± 10·0	60·0 ± 10·0	60·1 ± 5·4	59·9 ± 5·1	60·3 ± 6·9	60·2 ± 6·8	65·5 (55·3-74·0)	65·3 (56·3-73·5)
Sex (% men)	56·9	58·3	51·8	56·0	58·5	57·3	52·4	53·1
Ethnicity (% Caucasian)	52·7	62·3	98·0	98·7	95·8	93·4	-	-
Diabetes duration (years)	0	0	0	0	0	0	0	0
Current smoking (% yes)	15·2	10·2	26·3	21·4	26·9	27·8	**35·5**	**34·5**
Clinical parameters								
Body mass index (kg/m^2)	31·0 ± 5·9	31·5 ± 5·7	31·2 ± 5·1	30·4 ± 4·6	31·6 ± 5·6	31·6 ± 5·6	29·4 (26·2-33·0)	28·8 (26·0-32·3)
Systolic blood pressure (mmHg)	145·7 ± 18·5	148·4 ± 20·5	166 ± 23	163 ± 23	148·5 ± 22·1	149·8 ± 21·3	150 (130-164)	148 (130-160)
Diastolic blood pressure (mmHg)	87·8 ± 10·4	89·5 ± 10·7	90 ± 11	89 ± 10	86·1 ± 11·1	86·5 ± 11·3	85 (80-90)	85 (80-90)
5-year UKPDS CHD risk (%)	8·5 ± 5·8	9·3 ± 7·1	-	-	-	-	-	-

10-year UKDPS CHD risk (%)	-	-	-	-	-	-	-	-
Biochemical parameters								
HbA1c (%)	7·2 ± 1·5	7·3 ± 1·8	7·3 ± 1·6	7·4 ± 1·7	7·0 ± 1·6	7·0 ± 1·5	10·2 (8·6-11·6)	10·2 (8·7-11·9)
Total cholesterol (mmol/l)	**5·3 ± 1·2**	**5·6 ± 1·3**	5·6 ± 1·1	5·6 ± 1·1	5·5 ± 1·1	5·6 ± 1·2	6·2 (5·4-7·1)	6·2 (5·5-7·2)
HDL-cholesterol (mmol/l)	1·2 ± 0·4	1·2 ± 0·3	1·1 ± 0·4	1·1 ± 0·3	1·2 (1·0-1·5)	1·2 (1·0-1·5)	-	-
LDL-cholesterol (mmol/l)	**3·2 ± 1·0**	**3·5 ± 1·0**	3·7 ± 1·0	3·7 ± 1·0	3·4 ± 1·0	3·5 ± 1·0	-	-
Fasting glucose (mmol/l)	-	-	7·8 ± 2·3	8·1 ± 2·8	-	-	13·8 (10·7-17·0)	13·7 (10·7-17·0)
Creatinine (µmol/l)	-	-	-	-	83·4 ± 17·1	84·9 ± 18·6	90 (81-101)	88 (79-100)
Triglycerides (mmol/l)	2·1 ± 1·9	2·1 ± 1·4	1·9 ± 1·0	2·0 ± 1·6	1·6 (1·2-2·3)	1·7 (1·2-2·4)	2·03 (1·44-2·91)	1·98 (1·39-2·95)
Urinary albumin (mg/l)	-	-	-	-	-	-	11·7 (6·0-32·5)	11·8 (5·7-27·5)
Diabetes complications								
History of myocardial infarction (%)	15·8*	10·6*	-	-	6·8	6·1	6·6	7·7
History of stroke (%)			-	-	2·9	1·9	3·5	4·2
Diabetic retinopathy (%)	-	-	-	-	-	-	5·0	4·5
Peripheral neuropathy (%)	-	-	-	-	-	-	18·8	19·7

Values are mean ± sd, or median (interquartile range) or percentages. Bold font indicates that the comparison between intervention and control group was statistically significant.

* Defined as "*pre-existing CVD*", including myocardial infarction, stroke, and angina.

Appendix S3: Results

Other outcomes

Three[1-3] out of the seven trials included in this review had assessed fasting glucose levels (mmol/l). In Swiss patients with prevalent diabetes[2] no difference in change was found between the intervention and control group, while in Dutch patients with diabetes[1] there was a significantly higher reduction in glucose concentrations after one year of intervention, in favour of the control group. In newly diagnosed diabetes patients;[3] the intervention group was observed to have a significantly higher reduction in fasting glucose levels then the control group after six years of intervention.

Six[1 3-7] out of seven trials had measured triglyceride concentrations (mmol/l), yet, multifaceted care did not significantly impact triglyceride levels in any of the studies.

Creatinine levels were assessed in three[1 3 4] out of the seven trials. Only the pooled five-year results from Addition-Europe[4] showed a significant difference in change between the trial arms, favouring the control arm over the intervention arm.

Episodes of severe hypoglycaemia were assessed in only one[2] of the three studies with prevalent diabetes patients, in which severe hypoglycaemia was defined as having one or more episodes of hypoglycaemia with clinical symptoms and or requiring hospitalization. Episodes were reported for 19 (11·6%) patients in the intervention group and for eight (5·1%) in the control group, without further statistical evaluation. In the remaining trials;[3-5 7] the proportion of individuals reporting hypoglycaemia did not differ between intervention and control arm.

A major aim of the Dutch trial [1] and of the Addition studies[5 7-9] was to examine the effect of multifaceted care on cardiovascular risk. To that purpose, authors calculated the 10-year coronary heart disease risk estimate (%) as established by the UK Prospective Diabetes Study (UKPDS):[10] This risk score is calculated using the following variables: the date of diabetes onset, sex, ethnicity, smoking, HbA1c, systolic blood pressure, total cholesterol and

HDL-cholesterol. The Dutch authors observed a 1·4% greater decrease in 10-year UKPDS coronary heart disease risk in the intervention group compared to the control group:[1] Within the Addition-Leicester trial;[7] a five-year UKPDS risk of cardiovascular heart disease was calculated. A significant difference in risk reduction of 1·49% between intervention and control group was found in favour of the intervention group. In the Addition-Europe study;[4] the authors assessed hazard ratios for a composite endpoint of cardiovascular events (any cardiovascular death, myocardial infarction, stroke, revascularization and amputation) at 5 years of intervention. This endpoint occurred similarly frequent, and with similar risk, intervention and control patients. Furthermore, improvements in every singular component of this composite endpoint all favoured the intervention group over the control group, although no comparison reached statistical significance.

Out of the three trials with prevalent diabetes patients, only the Swiss trial[2] reported data on (changes in) medication use. The authors observed no significant changes between the two trial groups in medication use (yes/no variable) concerning antidiabetic therapy, antihypertensive therapy, and lipid-lowering therapy. In contrast to patients with prevalent diabetes, for patients with screen-detected diabetes[7] multifaceted care resulted in a larger number of antihypertensive-, lipid-lowering and anti-platelet therapy after one year, compared to usual care. This was also observed after pooling of the five-year findings from the Addition studies:[4] In newly diagnosed diabetes patients[3] however, the only between-group difference that was observed with regard to medication intake was the more extensive use of metformin in the intervention group (39 (9%)) compared to the control group (16 (4%)).

Macro- and microvascular diabetes complications during follow-up were reported by the two studies[3 4] with the longer intervention periods. The Addition-Europe study[4] had assessed cardiovascular death, myocardial infarction, stroke, coronary and peripheral revascularization, non-traumatic amputation, and total mortality in screen-diagnosed diabetes patients. Whereas the estimated hazard ratios for these events all favoured the intervention

group, none of the estimates reached statistical significance. In newly diagnosed diabetes patients;[3] multifaceted care had not resulted in differences between intervention and control group regarding risk of diabetic retinopathy, microalbuminuria, non-fatal myocardial infarction and stroke, peripheral neuropathy, angina pectoris, or intermittent claudication at six years.

Quality of life was reported by five[1 2 4 5 7] of the seven trials, most of which had used the 36-item Short form Health Survey (SF-36) to assess the different domains of health-related quality of life. In patients with prevalent diabetes[1 2] significant changes over time were absent for all scores of the SF-36 subscales for both the intervention and control arms. A superior effect of multifaceted care was observed only on the SF-36 subscale “health change” in the Dutch trial with prevalent diabetes patients:[1] For the two Addition studies reporting results after one year of intervention;[5 7] as for the pooled five-year data by Addition-Europe;[4] no significant changes in the physical and mental summary scores of the SF-36, or the abbreviated SF-12 version that was used in the Addition-Leicester trial;[7] could be demonstrated.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis.	9-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N.A.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11, Figure1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-12, Table 1, Appendix S2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	15-16, Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	16-20, Figure 3, Figure 4 Appendix S3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	16-18, Figure 3 Figure 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 3 Figure 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N.A.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20-22

PRISMA 2009 Checklist

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	23
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23-24
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	25

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Effectiveness of Chronic Care Models for the Management of Type 2 Diabetes Mellitus in Europe: a Systematic Review

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1. BACKGROUND

A growing number of European citizens suffer from diabetes, constituting a growing health, social, and economic burden. The number of individuals with diabetes in Europe in 2013 was estimated by the International Diabetes Federation to be 56.3 million, or 8.5% of the adult population (20-79 years), and is expected to increase to 68.9 million people, or 10.3% by the year 2035 [1]. It is generally believed that lifestyle, with diets high in saturated fat and decreased physical activity, together with an increased longevity, are the main factors in the current increase in T2DM. In individual, as well as in societal terms, the burden of T2DM is enormous, resulting in increased morbidity and mortality [1].

Historically, health care systems were developed to respond rapidly and efficiently to acute diseases. The focus was on the immediate problem, a rapid diagnosis, and the initiation of professional treatment; a process in which the patient´s role was largely passive. However, with the rapid aging of the population and the growing prevalence of chronic diseases, improvement in quality of chronic care requires more than evidence about effective diagnostic procedures and treatments. Despite much progress in clinical and behavioral interventions, it is suggested that many chronically-ill patients do not profit from these advances [2].

In the current health care systems in European countries, a shift from disease management to chronic care management may prevent costly complications and frailty in elderly with T2DM, enabling them to live independent, healthy and active lives as long as possible. With the aim of describing essential elements for improving outcomes in care of chronic diseases, the Chronic Care Model (CCM) was developed in the mid-1990s and was further refined in 1997 [3,4]. As such, CCM is a primary care-based comprehensive model, advocating evidence-based changes in health care of patients with chronic disease. The model is based on the assumption that improvements in care require an approach that incorporates patients, health care providers, and system level interventions. It can be applied to a variety of chronic illnesses, health care settings and target populations, with the goal of healthier patients, more satisfied providers, and cost savings.

The CCM comprises six components deemed essential for providing high-quality care to patients with chronic disease:

1. health care organization (i.e. providing leadership for securing resources and removing barriers to care),
2. self-management support (i.e. facilitating skills-based learning and patient empowerment),
3. decision support (i.e. providing guidance for implementing evidence-based care),

4. delivery system design (i.e. coordinating care processes),
5. clinical information systems (i.e. tracking progress through reporting outcomes to patients and providers), and
6. community resources and policies (i.e. sustaining care by using community-based resources and public health policy).

Reports indicate a widespread application of CCM to multiple illnesses [5,6], yet, to date, only one study has reviewed how CCM has been applied in diabetes care in primary care settings and what the outcomes were of this implementation [7]. This systematic review showed that CCM approaches in the United States have indeed been effective in improving the health of individuals with diabetes who receive care in primary care settings. Regarding quality of diabetes care in Europe, observational studies have been performed in different European countries [8-11]. The recently published GUIDANCE study [12] reported encouraging levels of adherence to the main recommended process measures in diabetes care, e.g. HbA1c levels <7%, blood pressure <130mmHg (systolic) and <80 mmHg (diastolic), and LDL cholesterol concentrations <2.6 mmol/l. The level of actual achievement of these target goals by the individual patients was, on the other hand, much lower. Findings from the GUIDANCE study supported previously made suggestions [13-15] that process adherence may only have a limited influence in terms of reaching target goals (risk factor control) or enhanced management, e.g. appropriate adjustments to medication. Also, the existence of substantial between-country variation in quality of diabetes care in Europe was confirmed by the GUIDANCE study [12].

2. AIMS

This systematic review will focus on the scientific evidence regarding the specific treatment and care of elderly suffering from T2DM and associated comorbidities. Its aim is to summarize previous research on the effects of current European disease management models specifically related to the complex interaction between T2DM and comorbidities in the elderly, and on improving outcomes of interest.

3. OBJECTIVES (Research Question)

To assess the effects of chronic care models with a duration of at least 6 months on the following outcomes in older patients with T2DM and diabetes-related comorbidities:

- biophysical outcomes (e.g. serum HbA1c concentrations, and change in BMI),
- patient-reported outcomes (e.g. diabetes-related quality of life),
- diabetes complications (e.g. micro- and macrovascular complications),

compared to routine diabetes care.

4. METHODS

In the case of substantial clinical or statistical heterogeneity, study results will be combined in a narrative review only. Without substantial clinical and statistical heterogeneity, study results will be combined in a meta-analysis, following the approach described below. The subsequent reporting of the systematic review will be conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) statement [16].

Criteria for considering studies for this review

Types of studies

Studies will be eligible for inclusion if they are a randomized clinical trial (RCT). Only studies that have assessed outcome measures six months or more from baseline will be investigated.

Types of participants

Individuals, regardless of gender and ethnicity, with diagnosed T2DM with or without one of the following comorbidities, assessed and reported at baseline:

- Mental health problems (stress, depression, anxiety)
- Cancer
- Cardiovascular disease
- Osteoporosis
- Rheumatic arthritis
- Chronic obstructive pulmonary disease
- Neurological diseases
- Kidney diseases.

Ideally, the diagnostic criteria for T2DM are described in the study and were established using the standard criteria that were valid at the beginning of the trial (ADA 1997, NDDG 1979, WHO 1980, WHO 1985, WHO 1999), in order to be consistent with changes in T2DM classification and diagnostic criteria throughout the years.

We will include only studies in which the average age of the study population is ≥60 years, given that this is the usual age of diagnosis for most patients in Europe.

Type of interventions

Chronic care models/programs that meet the following criteria:

- specific for individuals with T2DM,
- based on guidelines,
- providing integrated (multi-disciplinary) care,
- addressing patient empowerment,
- providing quality management (e.g. patient registry systems, recording of process measures/adherence to guidelines, achievement of treatment goals),
- delivered in primary care and secondary care.

Type of controls

The intervention group will be compared with those participants undergoing routine diabetes care (standard care recommended in that particular country, e.g. regular follow-up with the required health professional and a full diabetes annual review).

Types of outcome measures

Primary outcomes

Biophysical outcomes:

- Metabolic control: hypoglycemia, serum HbA1c concentrations, serum lipids levels (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides), blood pressure, and glomerular filtration rate
- Change in BMI and other anthropometric measures (waist circumference, waist to hip ratio)

Patient-reported outcomes:

- Diabetes-related quality of life
- Participation in life style changing programs
- Communication
- Patient empowerment

Diabetes complications:

- Microvascular complications: retinopathy, nephropathy, and neuropathy
- Macrovascular complications: cardiovascular disease, cardiovascular risk scores, and cerebrovascular disease
- Diabetes-related mortality: total mortality and mortality due to major adverse cardiac events

Secondary outcomes

Mental Health:

- Depression
- Cognitive dysfunction or dementia
- Anxiety

Functionality:

- Frailty index
- Self-management skills: dietary habits, physical activity, medication administration, use of equipment
- Nutritional status
- Dependency on care

Contact to Health Care System:

- Number of yearly hospital visits
- Hospitalization: number of emergency admissions, and number and duration (days) of hospital stays.
- Adherence to treatment recommendations
- Quality of care
- Polypharmacy

Search methods for identification of studies

Electronic searches

Electronic databases will be searched from January 2000 until January 2014. We will use the following sources for the identification of trials:

- CENTRAL (the Cochrane Central Register of Controlled Trials)
- MEDLINE (PubMed)
- EMBASE
- CINAHL

Searching other resources

We aim to further identify studies by searching the reference list of each relevant trial and systematic review identified. First authors are contacted whenever additional information is required.

Data collection and analysis

Selection of studies

To determine which studies are to be assessed further, two reviewers (BB, WR) will independently scan the titles, abstracts and key words of every record retrieved. Full text articles will be retrieved if the title/abstract/key words suggest that the trial:

- included patients with T2DM, and
- evaluated a chronic diabetes care model.

In case of any doubt regarding these criteria from the information given in the title and abstract, or if the abstract was absent, the complete article will be retrieved for clarification. Studies will be eliminated if both reviewers agree that the criteria for considering studies for the review are not being met. Inter-rater agreement for study selection will be measured using the Kappa statistic [17]. Any differences in opinion will be discussed and, if necessary, resolved by a third reviewer (KM).

Data extraction and management

A structured data extraction form will be developed including the following information:

- General information: published/unpublished, title, authors, source/reference, contact address, country, language of publication, year of publication, sponsoring.
- Trial characteristics: design, duration, (method of) randomization, use of validated questionnaires, (method of) blinding (if appropriate).
- Intervention: comparison group included (routine care/no intervention), intervention (duration, timing).
- Participants: method of sampling, exclusion criteria, total number (also for comparison group(s)), sex, age, body mass index, ethnicity, pre-existing comorbidities/other medical conditions, standards of diabetes care (HbA1c concentration, serum glucose levels, lipid profile, blood pressure), diagnostic criteria T2DM, duration of T2DM, baseline comparison of the groups (including comorbidities), withdrawal from study/losses to follow-up, assessment of subgroups.
- Outcome: as specified above, main outcome as assessed in the trial, other outcomes/events assessed, quality of reporting the outcomes.
- Results: reported for outcomes and times of assessment.

If there is missing information, the authors of the article will be contacted. Differences in data extraction at item level will be resolved by discussion and if consensus is not reached, the third reviewer (KM) will take the final decision.

Assessment of risk of bias in included studies

The quality of reporting of each experimental trail will be assessed by two review authors independently (BB, WR). Risk of bias will be assessed using the Cochrane Collaboration´s tool [18]. In particular, the following factors will be studied.

Minimization of selection bias

- Randomization procedure (*if applicable*): the procedure will be scored adequate if the resulting sequences were unpredictable (computer generated schemes, coin tossing, and tables of random numbers).

Minimization of attrition bias

- Handling of drop-outs: will be considered adequate when the trial reports a complete description of all patients failing to participate until the end of the trial and if the data were analyzed on intention-to-treat (ITT) (thus with all randomized patients included). An overall drop-out rate less than 15%, and a selective drop-out rate less than 10% (the at risk groups), will be considered justifiable.

Minimization of detection bias

- Method of blinding for the outcome: will be considered adequate if the outcome assessors were completely blind for the intervention.

Assessment of heterogeneity

Variation between studies (heterogeneity) will be examined to answer the question whether the combination of the different studies is meaningful.

Clinical heterogeneity of the selected studies will be evaluated according to key characteristics of the study participants (age, gender, diabetes duration, blood glucose levels), the intervention, and study outcomes. Statistical heterogeneity will be estimated by visual inspection of the forest plots (the less overlap of confidence intervals, the more likely the presence of heterogeneity). Furthermore, heterogeneity will be assessed using the I^2-statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance or sampling error [19]. It allows for calculation across studies of varying sizes, study types and with varying outcome data. In case there is significant heterogeneity (I^2 values >75%), more emphasis will be placed on the results of a random-effects model, despite that the given model cannot overcome the problem of heterogeneity.

Data synthesis

Data will be summarized statistically if they are available, sufficiently similar, and of sufficient quality.

Subgroup analysis and investigation of heterogeneity

To explore potential source of (clinical) heterogeneity, subgroup analyses will be performed. Where performed, subgroup analysis will have a tentative (hypothesis-generating) purpose. The following subgroup analyses will be considered:

- Gender
- Duration of the intervention
- Duration of diabetes below and over five years (individuals who have diabetes for a longer time are likely to have more advanced disease and increased insulin resistance, and more complications; hence any forms of care may have a smaller effect in more advanced disease)
- Number of comorbidities

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of certain factors on effect size:

- Repeating the analysis excluding unpublished studies (if selected and included).
- Repeating the analysis taking risk of bias into account.
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results.
- Repeating the analysis excluding studies by using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

The robustness of the results will further be tested by repeating the analysis using different measures of effects size (risk difference, odds ratio, etc) and different statistic models (fixed and random effects models).

5. OUTLOOK

As the population ages, the burden of chronic disease is expected to grow continuously. While healthcare organizations need to find effective ways to deal with increased care demands, the CCM has been developed to advocate evidence-based changes in health care of patients with chronic disease. The findings of the current systematic review will contribute to our understanding of the relationship between application of CCM and qualitative and quantitative T2DM outcomes in European primary care settings. Finally, the results can provide insights into new approaches to further integrate the CCM into primary health care initiatives in diabetes.

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Effectiveness of chronic care models for the management of type 2 diabetes mellitus in Europe: a systematic review and meta-analysis

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Effectiveness of chronic care models for the management of type 2 diabetes mellitus in Europe: a systematic review and meta-analysis

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ABSTRACT

Objectives: We evaluated the effectiveness of European chronic care programs for type 2 diabetes mellitus (characterized by integrative care and a multi-component framework for enhancing healthcare delivery), compared with usual diabetes care.

Design: Systematic review and meta-analysis.

Data sources: MEDLINE, Embase, CENTRAL, and CINAHL from January 2000 to July 2015.

Eligibility criteria: Randomized controlled trials focussing on (i) adults with type 2 diabetes, (ii) multifaceted diabetes care interventions specifically designed for type 2 diabetes and delivered in primary or secondary care, targeting patient, physician, and health care organization, and (iii) usual diabetes care as the control intervention.

Data extraction: Study characteristics, characteristics of the intervention, data on baseline demographics, and changes in patient outcomes.

Data analysis: Weighted mean differences in change in HbA1c and total cholesterol levels between intervention and control patients (95% confidence interval) were estimated using a random-effects model.

Results: Seven cluster randomized controlled trials were included for review (9,529 patients). One year of multifaceted care improved HbA1c levels in patients with screen-detected and newly diagnosed diabetes, but not in patients with prevalent diabetes, compared to usual diabetes care. Across all seven included trials the weighted mean difference in HbA1c change was -0·07% (95% confidence interval: -0·10 to -0·04) (-0·8 mmol/mol (95% confidence interval:-1·1 to -0·4)); I^2=21%. The findings for total cholesterol, LDL-cholesterol and blood pressure were similar to HbA1c, albeit statistical heterogeneity between studies was considerably larger. Compared to usual care, multifaceted care did not significantly change quality of life of the diabetes patient. Finally, measured for screen-

detected diabetes only, the risk of macro- and mircovascular complications at follow-up was not significantly different between intervention and control patients.

Conclusions: Effects of European multifaceted diabetes care patient outcomes are only small. Improvements are somewhat larger for screen-detected and newly diagnosed diabetes patients than for patients with prevalent diabetes.

Strengths and limitations of this study

- This is the first systematic review providing a comprehensive overview of studies that have evaluated the effectiveness of multifaceted diabetes care programs addressing all their components together, rather than separately.
- The focus in this systematic review was on European multifaceted diabetes care programs only, to meet the need for efficient and established programs to providing optimal chronic care due to the burden of increasing diabetes prevalence in Europe.
- There is an important lack of studies which evaluate the effectiveness of implementing all Chronic Care Model-components simultaneously.
- Overall, the studies included in this systematic review provided insufficient details to fully understand the intensity of the intervention, and there was only little overlap in the wide range of outcome measures evaluated.

INTRODUCTION

Chronic disease management relies on the assumption that providing optimal chronic care requires changes of both patients and professionals with regard to behaviour, culture, and communication.[1 2] Indeed, with aging of the population and the growing prevalence of chronic diseases, initiatives to improving quality of chronic care require more than evidence about effective diagnostic procedures and treatments in comparison to acute disorders.[3] Aimed at describing essential elements for improving outcomes in care of chronic diseases, the Chronic Care Model (CCM) was developed in the mid-1990s and was further refined in 1997.[2 4 5] This primary care-based model is based on the assumption that improvements in care require an approach that incorporates patients, health care providers, and system level interventions.[4 6] The CCM comprises six interrelated components deemed essential for providing high-quality care to patients with chronic disease: (i) health care organization (i.e. providing leadership for securing resources and removing barriers to care), (ii) self-management support (i.e. facilitating skills-based learning and patient empowerment), (iii) decision support (i.e. providing guidance for implementing evidence-based care), (iv) delivery system design (i.e. coordinating care processes), (v) clinical information systems (i.e. tracking progress through reporting outcomes to patients and providers, and (vi) community resources and policies (i.e. sustaining care by using community-based resources and public health policy).[7]

The current literature indicates a widespread application of the CCM to multiple illnesses and various studies have provided a rigorous evaluation of its individual components.[5 8-14] In general, these studies have reported positive effects on patient outcomes and processes of care. The reported effect sizes, however, are relatively small and many outcomes are flawed by a considerable level of statistical heterogeneity.[10 13-25]

An aspect that complicates the assessment of effectiveness of chronic care programs is their inherent multi-component nature.[14 20 25] While some authors found that the total number of CCM elements incorporated in the interventions did not influence patient outcomes,[9 10] others

concluded that interventions containing more than one CCM component were more successful at improving the quality of care than single-component interventions.[11 24 26 27] To date, no summative reviews have evaluated to which extent the complete CCM – thus all six components combined in interventions – improves diabetes care.

As such, the aim of the current review was to systematically identify studies of diabetes care assessing the effect of interventions addressing all six components of the CCM. We subsequently aimed to describe the effects of these models on biochemical outcomes, patient-reported outcomes, and diabetes complications in adult patients with type 2 diabetes compared to usual diabetes care by means of a meta-analysis.

METHODS

Our systematic review was based on a protocol with input from experts in diabetes care, statistical methods, and primary care. The protocol was composed according to the PRISMA-P guidelines (see supplementary file S1).[28]

Data sources and searches

We identified studies by searching MEDLINE, Embase, CINAHL and CENTRAL from January 2000 until July 2015. Search syntaxes were developed in consultation with the Cochrane Metabolic And Endocrine Disorders Group by adapting and combining published search strategies from previous systematic reviews on chronic (diabetes) care management.[10 12] Given that the CCM – and its terminology – had been introduced in the late 1990s, we restricted the search to publications from January 2000 onwards. In addition, reference lists of eligible studies and systematic reviews on multifaceted diabetes care were searched by hand to identify additional studies. The full MEDLINE search strategy is available in the online supplementary file S2.

Study selection

One reviewer (BB) identified potentially relevant studies for inclusion by screening title and abstract of all citations that resulted from our literature search. Two reviewers (BB and WR) then screened the full text of these articles. Only randomized controlled trials were considered eligible for inclusion. Non-randomized studies were excluded, as were studies written in a language other than English. Since this systematic review was part of a large European project on managed diabetes care that aimed at developing chronic care management standards and guidance for Europe,[29] we further excluded all non-European CCM trials. Trials eligible for inclusion had to comply with the following inclusion criteria.

Type of participants: individuals, regardless of gender and ethnicity, diagnosed with type 2 diabetes, and with or without comorbidities.

Type of intervention: previous systematic reviews on multifaceted chronic care have reported that randomized-controlled-trial-interventions are generally described poorly and incomprehensively, which complicates mapping the individual elements of the intervention to the six CCM components. To avoid mapping difficulties, we have reformulated the following inclusion criteria for the interventions: The intervention had to be described as a multifaceted chronic care model or program that (i) was designed specifically for individuals with type 2 diabetes, (ii) was based on guidelines, (iii) provided multi-disciplinary care, (iv) addressed patient empowerment, (v) provided quality management (e.g. patient registry systems, recording of process measurements and adherence to guidelines, achievement of treatment goals), (vi) was delivered in primary or secondary care, and (vii) had a minimum duration of six months. The control intervention had to be defined as usual diabetes care as recommended in that particular country (e.g. regular follow-up with the required health professional and a full diabetes annual review).

Type of outcome measures: we considered three categories of outcome measures: (i) biochemical outcomes, such as HbA1c, triglyceride and cholesterol levels, (ii) patient-reported outcomes, including diabetes-related quality of life and patient empowerment, and (iii) diabetes complications, such as retinopathy, nephropathy, neuropathy, cardiovascular disease, and mortality.

Any disagreements between the two reviewers regarding the in- or exclusion of studies were resolved by consensus.

Data extraction and quality assessment

Using a standard structured data abstraction form, one reviewer (BB) performed the data extraction which was confirmed by a second reviewer (WR). The extracted data included

study design, length of intervention/follow-up, sample size, in- and exclusion criteria, mean or median age of the included sample, percentage males, study setting (i.e., primary or secondary care), intervention details, and mean differences in change for various outcomes. When important information or outcome data were missing, trial authors of the included studies were contacted. When unavailable, the particular data were not included in the analyses.

The standard Cochrane EPOC Risk of Bias Tool was used to assess risk of bias for each of the selected studies.[30] Since all included studies were cluster-randomized controlled trials, additional attention was given to potential sources of bias specific to cluster-randomized trials: (i) recruitment bias: did recruitment of diabetes patients take place before or after randomization of the clusters?, (ii) did the intervention and control group differ in baseline characteristics?, (iii) did any of the clusters drop out during follow-up?, (iv) was clustering accounted for in the statistical analyses? If a certain domain could not be classified as “high” or “low” risk of bias due to inadequate reporting, it was deemed “unclear” risk of bias.

Data synthesis and analysis

Due to heterogeneity of the study populations and duration of the interventions, and due to the small overlap in outcomes of the individual trials, an extensive meta-analysis and meta-regression of all reported outcome variables was not possible. The available data only allowed to statistically pool the results for HbA1c concentrations and total cholesterol levels. Review Manager (RevMan 5.2.0; the Cochrane Collaboration) was used to compute the weighted mean difference in change in HbA1c and total cholesterol between intervention and control groups, employing the generic inverse variance method. To incorporate both between- and within-study variance we used a random effects model for estimating the weighted mean differences in change between intervention and control group across the included trials.[31] Mean differences were pooled separately for the different types of diabetes

patients (prevalent, screen-detected, and newly diagnosed), and subsequently for the entire patient population. The consistency of the findings across the studies was assessed using forest plots. We evaluated statistical heterogeneity by calculating the I^2 statistic, a measure independent of the number of studies and effect size metric.[32] All outcomes variables other than HbA1c and total cholesterol, we analysed descriptively.

RESULTS

Figure 1 summarises the identification of relevant studies and the numbers of excluded and included studies. The search of the electronic databases identified 9,464 abstracts of studies published between January 2000 and July 2015. After excluding duplicate citations (n=1,227) and studies unrelated to the current review´s topic (n=7,801), we considered 436 articles for full-text review. Of these, 424 studies failed to meet our explicit inclusion criteria including 128 systematic reviews on chronic diabetes management from which the reference lists were subsequently searched for additional relevant studies. In total, twelve articles met our inclusion criteria and were included in the current review.[33-43]

<insert figure 1 here>

Study Characteristics

The 12 included articles[33-43] reported on eight unique cluster randomized controlled trials,[33 35 39-41 43-45] carried out between 1989 and 2011. Two of these trials, Addition Denmark[40] and Addition Cambridge,[35] had not individually reported any follow-up results in sequel to their study protocols. Their five-year data however, were pooled in the Addition-Europe study[46] together with the five-year data of the Addition-Netherlands[39] and Addition-Leicester[43] trials. For the remainder of the methods section, we will describe the design features and assess risk of bias for the Addition-Denmark and Addition–Cambridge trials based on their published protocol, yet for the results section we will have to resort to the pooled five-year data from the Addition-Europe study. This means that although we identified eight unique trials,[33 35 39-41 43-45] there are just seven publications to extract data from.[33 39 41 43-46]

All trials had recruited either general practitioners or physician practices which represented the cluster level (level of randomization). In one study,[45] however, first-level clusters were formed by district (characterized as urban, rural and mixed) and second-level clusters by the

physicians. The total number of patients with type 2 diabetes enrolled by the physicians amounted to 9,529, of whom 8,921 (94%) had been included in the analyses.

The objective of each trial was the structured multifaceted management of diabetes, and the interventions were aimed at improving the patients´ cardiovascular risk profile[44 45] and metabolic control,[33 35 39 40 43 44] and assessing the effect of multifaceted care on the occurrence of cardiovascular events,[35 39 40 43] overall mortality,[41] and risk factors for clinical complications.[41] Interventions focused on all aspects of the CCM including more regular and frequent consultations, annual screening for diabetes complications, patient education/advice, guideline-based clinical treatment and physician education, regular/annual feedback reports to physicians, referrals, record keeping, formation of multidisciplinary (primary care provider) teams, delegation of routine diabetes tasks to a trained practice nurse, patient and physician reminders, and patient-physician communication and decision-making. The interventions were largely delivered by general practitioners and physicians, yet specialized nurses or practice nurses were also involved in the intervention-program as part of the practice team and to (partly) replace the physician in providing diabetes care.[33 35 39 40 43 44]

Two main aspects differed among the trials: the type of diabetes patient enrolled and the duration of the intervention. Three trials[33 44 45] had included patients with prevalent diabetes and intervened for one year. The average diabetes duration in these studies ranged from 5.8 to 9.5 years. One trial[41] had enrolled patients with newly diagnosed type 2 diabetes and assessed outcome measures after six years of intervention. Finally, there were four trials[35 39 40 43] that first had initiated a diabetes screening program and subsequently had recruited those with screen-detected diabetes to participate in the intervention study. Follow-up measurements were assessed at one year and at five years. Supplementary table S1 presents an overview of interventions and findings of the included publications. Tables 1a and 1b present the baseline patient characteristics for the trials that recruited patients with

prevalent diabetes[33 44 45] and for the trials that recruited patients with screen-detected[39 43 46] and newly diagnosed diabetes,[41] respectively.

<insert tables 1a and 1b here>

Data quality assessment

Figure 2 summarizes the risk of bias for the trials included in this review. Whereas the Addition-Denmark[40] and the Addition-Cambridge[35] trials had not published one-year data, they did provide five-year data for the Addition-Europe meta-analysis[46] and were thus included in the risk of bias assessment. However, since not having published actual trial data, we could not assess the domains of incomplete outcome data, selective reporting, and other bias, which resulted in the occurrence of blanks in Figure 2.

<insert figure 2 here>

Seven trials had at least one domain judged as unclear risk of bias. Five trials had at least one domain judged as high risk of bias. Only one study[44] had explicitly described that their physicians were unaware of being allocated to the intervention or control group when recruiting eligible patients. For the remaining studies prior knowledge of treatment allocation cannot be ruled out (recruitment bias). Furthermore, the Addition studies[35 39 40 43] were the only trials in which patients remained unaware of group assignment throughout the study.

In four studies[35 39 40 43] outcome assessment was performed completely blinded for patient allocation. In one study[45] only laboratory outcomes were assessed blinded, whereas clinical outcomes were obtained by contacting the general practitioner, introducing possible bias. No substantial baseline differences between the intervention and control groups existed with regard to the outcomes of interest.

Biochemical outcomes

All studies had assessed biochemical outcomes at follow-up, including HbA1c level, blood lipid levels, blood pressure, and BMI.

HbA1c levels

All studies assessed HbA1c values at follow-up. For six[33 39 43-46] of the seven study populations glycaemic control at baseline was moderate to good, as expressed by mean HbA1c concentrations ranging from 7·0% to 7·8% (53 to 62 mmol/mol) (Table S1a and S1b). The three trials with prevalent type 2 diabetes patients[33 44 45] observed no statistically significant difference in change in HbA1c levels between the intervention and control group after one year of intervention (Figure 3). There was no statistical heterogeneity between these three trials (I^2 = 0%) and the weighted mean difference in change between intervention and control groups was -0·06% (95% CI: -0·13 to 0·01) (-0·7 mmol/mol (95% CI: -1·4 to 0·1)), in favour of the intervention group. Using a similarly short intervention period, yet studying patients with screen-detected type 2 diabetes, the Addition-Leicester trial[43] observed a significant difference in change in HbA1c between the two trial arms of -0·20% (95% CI: -0·31 to -0·08) (-2·2 mmol/mol (95% CI: -3·4 to -0·9)). Whereas the Addition-Netherlands authors[39] did not report the actual difference in HbA1c change between the two groups, they stated in their paper that the improvement in HbA1c was significantly better in the intervention group, compared to the control group. The pooled five-year data from all four Addition-trials[46] showed a somewhat smaller, yet significantly greater improvement in HbA1c concentration in intervention patients, compared to control patients (-0·08% (95% CI: -0·14 to -0·02)) (-0·9 mmol/mol (95% CI: -1·5 to -0·2)) (Figure 3). Finally, the effect of multifaceted care in Danish patients with newly diagnosed diabetes[41] after six years of intervention was comparable to that in screen-detected patients after five years of intervention[46] (-0·06% (95% CI: -0·08 to -0·03)) (-0·7 mmol/mol (95% CI: -0·9 to -0·3)).

Pooling all seven trials, multifaceted care improved HbA1c concentration with -0·07% (95% CI: -0·10, -0·04) (-0·8 mmol/mol (95% CI: -1·1 to -0·4)) (Figure 3). Statistical heterogeneity across the seven trials was small to moderate (I^2 = 21%).

<insert figure 3 here>

Cholesterol levels

Figure 4 presents the mean differences in change in total cholesterol levels for all seven trials. Of the three trials that studied prevalent diabetes patients, only the Dutch trial[33] observed multifaceted care to significantly improve total cholesterol concentrations. In the remaining two studies,[44 45] cholesterol levels were similar between intervention and control arm. Statistical heterogeneity across the three studies was low (I^2=12%) and their weighted mean difference in change between intervention and control groups amounted to -0·14 mmol/l (95% CI: -0·22 to -0·07). Similar to HbA1c, the effect of multifaceted care on cholesterol seemed larger in screen-detected patients than in patients with prevalent diabetes. After one year of intervention, Addition-Leicester[43] found a mean difference in change between the intervention and control group of -0·56 mmol/l (95% CI: -0·87 to -0·25). The pooled five-year data from all four Addition trials also showed a significantly greater improvement in total cholesterol levels in intervention patients, compared to control patients (-0·27 mmol/l (95% CI: -0·34 to -0·19)). Finally, in Danish patients with newly diagnosed diabetes,[41] six years of multifaceted care had caused cholesterol levels to improve (-0·15 mmol/l (95% CI:-0·29 to -0·02)).

Pooling all trials, the effect of multifaceted care on improvement of total cholesterol resulted in a weighted difference in change between intervention and control patients of -0·20 mmol/l (95% CI: -0·28 to -0·11); I^2=64%.

In addition to improvements in total cholesterol levels, HDL-cholesterol levels appeared to be unaffected by multifaceted care in patients with prevalent diabetes.[33 44 45] LDL-cholesterol levels on the other hand, did improve (see supplementary figure S1 and S2). Both the Dutch[33] and the Swiss[44] study found significantly better improvements in LDL-cholesterol for the intervention group, when compared to the control group. The Addition-Netherlands[39] and Addition-Leicester[43] studies observed that multifaceted care significantly improved LDL-cholesterol levels after one year, while HDL-cholesterol remained largely unchanged. Similar results were reported for five years of intervention by the Addition-Europe study.[46] The Danish study[41] with newly diagnosed diabetes patients had not measured HDL and LDL-cholesterol levels.

<insert figure 4 here>

Blood pressure

Two[33 44] out of the three trials with patients with prevalent diabetes reported a difference in change in diastolic and systolic blood pressure, both being in favour of the intervention group (see supplementary figure S3 and S4). Better improvements in blood pressure were also seen in intervention patients with screen-detected diabetes, compared to control patients.[39 43 46] Improvements after one year of intervention[43] were larger than those after five years of intervention.[46] In patients with newly diagnosed diabetes[41] six years of multifaceted care significantly improved systolic, but not diastolic, blood pressure when compared to usual diabetes care. Similar to HbA1c and total cholesterol, the results for blood pressure were stronger for patients with screen-detected and newly diagnosed diabetes than for those with prevalent, long-standing diabetes.

Body mass index

With regard to the studies on prevalent diabetes, only the Austrian study[45] found a significant difference in change in BMI between the intervention group and control group after one year of intervention (see supplementary figure S5). In screen-detected diabetes patients[39 43] multifaceted care resulted in a significantly higher reduction in BMI, compared to usual diabetes care. Furthermore, Addition-Leicester[43] reported a higher reduction in both BMI and body weight (kg) for the intervention group compared to the control group, but observed no difference in reduction of waist circumference. After an intervention duration of five years, the pooled reduction in weight and waist circumference, but not in BMI, in screen-detected diabetes was significantly higher in the intervention group compared to the control group[46]. The Danish trial[41] with newly diagnosed diabetes patients observed no difference in weight change after six years of intervention, yet BMI had not been measured.

For further biochemical outcomes, see online supplementary file S3.

Patient-reported outcomes

The effect of a multifaceted care intervention on the patients´ quality of life accounted for the only patient-reported outcome assessed by the included trials.

Quality of life

Quality of life was reported by five[33 39 43 44 46] of the seven trials, most of which had used the 36-item Short Form Health Survey (SF-36) to assess the different domains of health-related quality of life. In patients with prevalent diabetes[33 44] significant changes over time were absent for all scores of the SF-36 subscales for both the intervention and control arms. A superior effect of multifaceted care was observed only on the SF-36 subscale “health

change" in the Dutch trial with prevalent diabetes patients.[33] For the two Addition studies reporting results after one year of intervention,[39 43] as for the pooled five-year data by Addition-Europe,[46] no significant changes in the physical and mental summary scores of the SF-36, or the abbreviated SF-12 version that was used in the Addition-Leicester trial,[43] could be demonstrated.

Diabetes complications

Only few trials had reported diabetes complications, including cardiovascular disease and mortality. Closely related to the prevention and occurrence of complications, some studies evaluated the effect of their intervention on processes of care, such as reaching target values for HbA1c and receiving regular eye and foot examinations.

Macro- and microvascular complications

Macro- and microvascular diabetes complications during follow-up were reported by the two studies[41 46] with the longer intervention periods. The Addition-Europe study[46] had assessed myocardial infarction, stroke, coronary and peripheral revascularization procedures, cardiovascular death and total mortality, and non-traumatic amputation in screen-diagnosed diabetes patients. Whereas the estimated hazard ratios for these events all favoured the intervention group, none of the estimates reached statistical significance. In newly diagnosed diabetes patients,[41] multifaceted care had not resulted in differences between intervention and control group regarding the risk of diabetic retinopathy, peripheral neuropathy, microalbuminuria, non-fatal myocardial infarction and stroke, angina pectoris, or intermittent claudication at six years.

Processes of care

Only three studies assessed processes of care or process quality measures.[33 45 46] The Dutch study[33] with prevalent diabetes patients observed that multifaceted care resulted in significantly more patients reaching treatment targets (18·9%) than usual diabetes care (13·4%) (treatment targets were defined as HbA1c ≤7% (53 mmol/mol), systolic blood pressure ≤140 mmHg, total cholesterol ≤4·5 mmol/l and LDL-cholesterol ≤2·5 mmol/l). Process quality measures at one year, defined as the percentage of patients receiving guideline-adherent foot-, eye-, and HbA1c-examinations, were reported by the Austrian study with prevalent diabetes patients[45] to be significantly higher in the intervention group. The pooled five-year results from the four Addition studies[46] showed that in both trial arms more patients had values below target thresholds for HbA1c (<7% (53 mmol/mol)), blood pressure (≤135/85 mmHg) and cholesterol level (<4·5 mmol/l), yet proportions were higher in the intervention group than in the control group.

For further diabetes complications and related outcomes, see online supplementary file S3.

DISCUSSION

This review assessed the effectiveness of chronic disease management models for type 2 diabetes on the improvement of patient outcomes, in Europe. In general, the effects of multifaceted care on patient outcomes were rather small and their magnitude seemed to differ according to the type of diabetes patient being studied. Our analysis suggested that in comparison to usual diabetes care, multifaceted care improves HbA1c levels for patients with screen-detected diabetes and patients with newly diagnosed diabetes, but not for patients with prevalent type 2 diabetes. Similar findings were observed for total cholesterol, LDL-cholesterol, BMI and body weight. The resulting improvements in blood pressure seemed less strongly related to the type of diabetes patient studied. Other outcomes, such as fasting glucose levels, triglycerides, quality of life, and diabetes complications, had been reported inconsequently and results varied widely across the included trials.

The few cluster randomized controlled trials that we identified from the literature were relatively heterogeneous with regard to the individual components of the implemented intervention, duration of the intervention, type of diabetes patient, and reported outcomes. For each trial, methodological quality was acceptable and there were very low rates of dropout among the enrolled patients. Still, details on the randomization procedure was frequently missing as well as information concerning concealment of allocation from general practitioners and physicians in advance to recruitment of eligible patients. Given the current literature, it is not possible to draw an unequivocal conclusion about the effectiveness of chronic multifaceted care on diabetes patient outcomes.

Overall, previous systematic reviews have reported that an integrated approach to diabetes care versus usual diabetes care may improve clinical and biochemical outcomes,[9 10 19 20 23 24 47] including HbA1c levels, blood pressure, and blood lipid concentrations. Those reviews that included a meta-analysis reported mean differences in HbA1c reduction between intervention and control groups ranging from -0.14 (95% CI: -0.25 to -0.05) to -0.5% (95% CI: -0.6 to -

0.3). Mean differences in total cholesterol have only been estimated by one meta-analysis, which reported a reduction of -0.24 mmol/l (95% CI: -0.41 to -0.06) in favour of the intervention group.[10] This study also reported a mean difference in diastolic blood pressure reduction of -1.3 mm Hg (95% CI: -0.21 to -0.6) and a mean difference in systolic blood pressure reduction of -2.2 mmHg (95% CI: -3.5 to -0.9), comparable with the summary estimate for systolic blood pressure from Elissen *et al.* (-2.8 (95% CI: -4.7 to -0.9)).[20] All other outcomes of multifaceted care interventions were described narratively. Improvements have been observed for frequency of retinopathy screening,[20 47 48] screening for peripheral polyneuropathy and foot lesions,[20 47 48] proteinuria measurements,[48] and the monitoring frequency of lipid and HbA1c levels.[48]In addition, there seems to be an economic benefit of integrated diabetes care.[49]. Yet, other systematic reviews have found no impact on patients outcomes and processes of care[18 25 48] or have disputed the clinical relevance of statistically significant findings.[19] A comparison of the reported effect estimates with our summary estimates for HbA1c and total cholesterol warrants caution, given the varying number of CCM elements the estimates were based on, the heterogeneity among the included diabetes patients, the different restrictions to geographical region, and the number of included studies in each review.

The novelty of the current systematic review is that it provides a comprehensive overview of diabetes care trials that have evaluated the effectiveness of the all the six components of the CCM combined, instead of one or more components. Overall, we found there is an important lack of studies which evaluate the implementation of all six CCM-components simultaneously. In current literature, findings on the issue of whether multifaceted chronic care is to be preferred over single-faceted care are conflicting.[9-12 24-26 50] However, improving the management of a complex disease like diabetes is a challenging goal which, we believe, may not be achieved by targeting single care aspects only. Another novel aspect of the current review is the focus on state-of-the-art diabetes management in Europe only. The narrow view relates to the enormous burden that type 2 diabetes represents in Europe, both

in individual and in societal terms.[51] The prevalence of diabetes in Europe is expected to increase from 59.8 million adults in 2015 to 71.1 million in 2040.[52]

As reflected by recent guidelines for the management of patients with type 2 diabetes,[53] health care providers have increasingly focused at improving and controlling cardiovascular risk factors to improve patient outcomes, including hyperglycaemia, overweight or obesity, elevated blood pressure, and dyslipidemia. Results from the Steno-2 trial support the view that even in high-risk patients with type 2 diabetes multifaceted care has the potential to reduce the risk of complications and mortality.[54] Randomizing 160 patients with type 2 diabetes and persistent microalbuminuria to an intensive multifactorial treatment and conventional therapy, the authors found that the multifactorial treatment was associated with a lower risk of cardiovascular events after 13·3 years of follow-up, as well as with a lower risk of death from cardiovascular disease, compared to conventional treatment . And while the CCM has been proposed as a tool to improve the quality of diabetes care and, subsequently, patient outcomes, the current review indicates that at least the existing programs have not been as successful in this respect as intended. The challenge thus remains to translate results from landmark studies like Steno-2, into primary care, where the majority of type 2 diabetes patients are being treated.

When aiming to improve chronic health care, it has been proposed that only assessing the effects of a multifaceted care intervention on patient outcomes is not sufficient. In order to gain insights into why and when certain interventions are effective, it is also important to focus on barriers and facilitators to the implementation process of the intervention and their effect on the interplay between intervention and outcomes.[55] This latter aspect is usually not evaluated or reported on by randomized controlled trials implementing a multifaceted care intervention.[56] As such, it has not yet been possible to analyse the relationships between context, mechanisms, and outcomes of multifaceted diabetes care interventions and to subsequently provide meaningful insights into how these have influenced the outcomes achieved.[56] There are some limitations of our work that need to be considered. First, many

studies provided insufficient detail in their methods section to fully understand the intensity of (specific components of) the intervention. This complicated our appraisal of whether all components of the CCM were covered. In addition, the different interventions that the trials have used to represent a given component of the CCM have possibly resulted in some heterogeneity across the trials. Second, whereas the aim of the current review was to investigate the effectiveness of chronic care models in Europe, the trials available for this review only represented the Western part of Europe. Countries with the highest prevalence of diabetes lie in Eastern Europe, i.e. Turkey, Montenegro, Macedonia, and Serbia.[51] The top-three countries in Western Europe with the highest diabetes prevalence are Germany, Spain, and Italy,[51] none of which were represented in this review. And third, the procedure of selecting relevant studies for the current review was largely performed by only one person. However, two reviewers subsequently screened the full text of all potentially relevant papers such that the final decision on inclusion was based on two opinions.

In conclusion, the available scientific evidence regarding the effectiveness of multifaceted chronic care programs for type 2 diabetes in older patients in Europe is low. In general, the current findings support the concept of the chronic care model, yet the improvements in patient outcomes and processes of care are only small. While key aspects of type 2 diabetes can be improved by a multifactorial intervention, it is not yet clear if these improvements will subsequently lower diabetes-related complications, such as cardiovascular disease and overall mortality. Furthermore, the effect of the interventions seemed, at least partly, to depend on the type of diabetes patient, which could suggest effect modification by disease duration and/or disease severity. Another aspect that could add to the differences in effectiveness between the individual interventions is the degree in which they facilitate changes in social behaviour. This implies that more attention in trials should be spent to factors like adherence to treatment strategies, level of self-management skills, and patients´ knowledge on their disease. These traits need to be positively affected before an improvement in clinical measures can even occur,[1] yet studies generally reveal little on

person-centred factors. And finally, there is a lack of knowledge (on information) on effective methods to address important pragmatic questions about improvement of care, for example, which specific mechanism or procedure of a chronic care model works, for which patients, and under which circumstances?[57] Future research would need to incorporate the measurement of context, mechanisms and outcomes of multifaceted care into study designs in order to deliver the full extent of insights needed to improve chronic diabetes care and, ultimately, patient outcomes.

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Contributors

BWCB designed the review by writing the review protocol, identified studies for inclusion, extracted and interpreted the data, and drafted and revised the article. KM contributed to the review protocol and to the discussion. He further revised the draft paper for intellectual content. JW was involved in conception of the review and he contributed to the review protocol, to interpretation of the data and to the discussion. Furthermore, JW revised the draft paper for intellectual content. CL contributed to the review protocol and to the discussion, and she revised the draft paper for intellectual content. PS conceived and

initiated the review, contributed to the review protocol and he contributed to the interpretation of the data, to the discussion and to revision of the draft paper. MR was involved in conception of the review and he revised the draft paper for intellectual content. WR contributed to the review protocol, identified studies for inclusion, extracted and interpreted the data and revised the draft paper for intellectual content. All authors approved the final completed article.

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ONLINE SUPPLEMENTARY INFORMATION

File S1. Review protocol

File S2. Search strategy MEDLINE

File S3. Results

Table S1. Characteristics of the included cluster randomized controlled trials.

Figure S1. Overview of the results for HDL-cholesterol levels

Figure S2. Overview of the results for LDL-cholesterol levels

Figure S3. Overview of the results for diastolic blood pressure

Figure S4. Overview of the results for systolic blood pressure

Figure S5. Overview of the results for BMI

Figure S6. Overview of the results for fasting glucose levels

Figure S7. Overview of the results for triglyceride levels

Figure S8. Overview of the results for creatinine levels

FIGURES TITLES AND LEGENDS

Figure 1: Flow chart summarizing the identification of studies for inclusion in the review.

Figure 2: Risk of bias graph.

Review authors' judgments about each risk of bias item presented as percentages across all included studies. Studies included are Cleveringa et al. (2008)[32]; Sönnichsen et al. (2008)[44]; Frei et al. (2010)[43]; Olivarius et al. (2001)[40]; Janssen et al. (2009)[38]; Webb et al. (2010)[42]; Lauritzen et al. (2000)[39]; and Echouffo et al. (2009)[34]. The studies from Lauritzen and Echouffo were included in the risk of bias assessment since their five-year follow-up data had been included in the Addition-Europe meta-analysis by Griffin et al.[45]. As the Addition-Europe publication only reported pooled data, no comprehensive overview of results was available for the studies by Lauritzen and Echouffo, which resulted in the blanks in the risk of bias graph.

Figure 3: Mean difference in change (95% confidence interval) in HbA1c levels (%) after multifaceted care between intervention and control groups. Results are stratified by type of diabetes patient.

IV, generic inverse variance method; CI, confidence interval; df, degrees of freedom

[a] Studies had an intervention duration of one year. [b] The methodology for calculating the difference in change between intervention and control group that Cleveringa et al.[32] have used (subtracting the HbA1c change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the HbA1c change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa et al.,[32] we have recalculated their HbA1c results according to the methodology

used by the other studies. [c] The study of Webb et al.[42] had an intervention duration of one year and the study of Griffin et al.[45] had a duration of five years. [d] This study combined the 5-year intervention data from all four Addition studies, including the five-year data from Webb et al.[42] [e] This study had an intervention duration of six years.

Figure 4: Mean difference in change (95% confidence interval) in total cholesterol levels (mmol/l) after multifaceted care between intervention and control groups. Results are stratified by type of diabetes patient.

IV, generic inverse variance method; CI, confidence interval; df, degrees of freedom

[a] Studies had an intervention duration of one year. [b] The methodology for calculating the difference in change between intervention and control group that Cleveringa et al.[32] have used (subtracting the total cholesterol change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the total cholesterol change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa et al.,[32] we have recalculated their cholesterol results according to the methodology used by the other studies. [c] The study of Webb et al.[42] had an intervention duration of one year and the study of Griffin et al.[45] had a duration of five years. [d] This study combined the 5-year intervention data from all four Addition studies, including the five-year data from Webb et al.[42] [e] This study had an intervention duration of six years.

Table 1a: Baseline patient characteristics of the included cluster randomized controlled trials studying patients with prevalent diabetes

	Cleveringa *et al*[33] *		Sönnichsen *et al*[45] †		Frei *et al*[44] ‡	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
N	1699	1692	649	840	162	164
Follow up duration (years)	1	1	1	1	1	1
Type of diabetes patients	Prevalent diabetes		Prevalent diabetes		Prevalent diabetes	
Country	Netherlands		Austria		Switzerland	
Baseline patient characteristics						
Age (years)	65.2 ± 11.3	65.0 ± 11.0	65.4 ± 10.4	65.5 ± 10.4	65.7 ± 10.4	68.3 ± 10.6
Sex (% men)	48.2	49.8	51.0	53.1	54	60
Ethnicity (% Caucasian)	97.7	97.6	-	-	-	-
Diabetes duration (years)	5.8 ± 5.7	5.4 ± 5.8	7.0 ± 6.5		9.5 ± 7.4	10.3 ± 7.8
Current smoking (% yes)	**22.6**	**16.6**	13.4		14	9
Body mass index (kg/m^2)	30.0 ± 5.3	30.2 ± 5.3	**30.4 ± 5.1**	**29.7 ± 4.9**	30.5 ± 5.3	30.7 ± 5.9
Systolic blood pressure (mmHg)	149 ± 22	149 ± 21	141 ± 19	139 ± 17	140 ± 18	138 ± 17
Diastolic blood pressure (mmHg)	83 ± 11	82 ± 11	83 ± 11	82 ± 10	83 ± 10	79 ± 10
UKDPS CHD risk (%)	22.5 ± 16.5[§]	21.7 ± 15.8[§]	-	-	-	-
HbA1c (%)	7.1 ± 1.3	7.0 ± 1.1	7.46 ± 1.53	7.34 ± 1.31	7.8 ± 1.5	7.6 ± 1.1
Total cholesterol (mmol/l)	5.0 ± 1.0	4.9 ± 1.1	**5.15 ± 1.14**	**5.02 ± 1.09**	5.0 ± 1.2	4.7 ± 1.1
HDL-cholesterol (mmol/l)	**1.36 ± 0.36**	**1.32 ± 0.35**	1.35 ± 0.39	1.32 ± 0.36	1.2 ± 0.3	1.3 ± 0.4
LDL-cholesterol (mmol/l)	2.8 ± 0.92	2.8 ± 0.95	2.87 ± 0.96	2·87 ± 0·91	2·8 ± 1·1	2·5 ± 1·1

Fasting glucose (mmol/l)	8·0 ± 2·4	7·8 ± 2·2	-	-	8·4 ± 2·5	7·7 ± 2·2
Creatinine (µmol/l)	87.5 ± 27.7	85.9 ± 22.5	84.9 ± 30.9	84.9 ± 34.5	-	-
Triglycerides (mmol/l)	1.8 ± 1.1	1.8 ± 1.3	2.14 ± 1.82	2.00 ± 1.73	-	-
Urinary albumin (mg/l)	-	-	-	-	-	-
Quality of life: PCS[¶]					43.9 ± 10.9	
Quality of life: MCS[¶]					50.1 ± 11.3	
History of myocardial infarction (%)	**47.1**	**63.3**	8.4		-	-
History of stroke (%)			7.0		-	-
Diabetic retinopathy (%)	2.9	3.3	-	-	9.3	8.1
Peripheral neuropathy (%)	-	-	-	-	18.6	13.4

UKPDS, UK Prospective Diabetes Study; CHD, coronary heart disease; PCS, physical component summary score; MCS, Mental component summary score.

Values are mean ± sd, or percentages. Bold font indicates that the particular baseline characteristic differed statistically significantly between intervention and control group.

* The information on BMI, fasting glucose, creatinine, triglycerides, and retinopathy was obtained through contacting the authors.

† The information on diabetes duration, smoking, history of myocardial infarction, and history of stroke was obtained from the publication describing baseline characteristics of the total study population and stratified by sex (Flamm *et al*. 2011).

‡ The quality of life summary scores for the physical and mental component were obtained from the publication describing baseline characteristics of the total study population (Frei *et al*. 2012). Peripheral neuropathy is represented by "*pathological foot status*" and diabetic retinopathy is represented by "*annual eye exam: pathological*".

§ Values concern the 10-year UKDPS CHD risk.

¶ Quality of life was assessed with the 36-item Short Form Health Survey (SF-36)

Table 1b

Table 1b: Baseline patient characteristics of the included cluster randomized controlled trials studying patients with screen-detected and newly diagnosed diabetes

	Webb *et al*[43]		Janssen *et al*[39]		Griffin *et al*[46]		Olivarius *et al*[41]	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
N	146	199	255	243	1678	1379	649	614
Follow up duration (years)	1	1	1	1	5	5	6	6
Type of diabetes patients	Screen-detected diabetes		Screen-detected diabetes		Screen-detected diabetes		Newly diagnosed diabetes	
Country	United Kingdom		Netherlands		United Kingdom, Netherlands, Denmark		Denmark	
Baseline patient characteristics								
Age (years)	59.4 ± 10.0	60.0 ± 10.0	60.1 ± 5.4	59.9 ± 5.1	60.3 ± 6.9	60.2 ± 6.8	65.5 (55.3-74.0)	65.3 (56.3-73.5)
Sex (% men)	56.9	58.3	51.8	56.0	58.5	57.3	52.4	53.1
Ethnicity (% Caucasian)	52.7	62.3	98.0	98.7	95.8	93.4	-	-
Diabetes duration (years)	0	0	0	0	0	0	0	0
Current smoking (% yes)	15.2	10.2	26.3	21.4	26.9	27.8	**35.5**	**34.5**
Body mass index (kg/m^2)	31.0 ± 5.9	31.5 ± 5.7	31.2 ± 5.1	30.4 ± 4.6	31.6 ± 5.6	31.6 ± 5.6	29.4 (26.2-33.0)	28.8 (26.0-32.3)
Systolic blood pressure (mmHg)	145.7 ± 18.5	148.4 ± 20.5	166 ± 23	163 ± 23	148.5 ± 22.1	149.8 ± 21.3	150 (130-164)	148 (130-160)
Diastolic blood pressure (mmHg)	87.8 ± 10.4	89.5 ± 10.7	90 ± 11	89 ± 10	86.1 ± 11.1	86.5 ± 11.3	85 (80-90)	85 (80-90)
UKPDS CHD risk (%)	8.5 ± 5.8†	9.3 ± 7.1†	-	-	-	-	-	-
HbA1c (%)	7.2 ± 1.5	7.3 ± 1.8	7.3 ± 1.6	7.4 ± 1.7	7.0 ± 1.6	7.0 ± 1.5	10.2 (8.6-11.6)	10.2 (8.7-11.9)
Total cholesterol (mmol/l)	**5.3 ± 1.2**	**5.6 ± 1.3**	5.6 ± 1.1	5.6 ± 1.1	5.5 ± 1.1	5.6 ± 1.2	6.2 (5.4-7.1)	6.2 (5.5-7.2)

HDL-cholesterol (mmol/l)	1.2 ± 0.4	1.2 ± 0.3	1.1 ± 0.4	1.1 ± 0.3	1.2 (1.0-1.5)	1.2 (1.0-1.5)	-	-
LDL-cholesterol (mmol/l)	**3.2 ± 1.0**	**3.5 ± 1.0**	3.7 ± 1.0	3.7 ± 1.0	3.4 ± 1.0	3.5 ± 1.0	-	-
Fasting glucose (mmol/l)	-	-	7.8 ± 2.3	8.1 ± 2.8	-	-	13.8 (10.7-17.0)	13.7 (10.7-17.0)
Creatinine (µmol/l)	-	-	-	-	83.4 ± 17.1	84.9 ± 18.6	90 (81-101)	88 (79-100)
Triglycerides (mmol/l)	2.1 ± 1.9	2.1 ± 1.4	1.9 ± 1.0	2.0 ± 1.6	1.6 (1.2-2.3)	1.7 (1.2-2.4)	2.03 (1.44-2.91)	1.98 (1.39-2.95)
Urinary albumin (mg/l)	-	-	-	-	-	-	11.7 (6.0-32.5)	11.8 (5.7-27.5)
Quality of life: PCS‡	39.0 (37.4-40.5)	38.5 (37.1- 40.0)	No summary scores reported		-	-	-	-
Quality of life: MCS‡	38.2 (35.2-41.2)	39.2 (36.5-41.9)	No summary scores reported		-	-	-	-
History of myocardial infarction (%)	15.8*	10.6*	-	-	6.8	6.1	6.6	7.7
History of stroke (%)			-	-	2.9	1.9	3.5	4.2
Diabetic retinopathy (%)	-	-	-	-	-	-	5.0	4.5
Peripheral neuropathy (%)	-	-	-	-	-	-	18.8	19.7

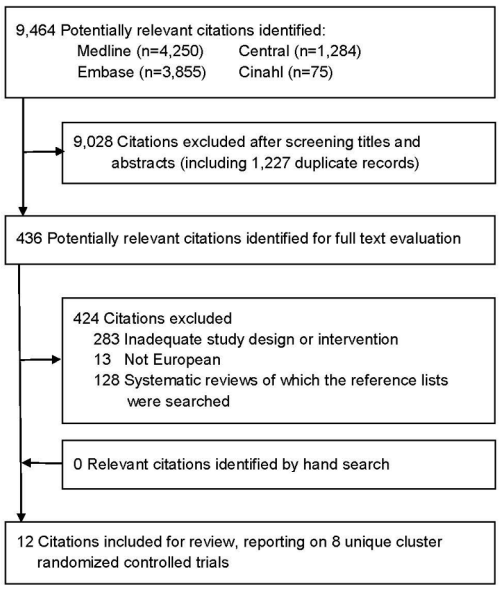
UKPDS, UK Prospective Diabetes Study; CHD, coronary heart disease; PCS, physical component summary score; MCS, Mental component summary score.

Values are mean ± sd, or median (interquartile range) or percentages. Bold font indicates that the comparison between intervention and control group was statistically significant.

* Defined as "*pre-existing CVD*", including myocardial infarction, stroke, and angina.

† Values concern the 5-year UKDPS CHD risk

‡ Quality of life was assessed with the 12-item Short Form Health Survey (SF-12) in de study by Webb *et al*., and with the 36-item Short Form Health Survey (SF-36) in de study by Janssen *et al*.



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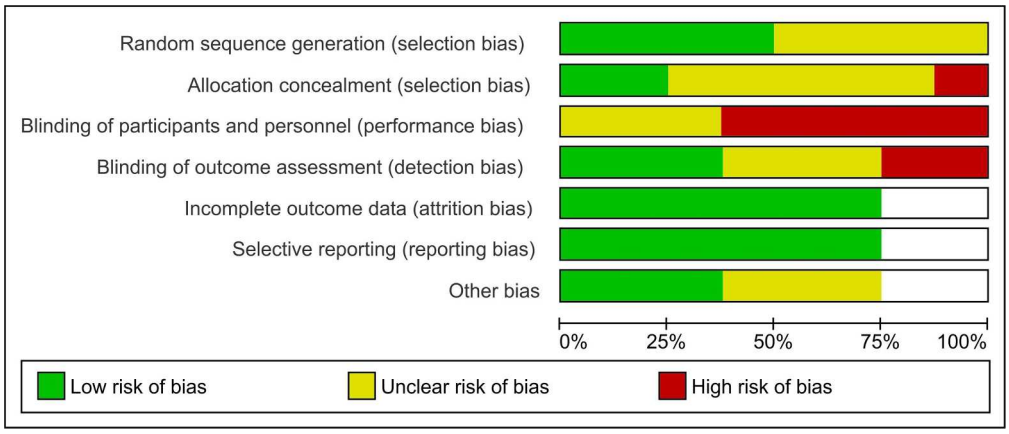

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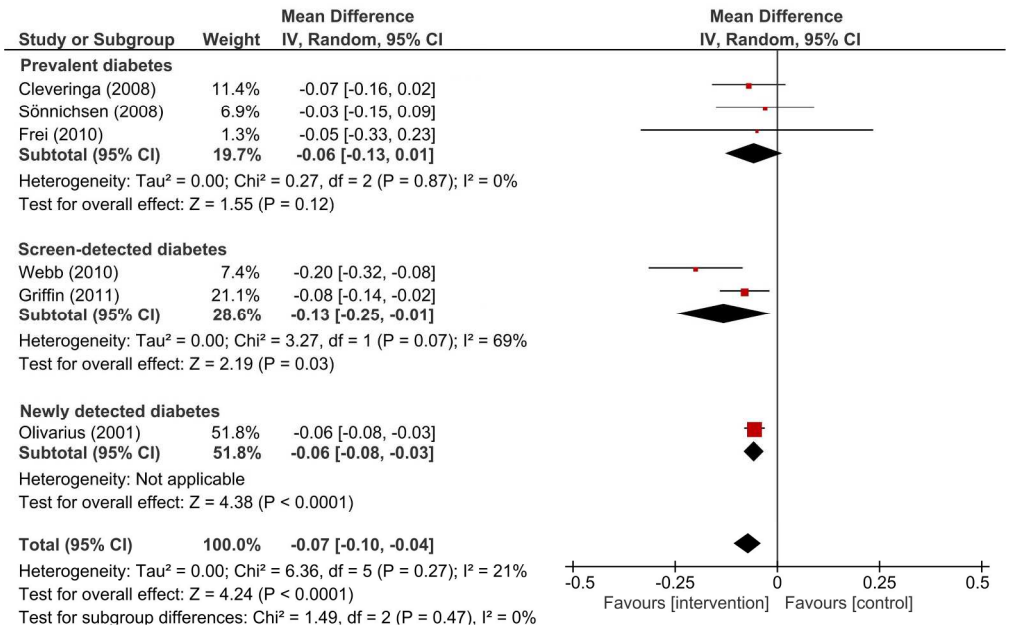

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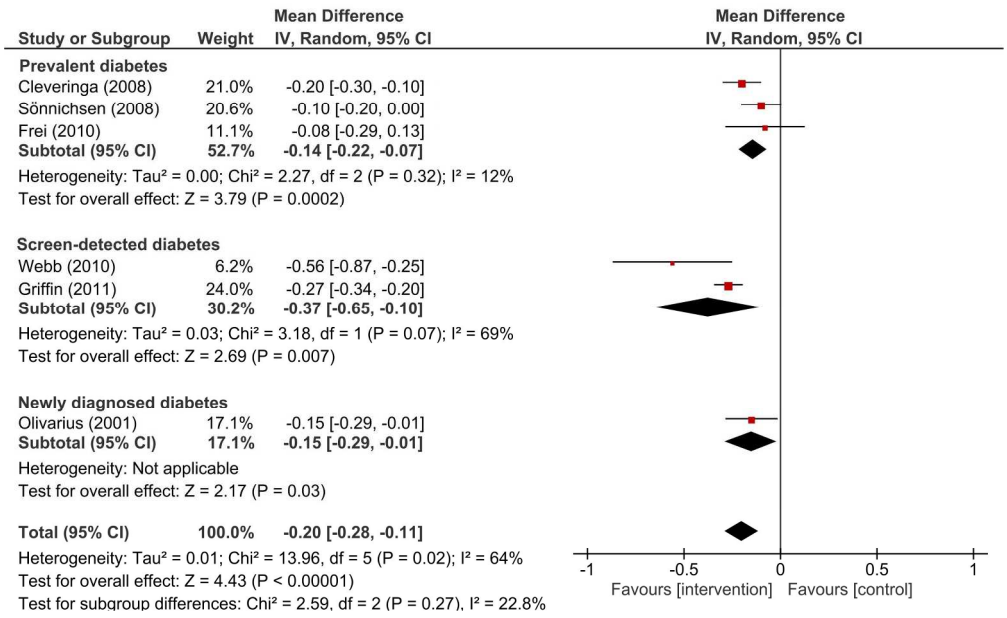

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Supplementary file S1

Review protocol (January 2014)

Effectiveness of Chronic Care Models for the Management of Type 2 Diabetes Mellitus in Europe: a Systematic Review

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1. BACKGROUND

A growing number of European citizens suffer from diabetes, constituting a growing health, social, and economic burden. The number of individuals with diabetes in Europe in 2013 was estimated by the International Diabetes Federation to be 56.3 million, or 8.5% of the adult population (20-79 years), and is expected to increase to 68.9 million people, or 10.3% by the year 2035 [1]. It is generally believed that lifestyle, with diets high in saturated fat and decreased physical activity, together with an increased longevity, are the main factors in the current increase in T2DM. In individual, as well as in societal terms, the burden of T2DM is enormous, resulting in increased morbidity and mortality [1].

Historically, health care systems were developed to respond rapidly and efficiently to acute diseases. The focus was on the immediate problem, a rapid diagnosis, and the initiation of professional treatment; a process in which the patient´s role was largely passive. However, with the rapid aging of the population and the growing prevalence of chronic diseases, improvement in quality of chronic care requires more than evidence about effective diagnostic procedures and treatments. Despite much progress in clinical and behavioral interventions, it is suggested that many chronically-ill patients do not profit from these advances [2].

In the current health care systems in European countries, a shift from disease management to chronic care management may prevent costly complications and frailty in elderly with T2DM, enabling them to live independent, healthy and active lives as long as possible. With the aim of describing essential elements for improving outcomes in care of chronic diseases, the Chronic Care Model (CCM) was developed in the mid-1990s and was further refined in 1997 [3,4]. As such, CCM is a primary care-based comprehensive model, advocating evidence-based changes in health care of patients with chronic disease. The model is based on the assumption that improvements in care require an approach that incorporates patients, health care providers, and system level interventions. It can be applied to a variety of chronic illnesses, health care settings and target populations, with the goal of healthier patients, more satisfied providers, and cost savings.

The CCM comprises six components deemed essential for providing high-quality care to patients with chronic disease:

1. health care organization (i.e. providing leadership for securing resources and removing barriers to care),
2. self-management support (i.e. facilitating skills-based learning and patient empowerment),
3. decision support (i.e. providing guidance for implementing evidence-based care),
4. delivery system design (i.e. coordinating care processes),
5. clinical information systems (i.e. tracking progress through reporting outcomes to patients and providers), and
6. community resources and policies (i.e. sustaining care by using community-based resources and public health policy).

Reports indicate a widespread application of CCM to multiple illnesses [5,6], yet, to date, only one study has reviewed how CCM has been applied in diabetes care in primary care settings and what the outcomes were of this implementation [7]. This systematic review showed that CCM approaches in the United States have indeed been effective in improving the health of individuals with diabetes who receive care in primary care settings. Regarding quality of diabetes care in Europe, observational studies have been performed in different European countries [8-11]. The recently published GUIDANCE study [12] reported encouraging levels of adherence to the main recommended process measures in diabetes care, e.g. HbA1c levels <7%, blood pressure <130mmHg (systolic) and <80 mmHg (diastolic), and LDL cholesterol concentrations <2.6 mmol/l. The level of actual achievement of these target goals by the individual patients was, on the other hand, much lower. Findings from the GUIDANCE study supported previously made suggestions [13-15] that process adherence may only have a limited influence in terms of reaching target goals (risk factor control) or enhanced management, e.g. appropriate adjustments to medication. Also, the existence of substantial between-country variation in quality of diabetes care in Europe was confirmed by the GUIDANCE study [12].

2. AIMS

This systematic review will focus on the scientific evidence regarding the specific treatment and care of elderly suffering from T2DM and associated comorbidities. Its aim is to summarize previous research on the effects of current European disease management models specifically related to the complex interaction between T2DM and comorbidities in the elderly, and on improving outcomes of interest.

3. OBJECTIVES (Research Question)

To assess the effects of chronic care models with a duration of at least 6 months on the following outcomes in older patients with T2DM and diabetes-related comorbidities:

- biophysical outcomes (e.g. serum HbA1c concentrations, and change in BMI),
- patient-reported outcomes (e.g. diabetes-related quality of life),
- diabetes complications (e.g. micro- and macrovascular complications),

compared to routine diabetes care.

4. METHODS

In the case of substantial clinical or statistical heterogeneity, study results will be combined in a narrative review only. Without substantial clinical and statistical heterogeneity, study results will be combined in a meta-analysis, following the approach described below. The subsequent reporting of the systematic review will be conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) statement [16].

Criteria for considering studies for this review

Types of studies

Studies will be eligible for inclusion if they are a randomized clinical trial (RCT). Only studies that have assessed outcome measures six months or more from baseline will be investigated.

Types of participants

Individuals, regardless of gender and ethnicity, with diagnosed T2DM with or without one of the following comorbidities, assessed and reported at baseline:

- Mental health problems (stress, depression, anxiety)
- Cancer
- Cardiovascular disease
- Osteoporosis
- Rheumatic arthritis
- Chronic obstructive pulmonary disease
- Neurological diseases
- Kidney diseases.

Ideally, the diagnostic criteria for T2DM are described in the study and were established using the standard criteria that were valid at the beginning of the trial (ADA 1997, NDDG 1979, WHO 1980, WHO 1985, WHO 1999), in order to be consistent with changes in T2DM classification and diagnostic criteria throughout the years.

We will include only studies in which the average age of the study population is ≥60 years, given that this is the usual age of diagnosis for most patients in Europe.

Type of interventions

Chronic care models/programs that meet the following criteria:

- specific for individuals with T2DM,
- based on guidelines,
- providing integrated (multi-disciplinary) care,
- addressing patient empowerment,
- providing quality management (e.g. patient registry systems, recording of process measures/adherence to guidelines, achievement of treatment goals),
- delivered in primary care and secondary care.

Type of controls

The intervention group will be compared with those participants undergoing routine diabetes care (standard care recommended in that particular country, e.g. regular follow-up with the required health professional and a full diabetes annual review).

Types of outcome measures

Primary outcomes

Biophysical outcomes:

- Metabolic control: hypoglycemia, serum HbA1c concentrations, serum lipids levels (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides), blood pressure, and glomerular filtration rate
- Change in BMI and other anthropometric measures (waist circumference, waist to hip ratio)

Patient-reported outcomes:

- Diabetes-related quality of life
- Participation in life style changing programs
- Communication
- Patient empowerment

Diabetes complications:

- Microvascular complications: retinopathy, nephropathy, and neuropathy
- Macrovascular complications: cardiovascular disease, cardiovascular risk scores, and cerebrovascular disease
- Diabetes-related mortality: total mortality and mortality due to major adverse cardiac events

Secondary outcomes

Mental Health:

- Depression
- Cognitive dysfunction or dementia
- Anxiety

Functionality:

- Frailty index
- Self-management skills: dietary habits, physical activity, medication administration, use of equipment
- Nutritional status
- Dependency on care

Contact to Health Care System:

- Number of yearly hospital visits
- Hospitalization: number of emergency admissions, and number and duration (days) of hospital stays.
- Adherence to treatment recommendations
- Quality of care
- Polypharmacy

Search methods for identification of studies

Electronic searches

Electronic databases will be searched from January 2000 until January 2014. We will use the following sources for the identification of trials:

- CENTRAL (the Cochrane Central Register of Controlled Trials)
- MEDLINE
- EMBASE
- CINAHL

Searching other resources

We aim to further identify studies by searching the reference list of each relevant trial and systematic review identified. First authors are contacted whenever additional information is required.

Data collection and analysis

Selection of studies

To determine which studies are to be assessed further, two reviewers (BB, WR) will independently scan the titles, abstracts and key words of every record retrieved. Full text articles will be retrieved if the title/abstract/key words suggest that the trial:

- included patients with T2DM, and
- evaluated a chronic diabetes care model.

In case of any doubt regarding these criteria from the information given in the title and abstract, or if the abstract was absent, the complete article will be retrieved for clarification. Studies will be eliminated if both reviewers agree that the criteria for considering studies for the review are not being met. Inter-rater agreement for study selection will be measured using the Kappa statistic [17]. Any differences in opinion will be discussed and, if necessary, resolved by a third reviewer (KM).

Data extraction and management

A structured data extraction form will be developed including the following information:

- General information: published/unpublished, title, authors, source/reference, contact address, country, language of publication, year of publication, sponsoring.
- Trial characteristics: design, duration, (method of) randomization, use of validated questionnaires, (method of) blinding (if appropriate).
- Intervention: comparison group included (routine care/no intervention), intervention (duration, timing).
- Participants: method of sampling, exclusion criteria, total number (also for comparison group(s)), sex, age, body mass index, ethnicity, pre-existing comorbidities/other medical conditions, standards of diabetes care (HbA1c concentration, serum glucose levels, lipid profile, blood pressure), diagnostic criteria T2DM, duration of T2DM, baseline comparison of the groups (including comorbidities), withdrawal from study/losses to follow-up, assessment of subgroups.

- Outcome: as specified above, main outcome as assessed in the trial, other outcomes/events assessed, quality of reporting the outcomes.
- Results: reported for outcomes and times of assessment.

If there is missing information, the authors of the article will be contacted. Differences in data extraction at item level will be resolved by discussion and if consensus is not reached, the third reviewer (KM) will take the final decision.

Assessment of risk of bias in included studies

The quality of reporting of each experimental trail will be assessed by two review authors independently (BB, WR). Risk of bias will be assessed using the Cochrane Collaboration´s tool [18]. In particular, the following factors will be studied.

Minimization of selection bias

- Randomization procedure (*if applicable*): the procedure will be scored adequate if the resulting sequences were unpredictable (computer generated schemes, coin tossing, and tables of random numbers).

Minimization of attrition bias

- Handling of drop-outs: will be considered adequate when the trial reports a complete description of all patients failing to participate until the end of the trial and if the data were analyzed on intention-to-treat (ITT) (thus with all randomized patients included). An overall drop-out rate less than 15%, and a selective drop-out rate less than 10% (the at risk groups), will be considered justifiable.

Minimization of detection bias

- Method of blinding for the outcome: will be considered adequate if the outcome assessors were completely blind for the intervention.

Assessment of heterogeneity

Variation between studies (heterogeneity) will be examined to answer the question whether the combination of the different studies is meaningful.

Clinical heterogeneity of the selected studies will be evaluated according to key characteristics of the study participants (age, gender, diabetes duration, blood glucose levels), the intervention, and study outcomes. Statistical heterogeneity will be estimated by visual inspection of the forest plots (the less overlap of confidence intervals, the more likely the presence of heterogeneity). Furthermore, heterogeneity will be assessed using the I^2-statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance or sampling error [19]. It allows for calculation across studies of varying sizes, study types and with varying outcome data. In case there is significant heterogeneity (I^2 values >75%), more emphasis will be placed on the results of a random-effects model, despite that the given model cannot overcome the problem of heterogeneity.

Data synthesis

Data will be summarized statistically if they are available, sufficiently similar, and of sufficient quality.

Subgroup analysis and investigation of heterogeneity

To explore potential source of (clinical) heterogeneity, subgroup analyses will be performed. Where performed, subgroup analysis will have a tentative (hypothesis-generating) purpose. The following subgroup analyses will be considered:

- Gender
- Duration of the intervention
- Duration of diabetes below and over five years (individuals who have diabetes for a longer time are likely to have more advanced disease and increased insulin resistance, and more complications; hence any forms of care may have a smaller effect in more advanced disease)
- Number of comorbidities

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of certain factors on effect size:

- Repeating the analysis excluding unpublished studies (if selected and included).
- Repeating the analysis taking risk of bias into account.
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results.
- Repeating the analysis excluding studies by using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

The robustness of the results will further be tested by repeating the analysis using different measures of effects size (risk difference, odds ratio, etc) and different statistic models (fixed and random effects models).

5. OUTLOOK

As the population ages, the burden of chronic disease is expected to grow continuously. While healthcare organizations need to find effective ways to deal with increased care demands, the CCM has been developed to advocate evidence-based changes in health care of patients with chronic disease. The findings of the current systematic review will contribute to our understanding of the relationship between application of CCM and qualitative and quantitative T2DM outcomes in European primary care settings. Finally, the results can provide insights into new approaches to further integrate the CCM into primary health care initiatives in diabetes.

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Supplementary file S2

Search strategy MEDLINE

1 Patient Education as Topic/

2 exp Self Care/

3 Self Efficacy/

4 ((patient* or consumer* or client*) adj3 (educat* or train* or teach* or instruct* or skill*)).tw.

5 (self care or self management or self efficacy or self monitoring).tw.

6 patient participation/

7 empowerment.tw.

8 (self adj (monitor* or manag* or care)).tw.

9 motivation/

10 (patient* adj2 (activation or psychosocial support or social support)).tw.

11 (collaborative decision making* or shared decision making*).tw.

12 or/1-11 (230620)

13 exp Education, Continuing/

14 Pamphlets/

15 Advance Directives/

16 (leaflet? or booklet? or poster or posters).tw.

17 ((written or printed or oral) adj information).tw.

18 Guideline Adherence/

19 (education* adj2 (program* or intervention* or meeting* or session* or strateg* or workshop* or visit*)).tw.

20 (behavio?r* adj2 intervention*).tw.

21 (education* adj1 (method? or material?)).tw.

22 ((opinion or education$ or influential) adj1 leader?).tw.

23 facilitator?.tw.

24 academic detailing.tw.

25 consensus conference?.tw.

26 (guideline? adj2 (introduc* or issu* or impact or effect* or disseminat* or distribut*)).tw.

27 ((effect* or impact or evaluat* or introduc* or compar*) adj2 training program*).tw.

28 practice guidelines as topic/

29 telemedicine/

30 ((effect? or impact or evaluat* or introduce* or compar*) adj2 (care program* or (prevent* adj program*))).tw.

31 guidelines as topic/

32 ((patient* or practice) adj guideline?).tw.

33 or/13-32

34 exp Patient Care planning/

35 Nurse clinicians/

36 Ambulatory Care/

37 Office Visits/

38 (nurse adj (clinician? or practitioner?)).tw.

39 (team? adj2 (care or treatment or assessment or consultation)).tw.

40 (integrat* adj2 (care or service?)).tw.

41 (care adj2 (coordinat* or program* or continuity)).tw.

42 (case adj1 management).tw.

43 outreach.tw.

44 disease management.tw.

45 disease management/

46 patient care team/

47 exp ambulatory care facilities/

48 nurse practitioners/

49 ((share* or step*) adj care).tw.

50 community matron*.tw.

51 or/34-50

52 Reminder Systems/

53 Medical Records/

54 Medical Records Systems, Computerized/

55 (register? or registry or registries).tw.

56 reminder?.tw.

57 (recall adj2 system*).tw.

58 (prompter? or prompting).tw.

59 chart review*.tw.

60 ((effect? or impact or records or chart?) adj2 audit).tw.

61 (information adj2 (management or system?)).tw.

62 hospital information systems/

63 ambulatory care information systems/

64 management information systems/

65 decision support systems, clinical/

66 ((introduce$ or impact or effect? or implement$ or computer$) adj2 protocol?).tw.

67 Feedback/ or feedback.tw.

68 (feedback adj1 (loop? or control? or regula* or mechanism? or inhib* or system? or circuit? or sensory or visual or audio* or auditory)).tw.

69 67 not 68

70 or/52-66,69

71 Reimbursement, incentive/

72 exp Reimbursement mechanisms/

73 Capitation Fee/

74 Physician Incentive Plans/

75 "Salaries and Fringe Benefits"/

76 Physician's Practice Patterns/

77 (quality adj (improvement or management or assurance)).tw.

78 ((continuous or total) adj quality).tw.

79 quality of health care/

80 quality assurance, health care/

81 total quality management/

82 quality improvement/

83 quality indicators, health care/

84 program evaluation/

85 technology assessment, biomedical/

86 exp Standard of care/

87 or/71-86

88 exp Diabetes Mellitus, Type 2/

89 exp Diabetes Complications/

90 (obes* adj3 diabet*).tw.

91 (MODY or NIDDM or T2DM or T2D).tw.

92 (non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend*).tw.

93 ((typ? 2 or typ? II or typ?2 or typ?II) adj3 diabet*).tw.

94 ((adult* or matur* or late or slow or stabl*) adj3 diabet*).tw.

95 or/88-94

96 exp Diabetes Insipidus/

97 diabet* insipidus.tw.

98 or/96-97

99 95 not 98

100 infan*.tw.

101 (newborn* or new born*).tw.

102 (perinat* or neonat*).tw.

103 (baby* or babies).tw.

104 toddler*.tw.

105 (boy or boys or boyhood).tw.

106 girl*.tw.

107 kid?.tw.

108 (child* or schoolchild*).tw.

109 adolescen*.tw.

110 juvenil*.tw.

111 youth*.tw.

112 teen*.tw.

113 pubescen*.tw.

114 Pediatrics/

115 p?ediatric*.tw.

116 school?.tw.

117 or/100-116

118 exp africa/

119 exp americas/

120 exp asia/

121 exp oceania/

122 or/118-121

123 randomized controlled trial.pt.

124 controlled clinical trial.pt.

125 randomized.ab.

126 placebo.ab.

127 drug therapy.fs.

128 randomly.ab.

129 trial.ab.

130 groups.ab.

131 exp animals/ not humans/

132 or/123-130

133 132 not 131

134 or/12,33,51,70,87

135 134 and 99 and 133

136 135 not 117 not 122

137 limit 136 to (english language and yr="2000 -Current")

Supplementary file S3

Results

Further biochemical outcomes

Three[33 44 41] out of the seven trials included in this review had assessed fasting glucose levels (mmol/l) (see supplementary figure S6). In Swiss patients with prevalent diabetes[44] no difference in change was found between the intervention and control group, while in Dutch patients with diabetes[33] there was a significantly higher reduction in glucose concentrations after one year of intervention, in favour of the control group. In newly diagnosed diabetes patients,[41] the intervention group was observed to have a significantly higher reduction in fasting glucose levels then the control group after six years of intervention.

Six[33 39 41 43 45 46] out of seven trials had measured triglyceride concentrations (mmol/l), yet, multifaceted care did not significantly impact triglyceride levels in any of the studies (see supplementary figure S7).

Creatinine levels were assessed in three[33 41 46] out of the seven trials. Only the pooled five-year results from Addition-Europe[46] showed a significant difference in change between the trial arms, favouring the control arm over the intervention arm (see supplementary figure S8).

Further diabetes complications and related outcomes

Episodes of severe hypoglycaemia were assessed in only one[44] of the three studies with prevalent diabetes patients, in which severe hypoglycaemia was defined as having one or more episodes of hypoglycaemia with clinical symptoms and or requiring hospitalization. Episodes were reported for 19 (11.6%) patients in the intervention group and for eight (5.1%) in the control

group, without further statistical evaluation. In the remaining trials[39 41 43 46] the proportion of individuals reporting hypoglycaemia did not differ between intervention and control arm.

A major aim of the Dutch trial[33] and of the Addition studies[35 39 40 43] was to examine the effect of multifaceted care on cardiovascular risk. To that purpose, authors calculated the 10-year coronary heart disease risk estimate (%) as established by the UK Prospective Diabetes Study (UKPDS). This risk score is calculated using the following variables: the date of diabetes onset, sex, ethnicity, smoking, HbA1c, systolic blood pressure, total cholesterol and HDL-cholesterol. The Dutch authors observed a 1.4% greater decrease in 10-year UKPDS coronary heart disease risk in the intervention group compared to the control group.[33] Within the Addition-Leicester trial,[43] a 5-year UKPDS risk of cardiovascular heart disease was calculated. A significant difference in risk reduction of 1.49% between intervention and control group was found in favour of the intervention group. In the Addition-Europe study,[46] the authors assessed hazard ratios for a composite endpoint of cardiovascular events (any cardiovascular death, myocardial infarction, stroke, revascularization and amputation) at five years of intervention. This endpoint occurred similarly frequent and with similar risk in intervention and control patients. Furthermore, improvements in every singular component of this composite endpoint all favoured the intervention group over the control group, although no comparison reached statistical significance.

Out of the three trials with prevalent diabetes patients, only the Swiss trial[44] reported data on (changes in) medication use. The authors observed no significant changes between the two trial groups in medication use (yes/no variable) concerning antidiabetic therapy, antihypertensive therapy, and lipid-lowering therapy. In contrast to patients with prevalent diabetes, for patients with screen-detected diabetes[43] multifaceted care resulted in a larger number of antihypertensive-, lipid-lowering and anti-platelet therapy after one year, compared to usual care. This was also observed after pooling of the five-year findings from the Addition studies.[46] In

newly diagnosed diabetes patients[41] however, the only between-group difference that was observed with regard to medication intake was the more extensive use of metformin in the intervention group (39 (9%)) compared to the control group (16 (4%)).

Supplementary table S1

Table S1: Characteristics of the included cluster randomized controlled trials

Study	Comparison	Effect on endpoints*	Notes
Cleveringa 2008[33]	Intervention: Patient consultation by a practice nurse + use of a computerized decision support system + guideline-based care + physician support by practice nurse + interdisciplinary care by a specialist team + individualised treatment advice + patient education + physician feedback + recall system + regular patient consultations by practice nurse + physician feedback *versus* Usual diabetes care (not further specified)	**Biochemical outcomes** HbA1c (0) Total cholesterol (+, i) HDL-cholesterol (0) LDL-cholesterol (+, i) Systolic blood pressure (+,i) Diastolic blood pressure (+,i) 10-year CHD risk (+, i) **Diabetes complications and processes of care** HbA1c below target value§ (+,i) Total cholesterol below target value§ (+,i) LDL-cholesterol below target value§ (+,i) Systolic blood pressure below target value§ (+,i) All treatment targets reached§ (+,i)	At baseline, patients in the intervention group had higher HDL-cholesterol levels, were more often smoker and more often had a history of CHD. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between intervention and control group were adjusted for cluster structure.
Sönnichsen 2008[45]	Intervention: Physician education +guideline-based care + patient education + use of a clinical information system tool + interdisciplinary care by a specialist team + patient reminders + physician reminders + goal setting + shared decision making patient and physician + regular consultations *versus* Usual diabetes care (not further specified)	**Biochemical outcomes** HbA1c (0) Total cholesterol (+, i) HDL-cholesterol (0) LDL-cholesterol (0) Systolic blood pressure (0) Diastolic blood pressure (0) Body mass index (+, i) Triglycerides (0) Creatinine (0) **Diabetes complications and processes of care** To the guidelines adherent: -number of eye examinations§ (+, i) -number of foot examinations§ (+, i) -provision of patient education§ (+, i) -regular HbA1c checks§ (+, i)	At baseline, patients in the intervention group had a higher BMI and higher cholesterol levels than patients in the control group. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between intervention and control group were adjusted for cluster structure and baseline values.
Frei 2010[44]	Intervention: Specialist team involving a practice nurse + practice nurse education + physician education + physician support by practice nurse + regular independent patient consultations by practice nurse + use of a clinical information system tool + guideline-based care + physician feedback + patient information leaflets + self-management support for patient + patient treatment	**Biochemical outcomes** HbA1c (0) Total cholesterol (0) HDL-cholesterol (0) LDL-cholesterol (+, i) Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (0) Fasting blood glucose (0) **Patient-reported outcomes** **Diabetes complications and processes of care**	There were no baseline differences in patient characteristics between intervention and control group. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. There was no evidence for

	groups *versus* Usual diabetes care (not further specified)	Number GP visits[§] (0) Change in antidiabetic therapy (0) Change in antihypertensive therapy (0) Change in lipid-lowering therapy (0)	a statistically significant clustering effect.
Webb 2010[43]	Intervention: Structured patient education + lifestyle advice and self-management with ongoing (bimonthly) professional support + individualized management + guideline-based care + shared decision making patient and health care professional + annual screening for diabetic complications + care delivered by a specialist team (specialty doctor, diabetes nurse educator, and a dietician) + patient reminders + physician reminders *versus* Usual diabetes care (not further specified)	**Biochemical outcomes** HbA1c (+, i) Total cholesterol (+, i) LDL-cholesterol (+, i) HDL-cholesterol (0) Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (+, i) Weight (+, i) Waist circumference (0) Triglycerides (0) 5-year CHD risk (+, i) 5-year CVD risk (+, i) **Patient-reported outcomes** Health-related quality of life (0) **Diabetes complications and processes of care** Hypoglycaemia[§] (+, i) Use of anti-hypertensive drugs[§] (+, i) Use of lipid-lowering drugs[§] (+, i) Use of anti-platelet therapy[§] (+, i) Use of metformin[§] (0) Use of sulfonylurea[§] (0)	At baseline, more patients in the intervention group were taking anti-hypertensive medication when entering the study and had higher total and LDL-cholesterol levels. Statistical analyses were conducted by intention-to-treat. It was not reported whether or not data were missing and how missing data were handled. Comparisons between intervention and control group were adjusted for cluster structure and baseline values (except quality of life which had not been measured at baseline).
Janssen 2009[39]	Intervention: Physician education + diabetes nurse education + lifestyle advice + guideline based care + physician support by diabetes nurse + evaluation and feed-back sessions diabetes nurse + frequent patient consultations with diabetes nurse + shared decision making patient, physician and diabetes nurse + physician reminders + patient reminders *versus* Usual diabetes care (not further specified)	**Biochemical outcomes** HbA1c (+, i) Total cholesterol (+, i) LDL-cholesterol (+, i) HDL-cholesterol (0) Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (+, i) Fasting blood glucose (+, i) Triglycerides (0) **Patient-reported outcomes** Health-related quality of life (0) **Diabetes complications and processes of care** Hypoglycaemia[§] (0)	There were no baseline differences in patient characteristics between intervention and control group. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between intervention and control group were adjusted for age, sex, baseline values, and clustering at practice level.
Griffin 2011[46]	This study combined the data after five years of a multifaceted care intervention from the i) Addition-Denmark study (Lauritzen et al [39]), ii) the Addition-Netherlands study (Janssen et al [38]), iii) the Addition-Cambridge study (Echouffo et al [34]), and iv) the Addition-Leicester study (Webb et al [42]) in a meta-analysis.	**Biochemical outcomes** HbA1c (+, i) Total cholesterol (+, i) LDL-cholesterol (+, i) HDL-cholesterol (0) Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (0) Weight (0) Waist circumference (0) Triglycerides (0) Creatinine (+, c)	Baseline characteristics were well matched between intervention and control group. In Denmark however, more patients were identified in practices assigned to the intervention arm then in those assigned to control arm. And in the intervention group, more patients had a history of

			ischemic heart disease.
		Patient-reported outcomes Health-related quality of life (0) **Diabetes complications and processes of care** All-cause mortality (0) CVD mortality (0) Myocardial infarction (0) Stroke (0) Revascularization procedures (0) Hypoglycaemia[§] (0) Meeting target values for: HbA1c (+, i) blood pressure (+, i) total cholesterol (+, i) Use of any glucose-lowering drugs (+, i) Change in any anti-hypertensive drugs (+, i) Change in any cholesterol-lowering drugs (+, i)	Statistical analyses were conducted by intention-to-treat and patients with missing outcome values were excluded from the analyses. Those with missing outcome baseline values were included according to the missing indicator method. Comparisons between intervention and control group were adjusted for cluster structure and baseline values.
Olivarius 2001[41]	Intervention: Patient follow-up every three months + annual screening for diabetes complications + shared decision making patient and physician + physician feedback + goal setting + clinical guidelines + physician education + patient leaflets and folders + lifestyle advise + protocol based care + physician recall system *versus* Usual diabetes care (not further specified)	**Biochemical outcomes** HbA1c (+, i) Total cholesterol (+, i) Systolic blood pressure (+, i) Diastolic blood pressure (0) Weight (0) Fasting blood glucose (+, i) Triglycerides (0) Creatinine (0) **Diabetes complications and processes of care** Overall mortality[§] (0) Severe hypoglycaemia[§] (0) Diabetic retinopathy[§] (0) Non-fatal myocardial infarction[§] (0) Non-fatal stroke[§] (0) Peripheral neuropathy[§] (0) Microalbuminuria[§] (0) Angina pectoris[§] (0) Intermittent claudication[§] (0)Number of consultations[§] (+, i) Number of referrals to diabetes clinic[§] (-, i) Number of hospital admissions[§ (0)] Use of metformin[§] (+, i) Use of other glucose-lowering drugs[§] (0) Use of anti-hypertensive drugs[§] (0) Use of lipid-lowering drugs[§] (0)	At baseline, more patients in the intervention group were excluded because of severe somatic disease than in the control group. Furthermore, occupation and smoking habits differed between the two groups. Statistical analyses were conducted by intention-to-treat. It was not reported whether or not data were missing and missing data were handled. Comparisons between intervention and control group were adjusted for baseline values, duration of diabetes, age, sex, occupation, smoking habits, and clustering at physician level.

T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; CVD, cardiovascular (heart) disease; GP, General Practitioner;

* +=positive effect; 0=no effect; -=negative effect; i=favouring intervention group; u=favouring control (usual care) group. The effects of the intervention are represented by the difference in change from baseline to follow-up between intervention and control group. [§] The effect of the intervention is represented by a difference in proportions of patients at follow-up between intervention and control group.

Supplementary Figure S1

HDL-Cholesterol (mmol/l)

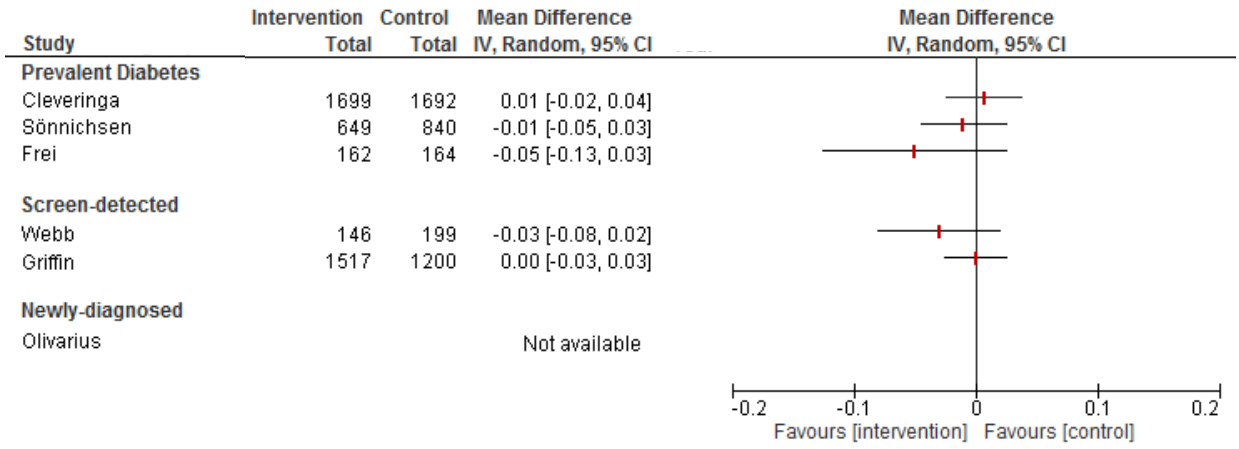

Figure S1: Overview of the mean differences in change (95% confidence interval) between intervention and control groups in HDL-cholesterol levels (mmol/l) after multifaceted care. Results are stratified by type of diabetes patient.

IV; generic inverse variance method, CI: confidence interval

The studies by Cleveringa[33], Sönnichsen[45], and Frei[44] *et al*. had an intervention duration of one year. The methodology for calculating the difference in change between intervention and control group that Cleveringa[33] *et al* have used (subtracting the mean difference in change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the mean difference in change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al.*,[33] we have recalculated their results for HDL-cholesterol levels according to the methodology applied by the other studies.

The study by Webb *et al.*[43] had an intervention duration of one year and the study by Griffin *et al.*[46] had a duration of five years. This study combined the five-year intervention data from all four Addition studies (Addition-Denmark, Addition-Netherlands, Addition-Cambridge, and Addition-Leicester), including the five-year data from Webb et al. (Addition-Leicester).[43]

The study by Olivarius *et al.*[41] had an intervention duration of six years.

Supplementary Figure S2

LDL-Cholesterol (mmol/l)

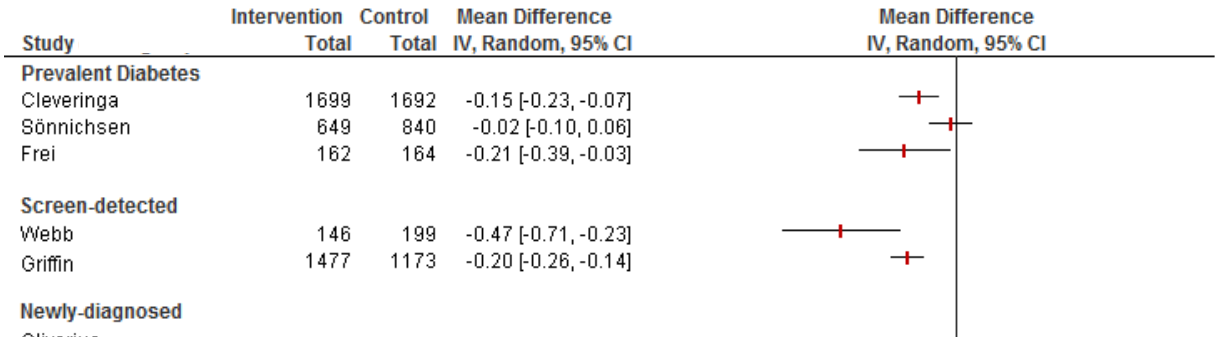

Figure S2: Overview of the mean differences in change (95% confidence interval) between intervention and control groups in LDL-cholesterol levels (mmol/l) after multifaceted care. Results are stratified by type of diabetes patient.

IV; generic inverse variance method, CI: confidence interval

The studies by Cleveringa[33], Sönnichsen[45], and Frei[44] *et al*. had an intervention duration of one year. The methodology for calculating the difference in change between intervention and control group that Cleveringa[33] *et al* have used (subtracting the mean difference in change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the mean difference in change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al.*,[33] we have recalculated their results for LDL-cholesterol levels according to the methodology applied by the other studies.

The study by Webb *et al.*[43] had an intervention duration of one year and the study by Griffin *et al.*[46] had a duration of five years. This study combined the five-year intervention data from all four Addition studies (Addition-Denmark, Addition-Netherlands, Addition-Cambridge, and Addition-Leicester), including the five-year data from Webb et al. (Addition-Leicester).[43]

The study by Olivarius *et al.*[41] had an intervention duration of six years.

Supplementary Figure S3

Diastolic blood pressure (mmHg)

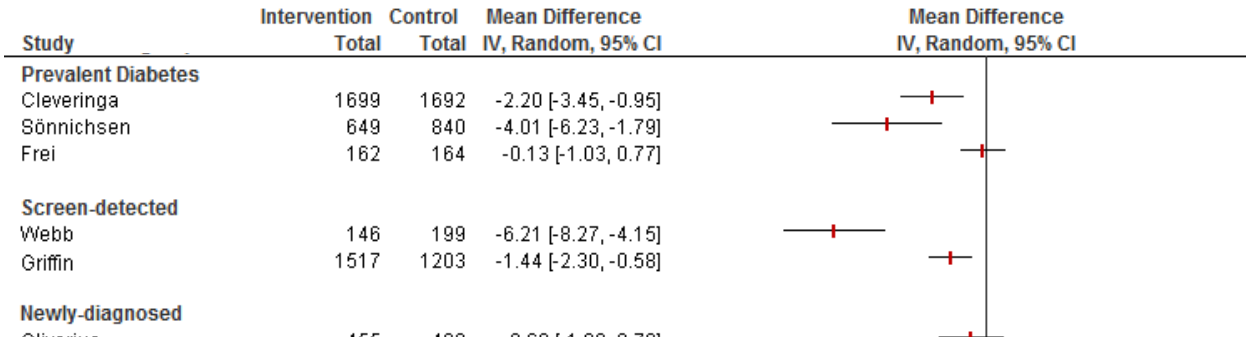

Figure S3: Overview of the mean differences in change (95% confidence interval) between intervention and control groups in diastolic blood pressure (mm Hg) after multifaceted care. Results are stratified by type of diabetes patient.

IV; generic inverse variance method, CI: confidence interval

The studies by Cleveringa[33], Sönnichsen[45], and Frei[44] *et al*. had an intervention duration of one year. The methodology for calculating the difference in change between intervention and control group that Cleveringa[33] *et al* have used (subtracting the mean difference in change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the mean difference in change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al.*,[33] we have recalculated their results for diastolic blood pressure according to the methodology applied by the other studies.

The study by Webb *et al.*[43] had an intervention duration of one year and the study by Griffin *et al.*[46] had a duration of five years. This study combined the five-year intervention data from all four Addition studies (Addition-Denmark, Addition-Netherlands, Addition-Cambridge, and Addition-Leicester), including the five-year data from Webb et al. (Addition-Leicester).[43]

The study by Olivarius *et al.*[41] had an intervention duration of six years.

Supplementary Figure S4

Systolic blood pressure (mmHg)

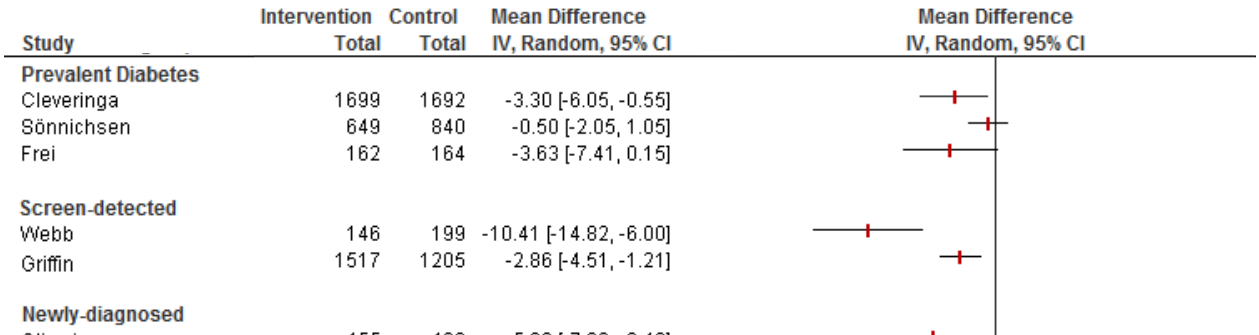

Figure S4: Overview of the mean differences in change (95% confidence interval) between intervention and control groups in systolic blood pressure (mm Hg) after multifaceted care. Results are stratified by type of diabetes patient.

IV; generic inverse variance method, CI: confidence interval

The studies by Cleveringa[33], Sönnichsen[45], and Frei[44] *et al*. had an intervention duration of one year. The methodology for calculating the difference in change between intervention and control group that Cleveringa[33] *et al* have used (subtracting the mean difference in change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the mean difference in change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al.*,[33] we have recalculated their results for systolic blood pressure according to the methodology applied by the other studies.

The study by Webb *et al.*[43] had an intervention duration of one year and the study by Griffin *et al.*[46] had a duration of five years. This study combined the five-year intervention data from all four Addition studies (Addition-Denmark, Addition-Netherlands, Addition-Cambridge, and Addition-Leicester), including the five-year data from Webb et al. (Addition-Leicester).[43]

The study by Olivarius *et al.*[41] had an intervention duration of six years.

Supplementary Figure S5

BMI

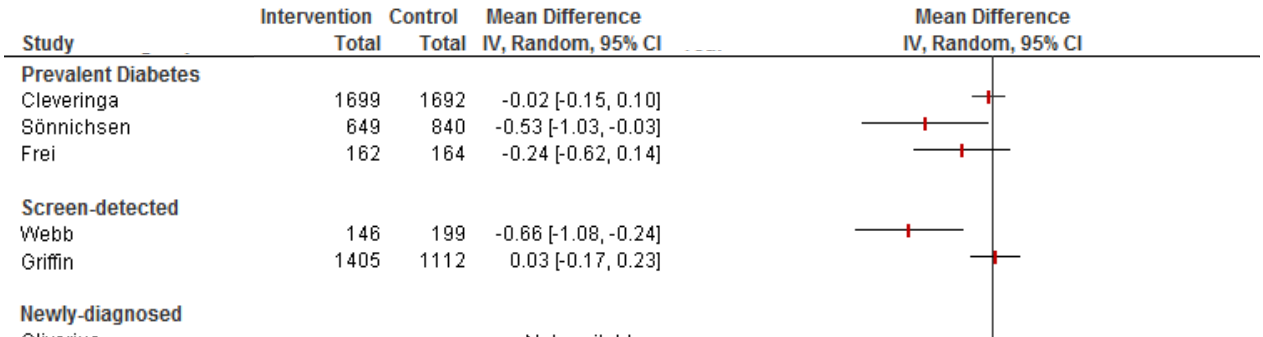

Figure S5: Overview of the mean differences in change (95% confidence interval) between intervention and control groups in BMI (kg/m^2) after multifaceted care. Results are stratified by type of diabetes patient.

IV; generic inverse variance method, CI: confidence interval

The studies by Cleveringa[33], Sönnichsen[45], and Frei[44] *et al*. had an intervention duration of one year. The methodology for calculating the difference in change between intervention and control group that Cleveringa[33] *et al* have used (subtracting the mean difference in change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the mean difference in change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al.*,[33] we have recalculated their results for BMI according to the methodology applied by the other studies.

The study by Webb *et al.*[43] had an intervention duration of one year and the study by Griffin *et al.*[46] had a duration of five years. This study combined the five-year intervention data from all four Addition studies (Addition-Denmark, Addition-Netherlands, Addition-Cambridge, and Addition-Leicester), including the five-year data from Webb et al. (Addition-Leicester).[43]

The study by Olivarius *et al.*[41] had an intervention duration of six years.

Supplementary Figure S6

Fasting glucose (mmol/l)

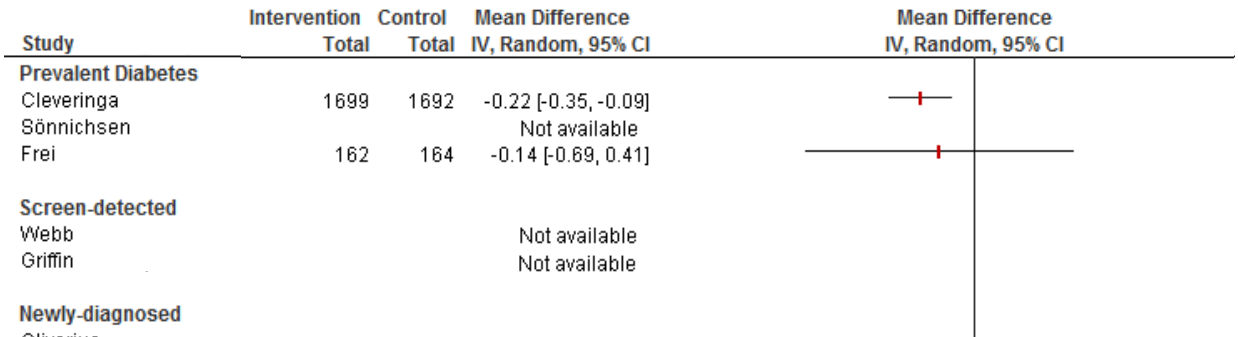

Figure S6: Overview of the mean differences in change (95% confidence interval) between intervention and control groups in fasting glucose concentrations (mmol/l) after multifaceted care. Results are stratified by type of diabetes patient.

IV; generic inverse variance method, CI: confidence interval

The studies by Cleveringa[33], Sönnichsen[45], and Frei[44] *et al*. had an intervention duration of one year. The methodology for calculating the difference in change between intervention and control group that Cleveringa[33] *et al* have used (subtracting the mean difference in change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the mean difference in change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al.*,[33] we have recalculated their results for fasting glucose levels according to the methodology applied by the other studies.

The study by Webb *et al.*[43] had an intervention duration of one year and the study by Griffin *et al.*[46] had a duration of five years. This study combined the five-year intervention data from all four Addition studies (Addition-Denmark, Addition-Netherlands, Addition-Cambridge, and Addition-Leicester), including the five-year data from Webb et al. (Addition-Leicester).[43]

The study by Olivarius *et al.*[41] had an intervention duration of six years.

Supplementary Figure S7

Triglycerides (mmol/l)

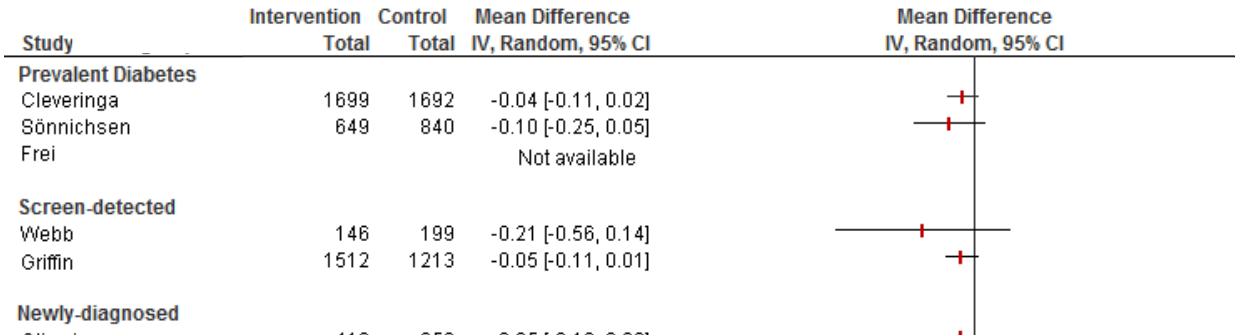

Figure S7: Overview of the mean differences in change (95% confidence interval) between intervention and control groups in triglyceride levels (mmol/l) after multifaceted care. Results are stratified by type of diabetes patient.

IV; generic inverse variance method, CI: confidence interval

The studies by Cleveringa[33], Sönnichsen[45], and Frei[44] *et al*. had an intervention duration of one year. The methodology for calculating the difference in change between intervention and control group that Cleveringa[33] *et al* have used (subtracting the mean difference in change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the mean difference in change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al.*,[33] we have recalculated their results for triglyceride levels according to the methodology applied by the other studies.

The study by Webb *et al.*[43] had an intervention duration of one year and the study by Griffin *et al.*[46] had a duration of five years. This study combined the five-year intervention data from all four Addition studies (Addition-Denmark, Addition-Netherlands, Addition-Cambridge, and Addition-Leicester), including the five-year data from Webb et al. (Addition-Leicester).[43]

The study by Olivarius *et al.*[41] had an intervention duration of six years.

Supplementary Figure S8

Creatinine (umol/l)

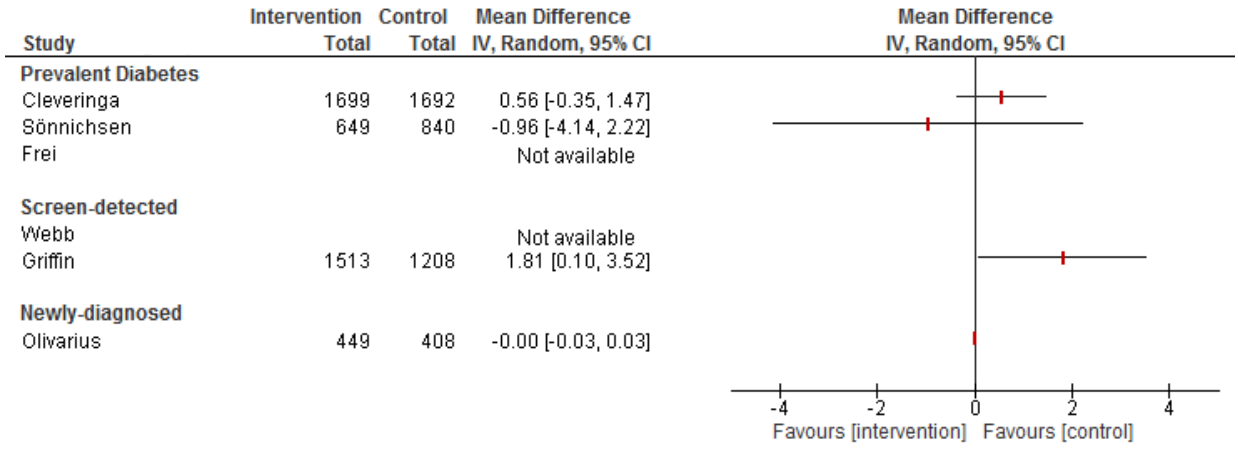

Figure S8: Overview of the mean differences in change (95% confidence interval) between intervention and control groups in creatinine levels (umol/l) after multifaceted care. Results are stratified by type of diabetes patient.

IV; generic inverse variance method, CI: confidence interval

The studies by Cleveringa[33], Sönnichsen[45], and Frei[44] *et al*. had an intervention duration of one year. The methodology for calculating the difference in change between intervention and control group that Cleveringa[33] *et al* have used (subtracting the mean difference in change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the mean difference in change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al.*,[33] we have recalculated their results for creatinine levels according to the methodology applied by the other studies.

The study by Webb *et al.*[43] had an intervention duration of one year and the study by Griffin *et al.*[46] had a duration of five years. This study combined the five-year intervention data from all four Addition studies (Addition-Denmark, Addition-Netherlands, Addition-Cambridge, and Addition-Leicester), including the five-year data from Webb et al. (Addition-Leicester).[43]

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Effectiveness of chronic care models for the management of type 2 diabetes mellitus in Europe: a systematic review and meta-analysis

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Effectiveness of chronic care models for the management of type 2 diabetes mellitus in Europe: a systematic review and meta-analysis

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ABSTRACT

Objectives: We evaluated the effectiveness of European chronic care programs for type 2 diabetes mellitus (characterized by integrative care and a multi-component framework for enhancing healthcare delivery), compared with usual diabetes care.

Design: Systematic review and meta-analysis.

Data sources: MEDLINE, Embase, CENTRAL, and CINAHL from January 2000 to July 2015.

Eligibility criteria: Randomized controlled trials focussing on (i) adults with type 2 diabetes, (ii) multifaceted diabetes care interventions specifically designed for type 2 diabetes and delivered in primary or secondary care, targeting patient, physician, and health care organization, and (iii) usual diabetes care as the control intervention.

Data extraction: Study characteristics, characteristics of the intervention, data on baseline demographics, and changes in patient outcomes.

Data analysis: Weighted mean differences in change in HbA1c and total cholesterol levels between intervention and control patients (95% confidence interval) were estimated using a random-effects model.

Results: Eight cluster randomized controlled trials were identified for inclusion (9,529 patients). One year of multifaceted care improved HbA1c levels in patients with screen-detected and newly diagnosed diabetes, but not in patients with prevalent diabetes, compared to usual diabetes care. Across all seven included trials the weighted mean difference in HbA1c change was -0·07% (95% confidence interval: -0·10 to -0·04) (-0·8 mmol/mol (95% confidence interval:-1·1 to -0·4)); I^2=21%. The findings for total cholesterol, LDL-cholesterol and blood pressure were similar to HbA1c, albeit statistical heterogeneity between studies was considerably larger. Compared to usual care, multifaceted care did not significantly change quality of life of the diabetes patient. Finally, measured for screen-

detected diabetes only, the risk of macro- and mircovascular complications at follow-up was not significantly different between intervention and control patients.

Conclusions: Effects of European multifaceted diabetes care patient outcomes are only small. Improvements are somewhat larger for screen-detected and newly diagnosed diabetes patients than for patients with prevalent diabetes.

Strengths and limitations of this study

- This is the first systematic review providing a comprehensive overview of studies that have evaluated the effectiveness of multifaceted diabetes care programs addressing all their components together, rather than separately.
- The focus in this systematic review was on European multifaceted diabetes care programs only, to meet the need for efficient and established programs to providing optimal chronic care due to the burden of increasing diabetes prevalence in Europe.
- There is an important lack of studies which evaluate the effectiveness of implementing all Chronic Care Model-components simultaneously.
- Overall, the studies included in this systematic review provided insufficient details to fully understand the intensity of the intervention, and there was only little overlap in the wide range of outcome measures evaluated.

INTRODUCTION

Chronic disease management relies on the assumption that providing optimal chronic care requires changes of both patients and professionals with regard to behaviour, culture, and communication.[1 2] Indeed, with aging of the population and the growing prevalence of chronic diseases, initiatives to improving quality of chronic care require more than evidence about effective diagnostic procedures and treatments in comparison to acute disorders.[3] Aimed at describing essential elements for improving outcomes in care of chronic diseases, the Chronic Care Model (CCM) was developed in the mid-1990s and was further refined in 1997.[2 4 5] This primary care-based model is based on the assumption that improvements in care require an approach that incorporates patients, health care providers, and system level interventions.[4 6] The CCM comprises six interrelated components deemed essential for providing high-quality care to patients with chronic disease: (i) health care organization (i.e. providing leadership for securing resources and removing barriers to care), (ii) self-management support (i.e. facilitating skills-based learning and patient empowerment), (iii) decision support (i.e. providing guidance for implementing evidence-based care), (iv) delivery system design (i.e. coordinating care processes), (v) clinical information systems (i.e. tracking progress through reporting outcomes to patients and providers, and (vi) community resources and policies (i.e. sustaining care by using community-based resources and public health policy).[7]

The current literature indicates a widespread application of the CCM to multiple illnesses and various studies have provided a rigorous evaluation of its individual components.[5 8-14] In general, these studies have reported positive effects on patient outcomes and processes of care. The reported effect sizes, however, are relatively small and many outcomes are flawed by a considerable level of statistical heterogeneity.[10 13-25]

An aspect that complicates the assessment of effectiveness of chronic care programs is their inherent multi-component nature.[14 20 25] While some authors found that the total number of CCM elements incorporated in the interventions did not influence patient outcomes,[9 10] others

concluded that interventions containing more than one CCM component were more successful at improving the quality of care than single-component interventions.[11 24 26 27] To date, no summative reviews have evaluated to which extent the complete CCM – thus all six components combined in interventions – improves diabetes care.

As such, the aim of the current review was to systematically identify studies of diabetes care assessing the effect of interventions addressing all six components of the CCM. We subsequently aimed to pool the effect of these models on biochemical outcomes (HbA1c, cholesterol levels, blood pressure, body mass index (BMI), fasting glucose, triglyceride, and creatinine levels), patient-reported outcomes (health-related quality of life), and diabetes complications (macro- and microvascular complications, hypoglycaemia, cardiovascular risk, medication use, and processes of care) in adult patients with type 2 diabetes compared to usual diabetes care by means of a meta-analysis.

METHODS

Our systematic review was based on a protocol with input from experts in diabetes care, statistical methods, and primary care. The protocol was composed according to the PRISMA-P guidelines (see supplementary file S1).[28]

Data sources and searches

We identified studies by searching MEDLINE, Embase, CINAHL and CENTRAL from January 2000 until July 2015. Search syntaxes were developed in consultation with the Cochrane Metabolic And Endocrine Disorders Group by adapting and combining published search strategies from previous systematic reviews on chronic (diabetes) care management.[10 12] Given that the CCM – and its terminology – had been introduced in the late 1990s, we restricted the search to publications from January 2000 onwards. In addition, reference lists of eligible studies and systematic reviews on multifaceted diabetes care were searched by hand to identify additional studies. The full MEDLINE search strategy is available in the online supplementary file S2.

Study selection

One reviewer (BB) identified potentially relevant studies for inclusion by screening title and abstract of all citations that resulted from our literature search. Two reviewers (BB and WR) then screened the full text of these articles. Only randomized controlled trials were considered eligible for inclusion. Non-randomized studies were excluded, as were studies written in a language other than English. Since this systematic review was part of a large European project on managed diabetes care that aimed at developing chronic care management standards and guidance for Europe,[29] we further excluded all non-European CCM trials. Trials eligible for inclusion had to comply with the following inclusion criteria.

Type of participants: individuals, regardless of gender and ethnicity, diagnosed with type 2 diabetes, and with or without comorbidities.

Type of intervention: previous systematic reviews on multifaceted chronic care have reported that randomized-controlled-trial-interventions are generally described poorly and incomprehensively, which complicates mapping the individual elements of the intervention to the six CCM components. To avoid mapping difficulties, we have reformulated the following inclusion criteria for the interventions: The intervention had to be described as a multifaceted chronic care model or program that (i) was designed specifically for individuals with type 2 diabetes, (ii) was based on guidelines, (iii) provided multi-disciplinary care, (iv) addressed patient empowerment, (v) provided quality management (e.g. patient registry systems, recording of process measurements and adherence to guidelines, achievement of treatment goals), (vi) was delivered in primary or secondary care, and (vii) had a minimum duration of six months. The control intervention had to be defined as usual diabetes care as recommended in that particular country (e.g. regular follow-up with the required health professional and a full diabetes annual review).

Type of outcome measures: we considered three categories of outcome measures: (i) biochemical outcomes, including HbA1c, cholesterol levels, blood pressure, BMI, fasting glucose, triglyceride, and creatinine levels, (ii) patient-reported outcomes, including health-related quality of life, and (iii) diabetes complications, including macro- and microvascular complications, hypoglycaemia, cardiovascular risk, medication use, and processes of care.

Any disagreements between the two reviewers regarding the in- or exclusion of studies were resolved by consensus.

Data extraction and quality assessment

Using a standard structured data abstraction form, one reviewer (BB) performed the data extraction which was confirmed by a second reviewer (WR). The extracted data included

study design, length of intervention/follow-up, sample size, in- and exclusion criteria, mean or median age of the included sample, percentage males, study setting (i.e., primary or secondary care), intervention details, and mean differences in change for various outcomes. When important information or outcome data were missing, trial authors of the included studies were contacted. When unavailable, the particular data were not included in the analyses.

The standard Cochrane EPOC Risk of Bias Tool was used to assess risk of bias for each of the selected studies.[30] Since all included studies were cluster-randomized controlled trials, additional attention was given to potential sources of bias specific to cluster-randomized trials: (i) recruitment bias: did recruitment of diabetes patients take place before or after randomization of the clusters?, (ii) did the intervention and control group differ in baseline characteristics?, (iii) did any of the clusters drop out during follow-up?, (iv) was clustering accounted for in the statistical analyses? If a certain domain could not be classified as “high” or “low” risk of bias due to inadequate reporting, it was deemed “unclear” risk of bias.

Data synthesis and analysis

Due to heterogeneity of the study populations and duration of the interventions, and due to the small overlap in outcomes of the individual trials, an extensive meta-analysis and meta-regression of all reported outcome variables was not possible. The available data only allowed to statistically pool the results for HbA1c concentrations and total cholesterol levels. Review Manager (RevMan 5.2.0; the Cochrane Collaboration) was used to compute the weighted mean difference in change in HbA1c and total cholesterol between intervention and control groups, employing the generic inverse variance method. To incorporate both between- and within-study variance we used a random effects model for estimating the weighted mean differences in change between intervention and control group across the included trials.[31] Mean differences were pooled separately for the different types of diabetes

patients (prevalent, screen-detected, and newly diagnosed), and subsequently for the entire patient population. The consistency of the findings across the studies was assessed using forest plots. We evaluated statistical heterogeneity by calculating the I^2 statistic, a measure independent of the number of studies and effect size metric.[32] All outcomes variables other than HbA1c and total cholesterol, we analysed descriptively.

RESULTS

Figure 1 summarises the identification of relevant studies and the numbers of excluded and included studies. The search of the electronic databases identified 9,464 abstracts of studies published between January 2000 and July 2015. After excluding duplicate citations (n=1,227) and studies unrelated to the current review´s topic (n=7,801), we considered 436 articles for full-text review. Of these, 424 studies failed to meet our explicit inclusion criteria. In total, twelve articles met our inclusion criteria and were included in the current review.[33-43] No relevant studies were retrieved by hand-search.

<insert figure 1 here>

Study Characteristics

The 12 included articles[33-43] reported on eight unique cluster randomized controlled trials,[33 35 39-41 43-45] carried out between 1989 and 2011. Two of these trials, Addition Denmark[40] and Addition Cambridge,[35] had not individually reported any follow-up results in sequel to their study protocols. Their five-year data however, were pooled in the Addition-Europe study[46] together with the five-year data of the Addition-Netherlands[39] and Addition-Leicester[43] trials. For the remainder of the methods section, we will describe the design features and assess risk of bias for the Addition-Denmark and Addition–Cambridge trials based on their published protocol, yet for the results section we will have to resort to the pooled five-year data from the Addition-Europe study. This means that although we identified eight unique trials,[33 35 39-41 43-45] there are just seven publications to extract data from.[33 39 41 43-46]

All trials had recruited either general practitioners or physician practices which represented the cluster level (level of randomization). In one study,[45] however, first-level clusters were formed by district (characterized as urban, rural and mixed) and second-level clusters by the

physicians. The total number of patients with type 2 diabetes enrolled by the physicians amounted to 9,529, of whom 8,921 (94%) had been included in the analyses.

The objective of each trial was the structured multifaceted management of diabetes, and the interventions were aimed at improving the patients´ cardiovascular risk profile[44 45] and metabolic control,[33 35 39 40 43 44] and assessing the effect of multifaceted care on the occurrence of cardiovascular events,[35 39 40 43] overall mortality,[41] and risk factors for clinical complications.[41] Interventions focused on all aspects of the CCM including more regular and frequent consultations, annual screening for diabetes complications, patient education/advice, guideline-based clinical treatment and physician education, regular/annual feedback reports to physicians, referrals, record keeping, formation of multidisciplinary (primary care provider) teams, delegation of routine diabetes tasks to a trained practice nurse, patient and physician reminders, and patient-physician communication and decision-making. The interventions were largely delivered by general practitioners and physicians, yet specialized nurses or practice nurses were also involved in the intervention-program as part of the practice team and to (partly) replace the physician in providing diabetes care.[33 35 39 40 43 44]

Two main aspects differed among the trials: the type of diabetes patient enrolled and the duration of the intervention. Three trials[33 44 45] had included patients with prevalent diabetes and intervened for one year. The average diabetes duration in these studies ranged from 5.8 to 9.5 years. One trial[41] had enrolled patients with newly diagnosed type 2 diabetes and assessed outcome measures after six years of intervention. Finally, there were four trials[35 39 40 43] that first had initiated a diabetes screening program and subsequently had recruited those with screen-detected diabetes to participate in the intervention study. Follow-up measurements were assessed at one year and at five years. Table 1 presents an overview of interventions and findings of the included publications. Tables 2a and 2b present the baseline patient characteristics for the trials that recruited patients with prevalent diabetes[33 44]

[45] and for the trials that recruited patients with screen-detected[39 43 46] and newly diagnosed diabetes,[41] respectively.

<insert table 1 here>

<insert tables 2a and 2b here>

Data quality assessment

Figure 2 summarizes the risk of bias for the trials included in this review. Whereas the Addition-Denmark[40] and the Addition-Cambridge[35] trials had not published one-year data, they did provide five-year data for the Addition-Europe meta-analysis[46] and were thus included in the risk of bias assessment. However, since not having published actual trial data, we could not assess the domains of incomplete outcome data, selective reporting, and other bias, which resulted in the occurrence of blanks in Figure 2.

<insert figure 2 here>

Seven trials had at least one domain judged as unclear risk of bias. Five trials had at least one domain judged as high risk of bias. Only one study[44] had explicitly described that their physicians were unaware of being allocated to the intervention or control group when recruiting eligible patients. For the remaining studies prior knowledge of treatment allocation cannot be ruled out (recruitment bias). Furthermore, the Addition studies[35 39 40 43] were the only trials in which patients remained unaware of group assignment throughout the study.

In four studies[35 39 40 43] outcome assessment was performed completely blinded for patient allocation. In one study[45] only laboratory outcomes were assessed blinded, whereas clinical outcomes were obtained by contacting the general practitioner, introducing possible bias. No substantial baseline differences between the intervention and control groups existed with regard to the outcomes of interest.

Biochemical outcomes

All studies had assessed biochemical outcomes at follow-up, including HbA1c level, blood lipid levels, blood pressure, and BMI.

HbA1c levels

All studies assessed HbA1c values at follow-up. For six[33 39 43-46] of the seven study populations glycaemic control at baseline was moderate to good, as expressed by mean HbA1c concentrations ranging from 7·0% to 7·8% (53 to 62 mmol/mol) (Table S1a and S1b). The three trials with prevalent type 2 diabetes patients[33 44 45] observed no statistically significant difference in change in HbA1c levels between the intervention and control group after one year of intervention (Figure 3). There was no statistical heterogeneity between these three trials (I^2 = 0%) and the weighted mean difference in change between intervention and control groups was -0·06% (95% CI: -0·13 to 0·01) (-0·7 mmol/mol (95% CI: -1·4 to 0·1)), in favour of the intervention group. Using a similarly short intervention period, yet studying patients with screen-detected type 2 diabetes, the Addition-Leicester trial[43] observed a significant difference in change in HbA1c between the two trial arms of -0·20% (95% CI: -0·31 to -0·08) (-2·2 mmol/mol (95% CI: -3·4 to -0·9)). Whereas the Addition-Netherlands authors[39] did not report the actual difference in HbA1c change between the two groups, they stated in their paper that the improvement in HbA1c was significantly better in the intervention group, compared to the control group. The pooled five-year data from all four Addition-trials[46] showed a somewhat smaller, yet significantly greater improvement in HbA1c concentration in intervention patients, compared to control patients (-0·08% (95% CI: -0·14 to -0·02)) (-0·9 mmol/mol (95% CI: -1·5 to -0·2)) (Figure 3). Finally, the effect of multifaceted care in Danish patients with newly diagnosed diabetes[41] after six years of intervention was comparable to that in screen-detected patients after five years of intervention[46] (-0·06% (95% CI: -0·08 to -0·03)) (-0·7 mmol/mol (95% CI: -0·9 to -0·3)).

Pooling all seven trials, multifaceted care improved HbA1c concentration with -0·07% (95% CI: -0·10, -0·04) (-0·8 mmol/mol (95% CI: -1·1 to -0·4)) (Figure 3). Statistical heterogeneity across the seven trials was small to moderate (I^2 = 21%).

<insert figure 3 here>

Cholesterol levels

Figure 4 presents the mean differences in change in total cholesterol levels for all seven trials. Of the three trials that studied prevalent diabetes patients, only the Dutch trial[33] observed multifaceted care to significantly improve total cholesterol concentrations. In the remaining two studies,[44 45] cholesterol levels were similar between intervention and control arm. Statistical heterogeneity across the three studies was low (I^2=12%) and their weighted mean difference in change between intervention and control groups amounted to -0·14 mmol/l (95% CI: -0·22 to -0·07). Similar to HbA1c, the effect of multifaceted care on cholesterol seemed larger in screen-detected patients than in patients with prevalent diabetes. After one year of intervention, Addition-Leicester[43] found a mean difference in change between the intervention and control group of -0·56 mmol/l (95% CI: -0·87 to -0·25). The pooled five-year data from all four Addition trials also showed a significantly greater improvement in total cholesterol levels in intervention patients, compared to control patients (-0·27 mmol/l (95% CI: -0·34 to -0·19)). Finally, in Danish patients with newly diagnosed diabetes,[41] six years of multifaceted care had caused cholesterol levels to improve (-0·15 mmol/l (95% CI:-0·29 to -0·02)).

Pooling all trials, the effect of multifaceted care on improvement of total cholesterol resulted in a weighted difference in change between intervention and control patients of -0·20 mmol/l (95% CI: -0·28 to -0·11); I^2=64%.

In addition to improvements in total cholesterol levels, HDL-cholesterol levels appeared to be unaffected by multifaceted care in patients with prevalent diabetes.[33 44 45] LDL-cholesterol levels on the other hand, did improve (see supplementary figure S1 and S2). Both the Dutch[33] and the Swiss[44] study found significantly better improvements in LDL-cholesterol for the intervention group, when compared to the control group. The Addition-Netherlands[39] and Addition-Leicester[43] studies observed that multifaceted care significantly improved LDL-cholesterol levels after one year, while HDL-cholesterol remained largely unchanged. Similar results were reported for five years of intervention by the Addition-Europe study.[46] The Danish study[41] with newly diagnosed diabetes patients had not measured HDL and LDL-cholesterol levels.

<insert figure 4 here>

Blood pressure

Two[33 44] out of the three trials with patients with prevalent diabetes reported a difference in change in diastolic and systolic blood pressure, both being in favour of the intervention group (see supplementary figure S3 and S4). Better improvements in blood pressure were also seen in intervention patients with screen-detected diabetes, compared to control patients.[39 43 46] Improvements after one year of intervention[43] were larger than those after five years of intervention.[46] In patients with newly diagnosed diabetes[41] six years of multifaceted care significantly improved systolic, but not diastolic, blood pressure when compared to usual diabetes care. Similar to HbA1c and total cholesterol, the results for blood pressure were stronger for patients with screen-detected and newly diagnosed diabetes than for those with prevalent, long-standing diabetes.

Body mass index

With regard to the studies on prevalent diabetes, only the Austrian study[45] found a significant difference in change in BMI between the intervention group and control group after one year of intervention (see supplementary figure S5). In screen-detected diabetes patients[39 43] multifaceted care resulted in a significantly higher reduction in BMI, compared to usual diabetes care. Furthermore, Addition-Leicester[43] reported a higher reduction in both BMI and body weight (kg) for the intervention group compared to the control group, but observed no difference in reduction of waist circumference. After an intervention duration of five years, the pooled reduction in weight and waist circumference, but not in BMI, in screen-detected diabetes was significantly higher in the intervention group compared to the control group[46]. The Danish trial[41] with newly diagnosed diabetes patients observed no difference in weight change after six years of intervention, yet BMI had not been measured.

For further biochemical outcomes, see online supplementary file S3.

Patient-reported outcomes

The effect of a multifaceted care intervention on the patients´ quality of life accounted for the only patient-reported outcome assessed by the included trials.

Health-related quality of life

Quality of life was reported by five[33 39 43 44 46] of the seven trials, most of which had used the 36-item Short Form Health Survey (SF-36) to assess the different domains of health-related quality of life. In patients with prevalent diabetes[33 44] significant changes over time were absent for all scores of the SF-36 subscales for both the intervention and control arms. A superior effect of multifaceted care was observed only on the SF-36 subscale “health

change" in the Dutch trial with prevalent diabetes patients.[33] For the two Addition studies reporting results after one year of intervention,[39 43] as for the pooled five-year data by Addition-Europe,[46] no significant changes in the physical and mental summary scores of the SF-36, or the abbreviated SF-12 version that was used in the Addition-Leicester trial,[43] could be demonstrated.

Diabetes complications

Only few trials had reported diabetes complications, including cardiovascular disease and mortality. Closely related to the prevention and occurrence of complications, some studies evaluated the effect of their intervention on processes of care, such as reaching target values for HbA1c and receiving regular eye and foot examinations.

Macro- and microvascular complications

Macro- and microvascular diabetes complications during follow-up were reported by the two studies[41 46] with the longer intervention periods. The Addition-Europe study[46] had assessed myocardial infarction, stroke, coronary and peripheral revascularization procedures, cardiovascular death and total mortality, and non-traumatic amputation in screen-diagnosed diabetes patients. Whereas the estimated hazard ratios for these events all favoured the intervention group, none of the estimates reached statistical significance. In newly diagnosed diabetes patients,[41] multifaceted care had not resulted in differences between intervention and control group regarding the risk of diabetic retinopathy, peripheral neuropathy, microalbuminuria, non-fatal myocardial infarction and stroke, angina pectoris, or intermittent claudication at six years.

Processes of care

Only three studies assessed processes of care or process quality measures.[33 45 46] The Dutch study[33] with prevalent diabetes patients observed that multifaceted care resulted in significantly more patients reaching treatment targets (18·9%) than usual diabetes care (13·4%) (treatment targets were defined as HbA1c ≤7% (53 mmol/mol), systolic blood pressure ≤140 mmHg, total cholesterol ≤4·5 mmol/l and LDL-cholesterol ≤2·5 mmol/l). Process quality measures at one year, defined as the percentage of patients receiving guideline-adherent foot-, eye-, and HbA1c-examinations, were reported by the Austrian study with prevalent diabetes patients[45] to be significantly higher in the intervention group. The pooled five-year results from the four Addition studies[46] showed that in both trial arms more patients had values below target thresholds for HbA1c (<7% (53 mmol/mol)), blood pressure (≤135/85 mmHg) and cholesterol level (<4·5 mmol/l), yet proportions were higher in the intervention group than in the control group.

For further diabetes complications and related outcomes, see online supplementary file S3.

DISCUSSION

This review assessed the effectiveness of chronic disease management models for type 2 diabetes on the improvement of patient outcomes, in Europe. In general, the effects of multifaceted care on patient outcomes were rather small and their magnitude seemed to differ according to the type of diabetes patient being studied. Our analysis suggested that in comparison to usual diabetes care, multifaceted care improves HbA1c levels for patients with screen-detected diabetes and patients with newly diagnosed diabetes, but not for patients with prevalent type 2 diabetes. Similar findings were observed for total cholesterol, LDL-cholesterol, BMI and body weight. The resulting improvements in blood pressure seemed less strongly related to the type of diabetes patient studied. Other outcomes, such as fasting glucose levels, triglycerides, quality of life, and diabetes complications, had been reported inconsequently and results varied widely across the included trials.

The few cluster randomized controlled trials that we identified from the literature were relatively heterogeneous with regard to the individual components of the implemented intervention, duration of the intervention, type of diabetes patient, and reported outcomes. For each trial, methodological quality was acceptable and there were very low rates of dropout among the enrolled patients. Still, details on the randomization procedure was frequently missing as well as information concerning concealment of allocation from general practitioners and physicians in advance to recruitment of eligible patients. Since the currently performed meta-analysis included only a small number of trials, caution is warranted not to overinterpret its results. The Chi-squared statistic for example, indicating homogeneity of the effect of the intervention on HbA1c and total cholesterol, has low power when based on only few, and small-sized, studies.[47] When interpreting the data, we thus prefer to look at the direction of the individual effect estimates and confidence intervals, rather than let the calculated statistics guide our conclusions. As such, given the current literature, it is not possible to draw an unequivocal conclusion about the effectiveness of chronic multifaceted care on diabetes patient outcomes.

Overall, previous systematic reviews have reported that an integrated approach to diabetes care versus usual diabetes care may improve clinical and biochemical outcomes,[9 10 19 20 23 24 48] including HbA1c levels, blood pressure, and blood lipid concentrations. Those reviews that included a meta-analysis reported mean differences in HbA1c reduction between intervention and control groups ranging from -0.14 (95% CI: -0.25 to -0.05) to -0.5% (95% CI: -0.6 to -0.3). Mean differences in total cholesterol have only been estimated by one meta-analysis, which reported a reduction of -0.24 mmol/l (95% CI: -0.41 to -0.06) in favour of the intervention group.[10] This study also reported a mean difference in diastolic blood pressure reduction of -1.3 mm Hg (95% CI: -0.21 to -0.6) and a mean difference in systolic blood pressure reduction of -2.2 mmHg (95% CI: -3.5 to -0.9), comparable with the summary estimate for systolic blood pressure from Elissen *et al.* (-2.8 (95% CI: -4.7 to -0.9)).[20] All other outcomes of multifaceted care interventions were described narratively. Improvements have been observed for frequency of retinopathy screening,[20 48 49] screening for peripheral polyneuropathy and foot lesions,[20 48 49] proteinuria measurements,[49] and the monitoring frequency of lipid and HbA1c levels.[49]In addition, there seems to be an economic benefit of integrated diabetes care.[50]. Yet, other systematic reviews have found no impact on patients outcomes and processes of care[18 25 49] or have disputed the clinical relevance of statistically significant findings.[19] A comparison of the reported effect estimates with our summary estimates for HbA1c and total cholesterol warrants caution, given the varying number of CCM elements the estimates were based on, the heterogeneity among the included diabetes patients, the different restrictions to geographical region, and the number of included studies in each review.

The novelty of the current systematic review is that it provides a comprehensive overview of diabetes care trials that have evaluated the effectiveness of the all the six components of the CCM combined, instead of one or more components. Overall, we found there is an important lack of studies which evaluate the implementation of all six CCM-components simultaneously. In current literature, findings on the issue of whether multifaceted chronic

care is to be preferred over single-faceted care are conflicting.[9-12 24-26 51] However, improving the management of a complex disease like diabetes is a challenging goal which, we believe, may not be achieved by targeting single care aspects only. Another novel aspect of the current review is the focus on state-of-the-art diabetes management in Europe only. The narrow view relates to the enormous burden that type 2 diabetes represents in Europe, both in individual and in societal terms.[52] The prevalence of diabetes in Europe is expected to increase from 59.8 million adults in 2015 to 71.1 million in 2040.[53]

As reflected by recent guidelines for the management of patients with type 2 diabetes,[54] health care providers have increasingly focused at improving and controlling cardiovascular risk factors to improve patient outcomes, including hyperglycaemia, overweight or obesity, elevated blood pressure, and dyslipidemia. Results from the Steno-2 trial support the view that even in high-risk patients with type 2 diabetes multifaceted care has the potential to reduce the risk of complications and mortality.[55] Randomizing 160 patients with type 2 diabetes and persistent microalbuminuria to an intensive multifactorial treatment and conventional therapy, the authors found that the multifactorial treatment was associated with a lower risk of cardiovascular events after 13·3 years of follow-up, as well as with a lower risk of death from cardiovascular disease, compared to conventional treatment . And while the CCM has been proposed as a tool to improve the quality of diabetes care and, subsequently, patient outcomes, the current review indicates that at least the existing programs have not been as successful in this respect as intended. The challenge thus remains to translate results from landmark studies like Steno-2, into primary care, where the majority of type 2 diabetes patients are being treated.

When aiming to improve chronic health care, it has been proposed that only assessing the effects of a multifaceted care intervention on patient outcomes is not sufficient. In order to gain insights into why and when certain interventions are effective, it is also important to focus on barriers and facilitators to the implementation process of the intervention and their effect on the interplay between intervention and outcomes.[56] This latter aspect is usually not

evaluated or reported on by randomized controlled trials implementing a multifaceted care intervention.[57] As such, it has not yet been possible to analyse the relationships between context, mechanisms, and outcomes of multifaceted diabetes care interventions and to subsequently provide meaningful insights into how these have influenced the outcomes achieved.[57]

There are some limitations of our work that need to be considered. First, many studies provided insufficient detail in their methods section to fully understand the intensity of (specific components of) the intervention. This complicated our appraisal of whether all components of the CCM were fully covered. Also, the different interventions that the trials have used to represent a given component of the CCM have possibly resulted in some heterogeneity across the trials. In addition to the insufficiently described interventions, standards for usual diabetes care were not elaborated on in any of the trials. Online versions of diabetes care guidelines were found to be published in the country´s native language and represented current versions only. However, most European countries define their standards according to the recommendations made by the joint task force convened by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[54 58] Indeed, identified guidelines from the Netherlands, Austria, and the United Kingdom did comply with the ADA/EASD recommendations. We do therefore not expect that practices of usual diabetes care in the individual trials have differed to the extent of causing a significant increase in heterogeneity. Second, whereas the aim of the current review was to investigate the effectiveness of chronic care models in Europe, the trials available for this review only represented the Western part of Europe. Countries with the highest prevalence of diabetes lie in Eastern Europe, i.e. Turkey, Montenegro, Macedonia, and Serbia.[52] The top-three countries in Western Europe with the highest diabetes prevalence are Germany, Spain, and Italy,[52] none of which were represented in this review. And third, the procedure of selecting relevant studies for the current review was largely performed by only one person.

However, two reviewers subsequently screened the full text of all potentially relevant papers such that the final decision on inclusion was based on two opinions.

In conclusion, the available scientific evidence regarding the effectiveness of multifaceted chronic care programs for type 2 diabetes in older patients in Europe is low. In general, the current findings support the concept of the chronic care model, yet the improvements in patient outcomes and processes of care are only small. While key aspects of type 2 diabetes can be improved by a multifactorial intervention, it is not yet clear if these improvements will subsequently lower diabetes-related complications, such as cardiovascular disease and overall mortality. Furthermore, the effect of the interventions seemed, at least partly, to depend on the type of diabetes patient, which could suggest effect modification by disease duration and/or disease severity. Another aspect that could add to the differences in effectiveness between the individual interventions is the degree in which they facilitate changes in social behaviour. This implies that more attention in trials should be spent to factors like adherence to treatment strategies, level of self-management skills, and patients´ knowledge on their disease. These traits need to be positively affected before an improvement in clinical measures can even occur,[1] yet studies generally reveal little on person-centred factors. And finally, there is a lack of knowledge (on information) on effective methods to address important pragmatic questions about improvement of care, for example, which specific mechanism or procedure of a chronic care model works, for which patients, and under which circumstances?[59] Future research would need to incorporate the measurement of context, mechanisms and outcomes of multifaceted care into study designs in order to deliver the full extent of insights needed to improve chronic diabetes care and, ultimately, patient outcomes.

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Contributors

BWCB designed the review by writing the review protocol, identified studies for inclusion, extracted and interpreted the data, and drafted and revised the article. KM contributed to the review protocol and to the discussion. He further revised the draft paper for intellectual content. JW was involved in conception of the review and he contributed to the review protocol, to interpretation of the data and to the discussion. Furthermore, JW revised the draft paper for intellectual content. CL contributed to the review protocol and to the discussion, and she revised the draft paper for intellectual content. PS conceived and initiated the review, contributed to the review protocol and he contributed to the interpretation of the data, to the discussion and to revision of the draft paper. MR was involved in conception of the review and he revised the draft paper for intellectual content. WR contributed to the review protocol, identified studies for inclusion, extracted and interpreted the data and revised the draft paper for intellectual content. All authors approved the final completed article.

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ONLINE SUPPLEMENTARY INFORMATION

FIGURES TITLES AND LEGENDS

Figure 1: Flow chart summarizing the identification of studies for inclusion in the review.

Figure 2: Risk of bias graph.

Review authors' judgments about each risk of bias item presented as percentages across all included studies. Studies included are Cleveringa et al. (2008);[33] Sönnichsen et al. (2008),[45] Frei et al. (2010),[44] Olivarius et al. (2001),[41] Janssen et al. (2009),[39] Webb et al. (2010),[43] Lauritzen et al. (2000),[40] and Echouffo et al. (2009).[35] The studies from Lauritzen and Echouffo were included in the risk of bias assessment since their five-year follow-up data had been included in the Addition-Europe meta-analysis by Griffin et al.[46] As the Addition-Europe publication only reported pooled data, no comprehensive overview of results was available for the studies by Lauritzen and Echouffo, which resulted in the blanks in the risk of bias graph.

Figure 3: Mean difference in change (95% confidence interval) in HbA1c levels (%) after multifaceted care between intervention and control groups. Results are stratified by type of diabetes patient.

IV, generic inverse variance method; CI, confidence interval; df, degrees of freedom

[a] Studies had an intervention duration of one year. [b] The methodology for calculating the difference in change between intervention and control group that Cleveringa et al.[33] have used (subtracting the HbA1c change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the HbA1c change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa et al.,[33] we have recalculated their HbA1c results according to the methodology

used by the other studies. [c] The study of Webb et al.[43] had an intervention duration of one year and the study of Griffin et al.[46] had a duration of five years. [d] This study combined the 5-year intervention data from all four Addition studies, including the five-year data from Webb et al.[43] [e] This study had an intervention duration of six years.

Figure 4: Mean difference in change (95% confidence interval) in total cholesterol levels (mmol/l) after multifaceted care between intervention and control groups. Results are stratified by type of diabetes patient.

IV, generic inverse variance method; CI, confidence interval; df, degrees of freedom

[a] Studies had an intervention duration of one year. [b] The methodology for calculating the difference in change between intervention and control group that Cleveringa et al.[33] have used (subtracting the total cholesterol change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the total cholesterol change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa et al.,[33] we have recalculated their cholesterol results according to the methodology used by the other studies. [c] The study of Webb et al.[43] had an intervention duration of one year and the study of Griffin et al.[46] had a duration of five years. [d] This study combined the 5-year intervention data from all four Addition studies, including the five-year data from Webb et al.[43] [e] This study had an intervention duration of six years.

Table 1

Table S1: Characteristics of the included cluster randomized controlled trials

Study	Comparison	Effect on endpoints*	Notes
Cleveringa 2008[33]	Intervention: Patient consultation by a practice nurse + use of a computerized decision support system + guideline-based care + physician support by practice nurse + interdisciplinary care by a specialist team + individualised treatment advice + patient education + physician feedback + recall system + regular patient consultations by practice nurse + physician feedback *versus* Usual diabetes care (not further specified)	**Biochemical outcomes** HbA1c (0) Total cholesterol (+, i) HDL-cholesterol (0) LDL-cholesterol (+, i) Systolic blood pressure (+,i) Diastolic blood pressure (+,i) 10-year CHD risk (+, i) **Diabetes complications and processes of care** HbA1c below target value§ (+,i) Total cholesterol below target value§ (+,i) LDL-cholesterol below target value§ (+,i) Systolic blood pressure below target value§ (+,i) All treatment targets reached§ (+,i)	At baseline, patients in the intervention group had higher HDL-cholesterol levels, were more often smoker and more often had a history of CHD. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between intervention and control group were adjusted for cluster structure.
Sönnichsen 2008[45]	Intervention: Physician education +guideline-based care + patient education + use of a clinical information system tool + interdisciplinary care by a specialist team + patient reminders + physician reminders + goal setting + shared decision making patient and physician + regular consultations *versus* Usual diabetes care (not further specified)	**Biochemical outcomes** HbA1c (0) Total cholesterol (+, i) HDL-cholesterol (0) LDL-cholesterol (0) Systolic blood pressure (0) Diastolic blood pressure (0) Body mass index (+, i) Triglycerides (0) Creatinine (0) **Diabetes complications and processes of care** To the guidelines adherent: -number of eye examinations§ (+, i) -number of foot examinations§ (+, i) -provision of patient education§ (+, i) -regular HbA1c checks§ (+, i)	At baseline, patients in the intervention group had a higher BMI and higher cholesterol levels than patients in the control group. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between intervention and control group were adjusted for cluster structure and baseline characteristics.
Frei 2010[44]	Intervention: Specialist team involving a practice nurse + practice nurse education + physician education + physician support by practice nurse + regular independent patient consultations by practice nurse + use of a clinical information system tool + guideline-based care + physician feedback + patient information leaflets + self-management support for patient + patient treatment groups *versus* Usual diabetes care (not further specified)	**Biochemical outcomes** HbA1c (0) Total cholesterol (0) HDL-cholesterol (0) LDL-cholesterol (+, i) Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (0) Fasting blood glucose (0) **Patient-reported outcomes** **Diabetes complications and processes of care** Number GP visits§ (0) Change in antidiabetic therapy (0) Change in antihypertensive therapy (0) Change in lipid-lowering therapy (0)	There were no baseline differences in patient characteristics between intervention and control group. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between intervention and control group were adjusted for cluster structure and baseline characteristics.

Webb 2010[43]	Intervention: Structured patient education + lifestyle advice and self-management with ongoing (bimonthly) professional support + individualized management + guideline-based care + shared decision making patient and health care professional + annual screening for diabetic complications + care delivered by a specialist team (specialty doctor, diabetes nurse educator, and a dietician) + patient reminders + physician reminders *versus* Usual diabetes care (not further specified)	**Biochemical outcomes** HbA1c (+, i) Total cholesterol (+, i) LDL-cholesterol (+, i) HDL-cholesterol (0) Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (+, i) Weight (+, i) Waist circumference (0) Triglycerides (0) 5-year CHD risk (+, i) 5-year CVD risk (+, i) **Patient-reported outcomes** Health-related quality of life (0) **Diabetes complications and processes of care** Hypoglycaemia§ (+, i) Use of anti-hypertensive drugs§ (+, i) Use of lipid-lowering drugs§ (+, i) Use of anti-platelet therapy§ (+, i) Use of metformin§ (0) Use of sulfonylurea§ (0)	At baseline, more patients in the intervention group were taking anti-hypertensive medication when entering the study and had higher total and LDL-cholesterol levels. Statistical analyses were conducted by intention-to-treat. It was not reported whether or not data were missing and how missing data were handled. Comparisons between intervention and control group were adjusted for cluster structure and baseline characteristics (except quality of life which had not been measured at baseline).
Janssen 2009[39]	Intervention: Physician education + diabetes nurse education + lifestyle advice + guideline based care + physician support by diabetes nurse + evaluation and feed-back sessions diabetes nurse + frequent patient consultations with diabetes nurse + shared decision making patient, physician and diabetes nurse + physician reminders + patient reminders *versus* Usual diabetes care (not further specified)	**Biochemical outcomes** HbA1c (+, i) Total cholesterol (+, i) LDL-cholesterol (+, i) HDL-cholesterol (0) Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (+, i) Fasting blood glucose (+, i) Triglycerides (0) **Patient-reported outcomes** Health-related quality of life (0) **Diabetes complications and processes of care** Hypoglycaemia§ (0)	There were no baseline differences in patient characteristics between intervention and control group. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between intervention and control group were adjusted for baseline characteristics, and clustering at practice level.
Griffin 2011[46]	This study combined the data after five years of a multifaceted care intervention from the i) Addition-Denmark study (Lauritzen et al[40]), ii) the Addition-Netherlands study (Janssen et al[39]), iii) the Addition-Cambridge study (Echouffo et al[35]), and iv) the Addition-Leicester study (Webb et al[43]) in a meta-analysis.	**Biochemical outcomes** HbA1c (+, i) Total cholesterol (+, i) LDL-cholesterol (+, i) HDL-cholesterol (0) Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (0) Weight (0) Waist circumference (0) Triglycerides (0) Creatinine (+, c) **Patient-reported outcomes** Health-related quality of life (0) **Diabetes complications and processes of care** All-cause mortality (0) CVD mortality (0) Myocardial infarction (0) Stroke (0) Revascularization procedures (0) Hypoglycaemia§ (0) Meeting target values for: HbA1c (+, i) blood pressure (+, i)	Baseline characteristics were well matched between intervention and control group. In Denmark however, more patients were identified in practices assigned to the intervention arm then in those assigned to control arm. And in the intervention group, more patients had a history of ischemic heart disease. Statistical analyses were conducted by intention-to-treat and patients with missing outcome values at baseline were excluded from the analyses. Those with missing outcome baseline values were included according to the missing indicator method. Comparisons between intervention and control

		total cholesterol (+, i) Use of any glucose-lowering drugs (+, i) Change in any anti-hypertensive drugs (+, i) Change in any cholesterol-lowering drugs (+, i)	group were adjusted for cluster structure and baseline characteristics.
Olivarius 2001[41]	Intervention: Patient follow-up every three months + annual screening for diabetes complications + shared decision making patient and physician + physician feedback + goal setting + clinical guidelines + physician education + patient leaflets and folders + lifestyle advise + protocol based care + physician recall system *versus* Usual diabetes care (not further specified)	**Biochemical outcomes** HbA1c (+, i) Total cholesterol (+, i) Systolic blood pressure (+, i) Diastolic blood pressure (0) Weight (0) Fasting blood glucose (+, i) Triglycerides (0) Creatinine (0) **Diabetes complications and processes of care** Overall mortality§ (0) Severe hypoglycaemia§ (0) Diabetic retinopathy§ (0) Non-fatal myocardial infarction§ (0) Non-fatal stroke§ (0) Peripheral neuropathy§ (0) Microalbuminuria§ (0) Angina pectoris§ (0) Intermittent claudication§ (0)Number of consultations§ (+, i) Number of referrals to diabetes clinic§ (-, i) Number of hospital admissions§ (0) Use of metformin§ (+, i) Use of other glucose-lowering drugs§ (0) Use of anti-hypertensive drugs§ (0) Use of lipid-lowering drugs§ (0)	At baseline, more patients in the intervention group were excluded because of severe somatic disease than in the control group. Furthermore, occupation and smoking habits differed between the two groups. Statistical analyses were conducted by intention-to-treat. It was not reported whether or not data were missing or how missing data were handled. Comparisons between intervention and control group were adjusted for cluster structure and baseline characteristics.

T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; CVD, cardiovascular (heart) disease; GP, General Practitioner;
* +=positive effect; 0=no effect; -=negative effect; i=favouring intervention group; u=favouring control (usual care) group. The effects of the intervention are represented by the difference in change from baseline to follow-up between intervention and control group. § The effect of the intervention is represented by a difference in proportions of patients at follow-up between intervention and control group.

1

Table 2a

Table 2a: Baseline patient characteristics of the included cluster randomized controlled trials studying patients with prevalent diabetes

	Cleveringa *et al*[33] *		Sönnichsen *et al*[45] †		Frei *et al*[44] ‡	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
N	1699	1692	649	840	162	164
Follow up duration (years)	1	1	1	1	1	1
Type of diabetes patients	Prevalent diabetes		Prevalent diabetes		Prevalent diabetes	
Country	Netherlands		Austria		Switzerland	
Baseline patient characteristics						
Age (years)	65.2 ± 11.3	65.0 ± 11.0	65.4 ± 10.4	65.5 ± 10.4	65.7 ± 10.4	68.3 ± 10.6
Sex (% men)	48.2	49.8	51.0	53.1	54	60
Ethnicity (% Caucasian)	97.7	97.6	-	-	-	-
Diabetes duration (years)	5.8 ± 5.7	5.4 ± 5.8	7.0 ± 6.5		9.5 ± 7.4	10.3 ± 7.8
Current smoking (% yes)	**22.6**	**16.6**	13.4		14	9
Body mass index (kg/m^2)	30.0 ± 5.3	30.2 ± 5.3	**30.4 ± 5.1**	**29.7 ± 4.9**	30.5 ± 5.3	30.7 ± 5.9
Systolic blood pressure (mmHg)	149 ± 22	149 ± 21	141 ± 19	139 ± 17	140 ± 18	138 ± 17
Diastolic blood pressure (mmHg)	83 ± 11	82 ± 11	83 ± 11	82 ± 10	83 ± 10	79 ± 10
UKDPS CHD risk (%)	22.5 ± 16.5[§]	21.7 ± 15.8[§]	-	-	-	-
HbA1c (%)	7.1 ± 1.3	7.0 ± 1.1	7.46 ± 1.53	7.34 ± 1.31	7.8 ± 1.5	7.6 ± 1.1
Total cholesterol (mmol/l)	5.0 ± 1.0	4.9 ± 1.1	**5.15 ± 1.14**	**5.02 ± 1.09**	5.0 ± 1.2	4.7 ± 1.1

HDL-cholesterol (mmol/l)	**1.36 ± 0.36**	**1.32 ± 0.35**	1.35 ± 0.39	1.32 ± 0.36	1.2 ± 0.3	1.3 ± 0.4
LDL-cholesterol (mmol/l)	2.8 ± 0.92	2.8 ± 0.95	2.87 ± 0.96	2·87 ± 0·91	2·8 ± 1·1	2·5 ± 1·1
Fasting glucose (mmol/l)	8·0 ± 2·4	7·8 ± 2·2	-	-	8·4 ± 2·5	7·7 ± 2·2
Creatinine (µmol/l)	87.5 ± 27.7	85.9 ± 22.5	84.9 ± 30.9	84.9 ± 34.5	-	-
Triglycerides (mmol/l)	1.8 ± 1.1	1.8 ± 1.3	2.14 ± 1.82	2.00 ± 1.73	-	-
Urinary albumin (mg/l)	-	-	-	-	-	-
Quality of life: PCS¶					43.9 ± 10.9	
Quality of life: MCS¶					50.1 ± 11.3	
History of myocardial infarction (%)	**47.1**	**63.3**	8.4		-	-
History of stroke (%)			7.0		-	-
Diabetic retinopathy (%)	2.9	3.3	-	-	9.3	8.1
Peripheral neuropathy (%)	-	-	-	-	18.6	13.4

UKPDS, UK Prospective Diabetes Study; CHD, coronary heart disease; PCS, physical component summary score; MCS, Mental component summary score.

Values are mean ± sd, or percentages. Bold font indicates that the particular baseline characteristic differed statistically significantly between intervention and control group.

* The information on BMI, fasting glucose, creatinine, triglycerides, and retinopathy was obtained through contacting the authors.

† The information on diabetes duration, smoking, history of myocardial infarction, and history of stroke was obtained from the publication describing baseline characteristics of the total study population and stratified by sex (Flamm *et al*. 2011).

‡ The quality of life summary scores for the physical and mental component were obtained from the publication describing baseline characteristics of the total study population (Frei *et al*. 2012).

Peripheral neuropathy is represented by "*pathological foot status*" and diabetic retinopathy is represented by "*annual eye exam: pathological*".

§ Values concern the 10-year UKDPS CHD risk.

¶ Quality of life was assessed with the 36-item Short Form Health Survey (SF-36)

Table 2b

Table 2b: Baseline patient characteristics of the included cluster randomized controlled trials studying patients with screen-detected and newly diagnosed diabetes

	Webb *et al*[43]		Janssen *et al*[39]		Griffin *et al*[46]		Olivarius *et al*[41]	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
N	146	199	255	243	1678	1379	649	614
Follow up duration (years)	1	1	1	1	5	5	6	6
Type of diabetes patients	Screen-detected diabetes		Screen-detected diabetes		Screen-detected diabetes		Newly diagnosed diabetes	
Country	United Kingdom		Netherlands		United Kingdom, Netherlands, Denmark		Denmark	
Baseline patient characteristics								
Age (years)	59.4 ± 10.0	60.0 ± 10.0	60.1 ± 5.4	59.9 ± 5.1	60.3 ± 6.9	60.2 ± 6.8	65.5 (55.3-74.0)	65.3 (56.3-73.5)
Sex (% men)	56.9	58.3	51.8	56.0	58.5	57.3	52.4	53.1
Ethnicity (% Caucasian)	52.7	62.3	98.0	98.7	95.8	93.4	-	-
Diabetes duration (years)	0	0	0	0	0	0	0	0
Current smoking (% yes)	15.2	10.2	26.3	21.4	26.9	27.8	**35.5**	**34.5**
Body mass index (kg/m^2)	31.0 ± 5.9	31.5 ± 5.7	31.2 ± 5.1	30.4 ± 4.6	31.6 ± 5.6	31.6 ± 5.6	29.4 (26.2-33.0)	28.8 (26.0-32.3)
Systolic blood pressure (mmHg)	145.7 ± 18.5	148.4 ± 20.5	166 ± 23	163 ± 23	148.5 ± 22.1	149.8 ± 21.3	150 (130-164)	148 (130-160)
Diastolic blood pressure (mmHg)	87.8 ± 10.4	89.5 ± 10.7	90 ± 11	89 ± 10	86.1 ± 11.1	86.5 ± 11.3	85 (80-90)	85 (80-90)
UKPDS CHD risk (%)	8.5 ± 5.8†	9.3 ± 7.1†	-	-	-	-	-	-
HbA1c (%)	7.2 ± 1.5	7.3 ± 1.8	7.3 ± 1.6	7.4 ± 1.7	7.0 ± 1.6	7.0 ± 1.5	10.2 (8.6-11.6)	10.2 (8.7-11.9)
Total cholesterol (mmol/l)	**5.3 ± 1.2**	**5.6 ± 1.3**	5.6 ± 1.1	5.6 ± 1.1	5.5 ± 1.1	5.6 ± 1.2	6.2 (5.4-7.1)	6.2 (5.5-7.2)

HDL-cholesterol (mmol/l)	1.2 ± 0.4	1.2 ± 0.3	1.1 ± 0.4	1.1 ± 0.3	1.2 (1.0-1.5)	1.2 (1.0-1.5)	-	-
LDL-cholesterol (mmol/l)	**3.2 ± 1.0**	**3.5 ± 1.0**	3.7 ± 1.0	3.7 ± 1.0	3.4 ± 1.0	3.5 ± 1.0	-	-
Fasting glucose (mmol/l)	-	-	7.8 ± 2.3	8.1 ± 2.8	-	-	13.8 (10.7-17.0)	13.7 (10.7-17.0)
Creatinine (µmol/l)	-	-	-	-	83.4 ± 17.1	84.9 ± 18.6	90 (81-101)	88 (79-100)
Triglycerides (mmol/l)	2.1 ± 1.9	2.1 ± 1.4	1.9 ± 1.0	2.0 ± 1.6	1.6 (1.2-2.3)	1.7 (1.2-2.4)	2.03 (1.44-2.91)	1.98 (1.39-2.95)
Urinary albumin (mg/l)	-	-	-	-	-	-	11.7 (6.0-32.5)	11.8 (5.7-27.5)
Quality of life: PCS‡	39.0 (37.4-40.5)	38.5 (37.1- 40.0)	No summary scores reported		-	-	-	-
Quality of life: MCS‡	38.2 (35.2-41.2)	39.2 (36.5-41.9)	No summary scores reported		-	-	-	-
History of myocardial infarction (%)	15.8*	10.6*	-	-	6.8	6.1	6.6	7.7
History of stroke (%)			-	-	2.9	1.9	3.5	4.2
Diabetic retinopathy (%)	-	-	-	-	-	-	5.0	4.5
Peripheral neuropathy (%)	-	-	-	-	-	-	18.8	19.7

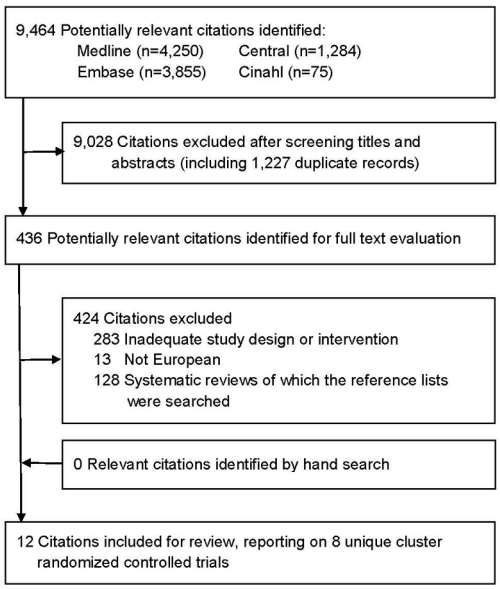
UKPDS, UK Prospective Diabetes Study; CHD, coronary heart disease; PCS, physical component summary score; MCS, Mental component summary score.

Values are mean ± sd, or median (interquartile range) or percentages. Bold font indicates that the comparison between intervention and control group was statistically significant.

* Defined as "*pre-existing CVD*", including myocardial infarction, stroke, and angina.

† Values concern the 5-year UKDPS CHD risk

‡ Quality of life was assessed with the 12-item Short Form Health Survey (SF-12) in de study by Webb *et al*., and with the 36-item Short Form Health Survey (SF-36) in de study by Janssen *et al*.



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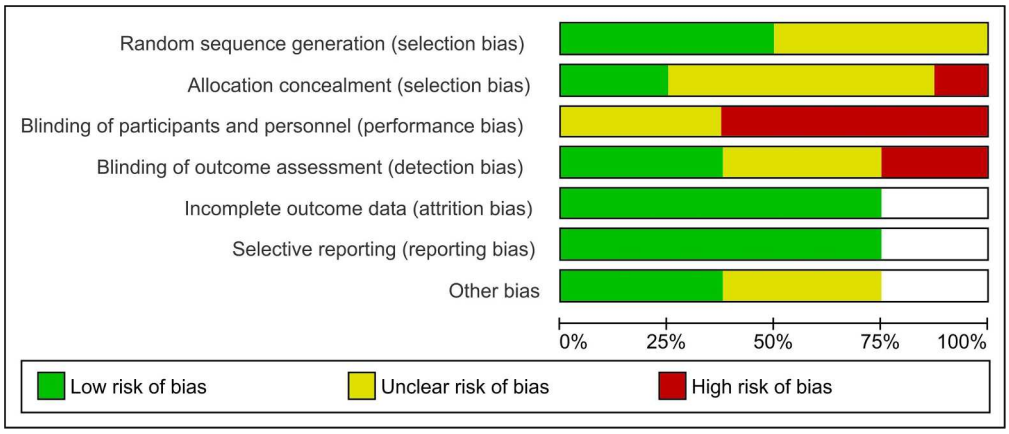

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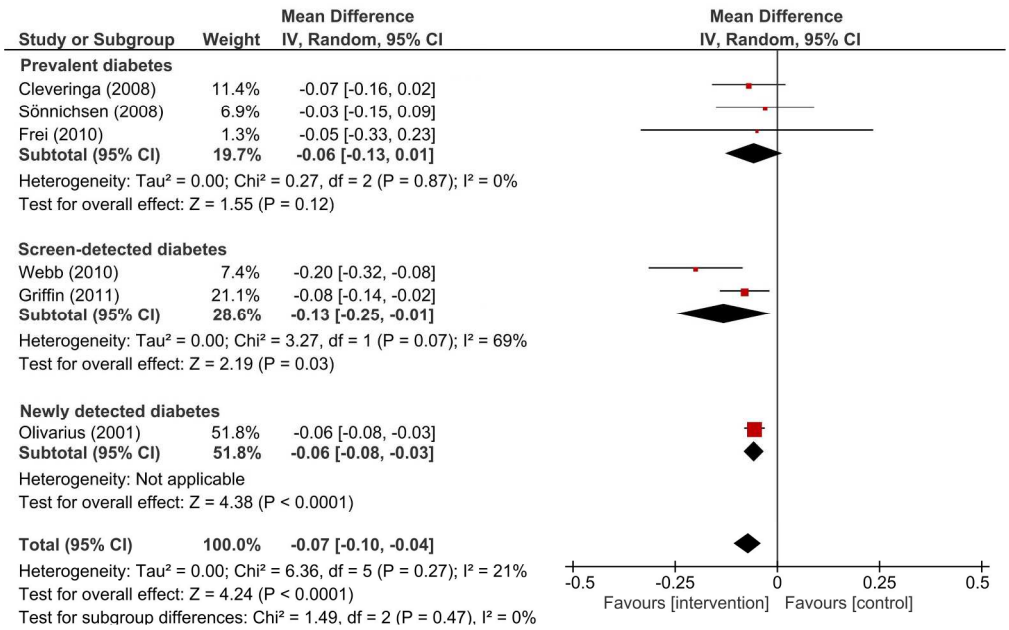

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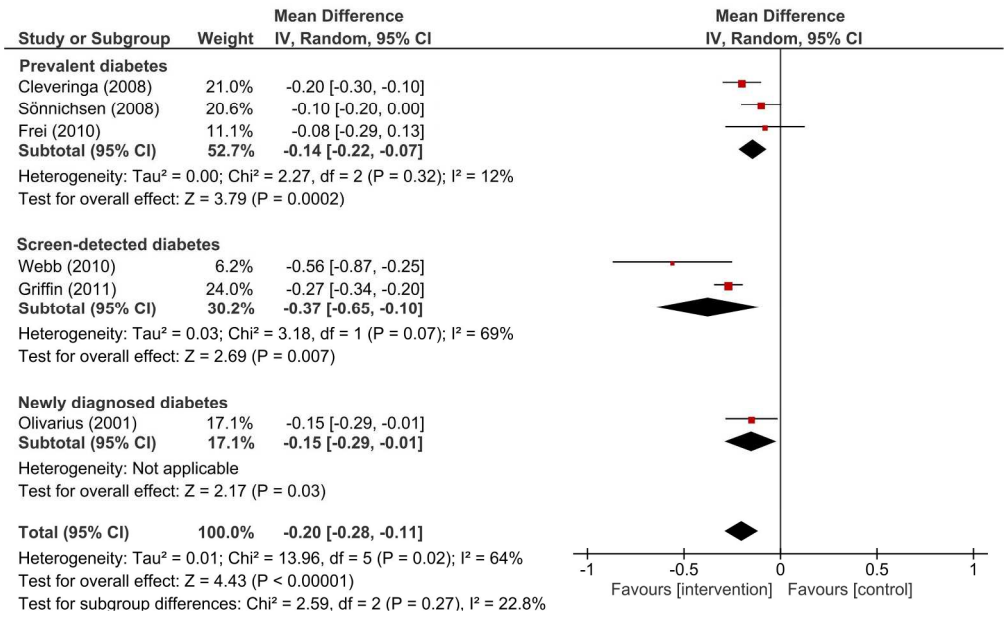

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Supplementary file S1

Review protocol (January 2014)

Effectiveness of Chronic Care Models for the Management of Type 2 Diabetes Mellitus in Europe: a Systematic Review

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1. BACKGROUND

A growing number of European citizens suffer from diabetes, constituting a growing health, social, and economic burden. The number of individuals with diabetes in Europe in 2013 was estimated by the International Diabetes Federation to be 56.3 million, or 8.5% of the adult population (20-79 years), and is expected to increase to 68.9 million people, or 10.3% by the year 2035 [1]. It is generally believed that lifestyle, with diets high in saturated fat and decreased physical activity, together with an increased longevity, are the main factors in the current increase in T2DM. In individual, as well as in societal terms, the burden of T2DM is enormous, resulting in increased morbidity and mortality [1].

Historically, health care systems were developed to respond rapidly and efficiently to acute diseases. The focus was on the immediate problem, a rapid diagnosis, and the initiation of professional treatment; a process in which the patient´s role was largely passive. However, with the rapid aging of the population and the growing prevalence of chronic diseases, improvement in quality of chronic care requires more than evidence about effective diagnostic procedures and treatments. Despite much progress in clinical and behavioral interventions, it is suggested that many chronically-ill patients do not profit from these advances [2].

In the current health care systems in European countries, a shift from disease management to chronic care management may prevent costly complications and frailty in elderly with T2DM, enabling them to live independent, healthy and active lives as long as possible. With the aim of describing essential elements for improving outcomes in care of chronic diseases, the Chronic Care Model (CCM) was developed in the mid-1990s and was further refined in 1997 [3,4]. As such, CCM is a primary care-based comprehensive model, advocating evidence-based changes in health care of patients with chronic disease. The model is based on the assumption that improvements in care require an approach that incorporates patients, health care providers, and system level interventions. It can be applied to a variety of chronic illnesses, health care settings and target populations, with the goal of healthier patients, more satisfied providers, and cost savings.

The CCM comprises six components deemed essential for providing high-quality care to patients with chronic disease:

1. health care organization (i.e. providing leadership for securing resources and removing barriers to care),
2. self-management support (i.e. facilitating skills-based learning and patient empowerment),
3. decision support (i.e. providing guidance for implementing evidence-based care),
4. delivery system design (i.e. coordinating care processes),
5. clinical information systems (i.e. tracking progress through reporting outcomes to patients and providers), and
6. community resources and policies (i.e. sustaining care by using community-based resources and public health policy).

Reports indicate a widespread application of CCM to multiple illnesses [5,6], yet, to date, only one study has reviewed how CCM has been applied in diabetes care in primary care settings and what the outcomes were of this implementation [7]. This systematic review showed that CCM approaches in the United States have indeed been effective in improving the health of individuals with diabetes who receive care in primary care settings. Regarding quality of diabetes care in Europe, observational studies have been performed in different European countries [8-11]. The recently published GUIDANCE study [12] reported encouraging levels of adherence to the main recommended process measures in diabetes care, e.g. HbA1c levels <7%, blood pressure <130mmHg (systolic) and <80 mmHg (diastolic), and LDL cholesterol concentrations <2.6 mmol/l. The level of actual achievement of these target goals by the individual patients was, on the other hand, much lower. Findings from the GUIDANCE study supported previously made suggestions [13-15] that process adherence may only have a limited influence in terms of reaching target goals (risk factor control) or enhanced management, e.g. appropriate adjustments to medication. Also, the existence of substantial between-country variation in quality of diabetes care in Europe was confirmed by the GUIDANCE study [12].

2. AIMS

This systematic review will focus on the scientific evidence regarding the specific treatment and care of elderly suffering from T2DM and associated comorbidities. Its aim is to summarize previous research on the effects of current European disease management models specifically related to the complex interaction between T2DM and comorbidities in the elderly, and on improving outcomes of interest.

3. OBJECTIVES (Research Question)

To assess the effects of chronic care models with a duration of at least 6 months on the following outcomes in older patients with T2DM and diabetes-related comorbidities:

- biophysical outcomes (e.g. serum HbA1c concentrations, and change in BMI),
- patient-reported outcomes (e.g. diabetes-related quality of life),
- diabetes complications (e.g. micro- and macrovascular complications),

compared to routine diabetes care.

4. METHODS

In the case of substantial clinical or statistical heterogeneity, study results will be combined in a narrative review only. Without substantial clinical and statistical heterogeneity, study results will be combined in a meta-analysis, following the approach described below. The subsequent reporting of the systematic review will be conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) statement [16].

Criteria for considering studies for this review

Types of studies

Studies will be eligible for inclusion if they are a randomized clinical trial (RCT). Only studies that have assessed outcome measures six months or more from baseline will be investigated.

Types of participants

Individuals, regardless of gender and ethnicity, with diagnosed T2DM with or without one of the following comorbidities, assessed and reported at baseline:

- Mental health problems (stress, depression, anxiety)
- Cancer
- Cardiovascular disease
- Osteoporosis
- Rheumatic arthritis
- Chronic obstructive pulmonary disease
- Neurological diseases
- Kidney diseases.

Ideally, the diagnostic criteria for T2DM are described in the study and were established using the standard criteria that were valid at the beginning of the trial (ADA 1997, NDDG 1979, WHO 1980, WHO 1985, WHO 1999), in order to be consistent with changes in T2DM classification and diagnostic criteria throughout the years.

We will include only studies in which the average age of the study population is ≥60 years, given that this is the usual age of diagnosis for most patients in Europe.

Type of interventions

Chronic care models/programs that meet the following criteria:

- specific for individuals with T2DM,
- based on guidelines,
- providing integrated (multi-disciplinary) care,
- addressing patient empowerment,
- providing quality management (e.g. patient registry systems, recording of process measures/adherence to guidelines, achievement of treatment goals),
- delivered in primary care and secondary care.

Type of controls

The intervention group will be compared with those participants undergoing routine diabetes care (standard care recommended in that particular country, e.g. regular follow-up with the required health professional and a full diabetes annual review).

Types of outcome measures

Primary outcomes

Biophysical outcomes:

- Metabolic control: hypoglycemia, serum HbA1c concentrations, serum lipids levels (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides), blood pressure, and glomerular filtration rate
- Change in BMI and other anthropometric measures (waist circumference, waist to hip ratio)

Patient-reported outcomes:

- Diabetes-related quality of life
- Participation in life style changing programs
- Communication
- Patient empowerment

Diabetes complications:

- Microvascular complications: retinopathy, nephropathy, and neuropathy
- Macrovascular complications: cardiovascular disease, cardiovascular risk scores, and cerebrovascular disease
- Diabetes-related mortality: total mortality and mortality due to major adverse cardiac events

Secondary outcomes

Mental Health:

- Depression
- Cognitive dysfunction or dementia
- Anxiety

Functionality:

- Frailty index
- Self-management skills: dietary habits, physical activity, medication administration, use of equipment
- Nutritional status
- Dependency on care

Contact to Health Care System:

- Number of yearly hospital visits
- Hospitalization: number of emergency admissions, and number and duration (days) of hospital stays.
- Adherence to treatment recommendations
- Quality of care
- Polypharmacy

Search methods for identification of studies

Electronic searches

Electronic databases will be searched from January 2000 until January 2014. We will use the following sources for the identification of trials:

- CENTRAL (the Cochrane Central Register of Controlled Trials)
- MEDLINE
- EMBASE
- CINAHL

Searching other resources

We aim to further identify studies by searching the reference list of each relevant trial and systematic review identified. First authors are contacted whenever additional information is required.

Data collection and analysis

Selection of studies

To determine which studies are to be assessed further, two reviewers (BB, WR) will independently scan the titles, abstracts and key words of every record retrieved. Full text articles will be retrieved if the title/abstract/key words suggest that the trial:

- included patients with T2DM, and
- evaluated a chronic diabetes care model.

In case of any doubt regarding these criteria from the information given in the title and abstract, or if the abstract was absent, the complete article will be retrieved for clarification. Studies will be eliminated if both reviewers agree that the criteria for considering studies for the review are not being met. Inter-rater agreement for study selection will be measured using the Kappa statistic [17]. Any differences in opinion will be discussed and, if necessary, resolved by a third reviewer (KM).

Data extraction and management

A structured data extraction form will be developed including the following information:

- General information: published/unpublished, title, authors, source/reference, contact address, country, language of publication, year of publication, sponsoring.
- Trial characteristics: design, duration, (method of) randomization, use of validated questionnaires, (method of) blinding (if appropriate).
- Intervention: comparison group included (routine care/no intervention), intervention (duration, timing).
- Participants: method of sampling, exclusion criteria, total number (also for comparison group(s)), sex, age, body mass index, ethnicity, pre-existing comorbidities/other medical conditions, standards of diabetes care (HbA1c concentration, serum glucose levels, lipid profile, blood pressure), diagnostic criteria T2DM, duration of T2DM, baseline comparison of the groups (including comorbidities), withdrawal from study/losses to follow-up, assessment of subgroups.

- Outcome: as specified above, main outcome as assessed in the trial, other outcomes/events assessed, quality of reporting the outcomes.
- Results: reported for outcomes and times of assessment.

If there is missing information, the authors of the article will be contacted. Differences in data extraction at item level will be resolved by discussion and if consensus is not reached, the third reviewer (KM) will take the final decision.

Assessment of risk of bias in included studies

The quality of reporting of each experimental trail will be assessed by two review authors independently (BB, WR). Risk of bias will be assessed using the Cochrane Collaboration´s tool [18]. In particular, the following factors will be studied.

Minimization of selection bias

- Randomization procedure (*if applicable*): the procedure will be scored adequate if the resulting sequences were unpredictable (computer generated schemes, coin tossing, and tables of random numbers).

Minimization of attrition bias

- Handling of drop-outs: will be considered adequate when the trial reports a complete description of all patients failing to participate until the end of the trial and if the data were analyzed on intention-to-treat (ITT) (thus with all randomized patients included). An overall drop-out rate less than 15%, and a selective drop-out rate less than 10% (the at risk groups), will be considered justifiable.

Minimization of detection bias

- Method of blinding for the outcome: will be considered adequate if the outcome assessors were completely blind for the intervention.

Assessment of heterogeneity

Variation between studies (heterogeneity) will be examined to answer the question whether the combination of the different studies is meaningful.

Clinical heterogeneity of the selected studies will be evaluated according to key characteristics of the study participants (age, gender, diabetes duration, blood glucose levels), the intervention, and study outcomes. Statistical heterogeneity will be estimated by visual inspection of the forest plots (the less overlap of confidence intervals, the more likely the presence of heterogeneity). Furthermore, heterogeneity will be assessed using the I^2-statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance or sampling error [19]. It allows for calculation across studies of varying sizes, study types and with varying outcome data. In case there is significant heterogeneity (I^2 values >75%), more emphasis will be placed on the results of a random-effects model, despite that the given model cannot overcome the problem of heterogeneity.

Data synthesis

Data will be summarized statistically if they are available, sufficiently similar, and of sufficient quality.

Subgroup analysis and investigation of heterogeneity

To explore potential source of (clinical) heterogeneity, subgroup analyses will be performed. Where performed, subgroup analysis will have a tentative (hypothesis-generating) purpose. The following subgroup analyses will be considered:

- Gender
- Duration of the intervention
- Duration of diabetes below and over five years (individuals who have diabetes for a longer time are likely to have more advanced disease and increased insulin resistance, and more complications; hence any forms of care may have a smaller effect in more advanced disease)
- Number of comorbidities

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of certain factors on effect size:

- Repeating the analysis excluding unpublished studies (if selected and included).
- Repeating the analysis taking risk of bias into account.
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results.
- Repeating the analysis excluding studies by using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

The robustness of the results will further be tested by repeating the analysis using different measures of effects size (risk difference, odds ratio, etc) and different statistic models (fixed and random effects models).

5. OUTLOOK

As the population ages, the burden of chronic disease is expected to grow continuously. While healthcare organizations need to find effective ways to deal with increased care demands, the CCM has been developed to advocate evidence-based changes in health care of patients with chronic disease. The findings of the current systematic review will contribute to our understanding of the relationship between application of CCM and qualitative and quantitative T2DM outcomes in European primary care settings. Finally, the results can provide insights into new approaches to further integrate the CCM into primary health care initiatives in diabetes.

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Supplementary file S2

Search strategy MEDLINE

1 Patient Education as Topic/

2 exp Self Care/

3 Self Efficacy/

4 ((patient* or consumer* or client*) adj3 (educat* or train* or teach* or instruct* or skill*)).tw.

5 (self care or self management or self efficacy or self monitoring).tw.

6 patient participation/

7 empowerment.tw.

8 (self adj (monitor* or manag* or care)).tw.

9 motivation/

10 (patient* adj2 (activation or psychosocial support or social support)).tw.

11 (collaborative decision making* or shared decision making*).tw.

12 or/1-11 (230620)

13 exp Education, Continuing/

14 Pamphlets/

15 Advance Directives/

16 (leaflet? or booklet? or poster or posters).tw.

17 ((written or printed or oral) adj information).tw.

18 Guideline Adherence/

19 (education* adj2 (program* or intervention* or meeting* or session* or strateg* or workshop* or visit*)).tw.

20 (behavio?r* adj2 intervention*).tw.

21 (education* adj1 (method? or material?)).tw.

22 ((opinion or education$ or influential) adj1 leader?).tw.

23 facilitator?.tw.

24 academic detailing.tw.

25 consensus conference?.tw.

26 (guideline? adj2 (introduc* or issu* or impact or effect* or disseminat* or distribut*)).tw.

27 ((effect* or impact or evaluat* or introduc* or compar*) adj2 training program*).tw.

28 practice guidelines as topic/

29 telemedicine/

30 ((effect? or impact or evaluat* or introduce* or compar*) adj2 (care program* or (prevent* adj program*))).tw.

31 guidelines as topic/

32 ((patient* or practice) adj guideline?).tw.

33 or/13-32

34 exp Patient Care planning/

35 Nurse clinicians/

36 Ambulatory Care/

37 Office Visits/

38 (nurse adj (clinician? or practitioner?)).tw.

39 (team? adj2 (care or treatment or assessment or consultation)).tw.

40 (integrat* adj2 (care or service?)).tw.

41 (care adj2 (coordinat* or program* or continuity)).tw.

42 (case adj1 management).tw.

43 outreach.tw.

44 disease management.tw.

45 disease management/

46 patient care team/

47 exp ambulatory care facilities/

48 nurse practitioners/

49 ((share* or step*) adj care).tw.

50 community matron*.tw.

51 or/34-50

52 Reminder Systems/

53 Medical Records/

54 Medical Records Systems, Computerized/

55 (register? or registry or registries).tw.

56 reminder?.tw.

57 (recall adj2 system*).tw.

58 (prompter? or prompting).tw.

59 chart review*.tw.

60 ((effect? or impact or records or chart?) adj2 audit).tw.

61 (information adj2 (management or system?)).tw.

62 hospital information systems/

63 ambulatory care information systems/

64 management information systems/

65 decision support systems, clinical/

66 ((introduce$ or impact or effect? or implement$ or computer$) adj2 protocol?).tw.

67 Feedback/ or feedback.tw.

68 (feedback adj1 (loop? or control? or regula* or mechanism? or inhib* or system? or circuit? or sensory or visual or audio* or auditory)).tw.

69 67 not 68

70 or/52-66,69

71 Reimbursement, incentive/

72 exp Reimbursement mechanisms/

73 Capitation Fee/

74 Physician Incentive Plans/

75 "Salaries and Fringe Benefits"/

76 Physician's Practice Patterns/

77 (quality adj (improvement or management or assurance)).tw.

78 ((continuous or total) adj quality).tw.

79 quality of health care/

80 quality assurance, health care/

81 total quality management/

82 quality improvement/

83 quality indicators, health care/

84 program evaluation/

85 technology assessment, biomedical/

86 exp Standard of care/

87 or/71-86

88 exp Diabetes Mellitus, Type 2/

89 exp Diabetes Complications/

90 (obes* adj3 diabet*).tw.

91 (MODY or NIDDM or T2DM or T2D).tw.

92 (non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend*).tw.

93 ((typ? 2 or typ? II or typ?2 or typ?II) adj3 diabet*).tw.

94 ((adult* or matur* or late or slow or stabl*) adj3 diabet*).tw.

95 or/88-94

96 exp Diabetes Insipidus/

97 diabet* insipidus.tw.

98 or/96-97

99 95 not 98

100 infan*.tw.

101 (newborn* or new born*).tw.

102 (perinat* or neonat*).tw.

103 (baby* or babies).tw.

104 toddler*.tw.

105 (boy or boys or boyhood).tw.

106 girl*.tw.

107 kid?.tw.

108 (child* or schoolchild*).tw.

109 adolescen*.tw.

110 juvenil*.tw.

111 youth*.tw.

112 teen*.tw.

113 pubescen*.tw.

114 Pediatrics/

115 p?ediatric*.tw.

116 school?.tw.

117 or/100-116

118 exp africa/

119 exp americas/

120 exp asia/

121 exp oceania/

122 or/118-121

123 randomized controlled trial.pt.

124 controlled clinical trial.pt.

125 randomized.ab.

126 placebo.ab.

127 drug therapy.fs.

128 randomly.ab.

129 trial.ab.

130 groups.ab.

131 exp animals/ not humans/

132 or/123-130

133 132 not 131

134 or/12,33,51,70,87

135 134 and 99 and 133

136 135 not 117 not 122

137 limit 136 to (english language and yr="2000 -Current")

Supplementary file S3

Results

Further biochemical outcomes

Three[33 44 41] out of the seven trials included in this review had assessed fasting glucose levels (mmol/l) (see supplementary figure S6). In Swiss patients with prevalent diabetes[44] no difference in change was found between the intervention and control group, while in Dutch patients with diabetes[33] there was a significantly higher reduction in glucose concentrations after one year of intervention, in favour of the control group. In newly diagnosed diabetes patients,[41] the intervention group was observed to have a significantly higher reduction in fasting glucose levels then the control group after six years of intervention.

Six[33 39 41 43 45 46] out of seven trials had measured triglyceride concentrations (mmol/l), yet, multifaceted care did not significantly impact triglyceride levels in any of the studies (see supplementary figure S7).

Creatinine levels were assessed in three[33 41 46] out of the seven trials. Only the pooled five-year results from Addition-Europe[46] showed a significant difference in change between the trial arms, favouring the control arm over the intervention arm (see supplementary figure S8).

Further diabetes complications and related outcomes

Episodes of severe hypoglycaemia were assessed in only one[44] of the three studies with prevalent diabetes patients, in which severe hypoglycaemia was defined as having one or more episodes of hypoglycaemia with clinical symptoms and or requiring hospitalization. Episodes were reported for 19 (11.6%) patients in the intervention group and for eight (5.1%) in the control

group, without further statistical evaluation. In the remaining trials[39 41 43 46] the proportion of individuals reporting hypoglycaemia did not differ between intervention and control arm.

A major aim of the Dutch trial[33] and of the Addition studies[35 39 40 43] was to examine the effect of multifaceted care on cardiovascular risk. To that purpose, authors calculated the 10-year coronary heart disease risk estimate (%) as established by the UK Prospective Diabetes Study (UKPDS). This risk score is calculated using the following variables: the date of diabetes onset, sex, ethnicity, smoking, HbA1c, systolic blood pressure, total cholesterol and HDL-cholesterol. The Dutch authors observed a 1.4% greater decrease in 10-year UKPDS coronary heart disease risk in the intervention group compared to the control group.[33] Within the Addition-Leicester trial,[43] a 5-year UKPDS risk of cardiovascular heart disease was calculated. A significant difference in risk reduction of 1.49% between intervention and control group was found in favour of the intervention group. In the Addition-Europe study,[46] the authors assessed hazard ratios for a composite endpoint of cardiovascular events (any cardiovascular death, myocardial infarction, stroke, revascularization and amputation) at five years of intervention. This endpoint occurred similarly frequent and with similar risk in intervention and control patients. Furthermore, improvements in every singular component of this composite endpoint all favoured the intervention group over the control group, although no comparison reached statistical significance.

Out of the three trials with prevalent diabetes patients, only the Swiss trial[44] reported data on (changes in) medication use. The authors observed no significant changes between the two trial groups in medication use (yes/no variable) concerning antidiabetic therapy, antihypertensive therapy, and lipid-lowering therapy. In contrast to patients with prevalent diabetes, for patients with screen-detected diabetes[43] multifaceted care resulted in a larger number of antihypertensive-, lipid-lowering and anti-platelet therapy after one year, compared to usual care. This was also observed after pooling of the five-year findings from the Addition studies.[46] In

newly diagnosed diabetes patients[41] however, the only between-group difference that was observed with regard to medication intake was the more extensive use of metformin in the intervention group (39 (9%)) compared to the control group (16 (4%)).

Supplementary Figure S1

HDL-Cholesterol (mmol/l)

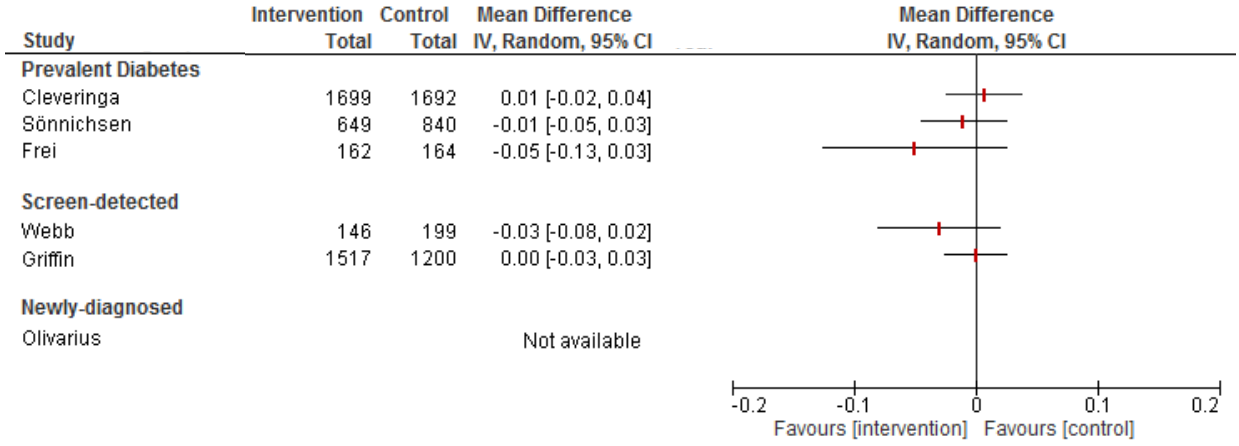

Figure S1: Overview of the mean differences in change (95% confidence interval) between intervention and control groups in HDL-cholesterol levels (mmol/l) after multifaceted care. Results are stratified by type of diabetes patient.

IV; generic inverse variance method, CI: confidence interval

The studies by Cleveringa[33], Sönnichsen[45], and Frei[44] *et al*. had an intervention duration of one year. The methodology for calculating the difference in change between intervention and control group that Cleveringa[33] *et al* have used (subtracting the mean difference in change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the mean difference in change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al.*,[33] we have recalculated their results for HDL-cholesterol levels according to the methodology applied by the other studies.

The study by Webb *et al.*[43] had an intervention duration of one year and the study by Griffin *et al.*[46] had a duration of five years. This study combined the five-year intervention data from all four Addition studies (Addition-Denmark, Addition-Netherlands, Addition-Cambridge, and Addition-Leicester), including the five-year data from Webb et al. (Addition-Leicester).[43]

The study by Olivarius *et al.*[41] had an intervention duration of six years.

Supplementary Figure S2

LDL-Cholesterol (mmol/l)

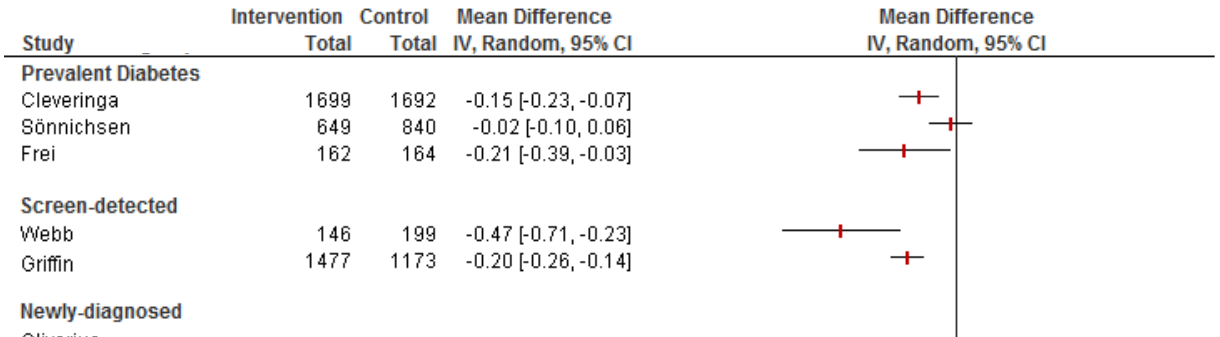

Figure S2: Overview of the mean differences in change (95% confidence interval) between intervention and control groups in LDL-cholesterol levels (mmol/l) after multifaceted care. Results are stratified by type of diabetes patient.

IV; generic inverse variance method, CI: confidence interval

The studies by Cleveringa[33], Sönnichsen[45], and Frei[44] *et al*. had an intervention duration of one year. The methodology for calculating the difference in change between intervention and control group that Cleveringa[33] *et al* have used (subtracting the mean difference in change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the mean difference in change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al.*,[33] we have recalculated their results for LDL-cholesterol levels according to the methodology applied by the other studies.

The study by Webb *et al.*[43] had an intervention duration of one year and the study by Griffin *et al.*[46] had a duration of five years. This study combined the five-year intervention data from all four Addition studies (Addition-Denmark, Addition-Netherlands, Addition-Cambridge, and Addition-Leicester), including the five-year data from Webb et al. (Addition-Leicester).[43]

The study by Olivarius *et al.*[41] had an intervention duration of six years.

Supplementary Figure S3

Diastolic blood pressure (mmHg)

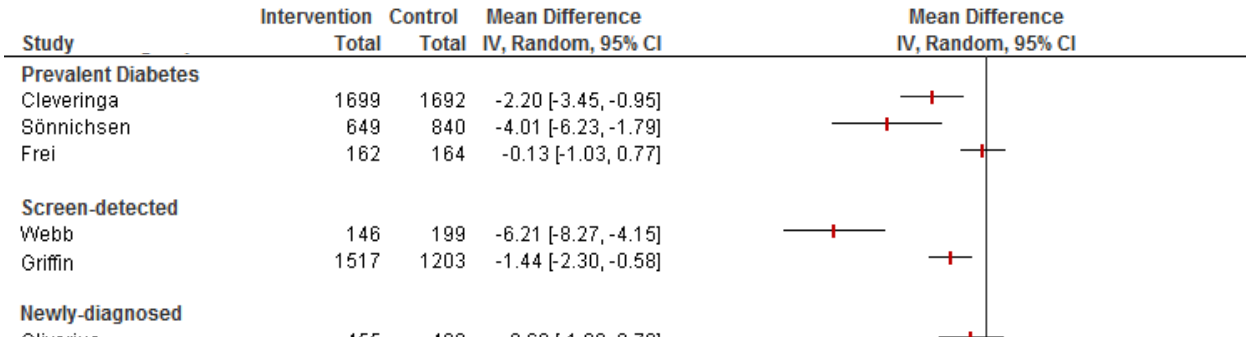

Figure S3: Overview of the mean differences in change (95% confidence interval) between intervention and control groups in diastolic blood pressure (mm Hg) after multifaceted care. Results are stratified by type of diabetes patient.

IV; generic inverse variance method, CI: confidence interval

The studies by Cleveringa[33], Sönnichsen[45], and Frei[44] *et al*. had an intervention duration of one year. The methodology for calculating the difference in change between intervention and control group that Cleveringa[33] *et al* have used (subtracting the mean difference in change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the mean difference in change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al.*,[33] we have recalculated their results for diastolic blood pressure according to the methodology applied by the other studies.

The study by Webb *et al.*[43] had an intervention duration of one year and the study by Griffin *et al.*[46] had a duration of five years. This study combined the five-year intervention data from all four Addition studies (Addition-Denmark, Addition-Netherlands, Addition-Cambridge, and Addition-Leicester), including the five-year data from Webb et al. (Addition-Leicester).[43]

The study by Olivarius *et al.*[41] had an intervention duration of six years.

Supplementary Figure S4

Systolic blood pressure (mmHg)

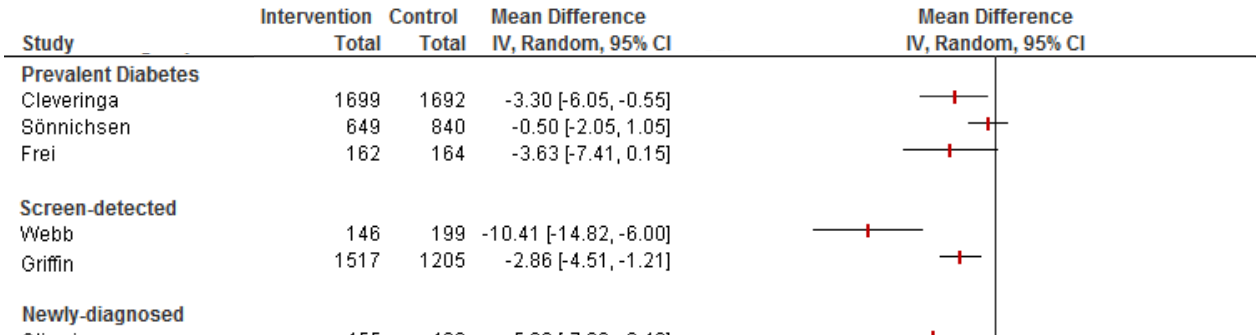

Figure S4: Overview of the mean differences in change (95% confidence interval) between intervention and control groups in systolic blood pressure (mm Hg) after multifaceted care. Results are stratified by type of diabetes patient.

IV; generic inverse variance method, CI: confidence interval

The studies by Cleveringa[33], Sönnichsen[45], and Frei[44] *et al*. had an intervention duration of one year. The methodology for calculating the difference in change between intervention and control group that Cleveringa[33] *et al* have used (subtracting the mean difference in change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the mean difference in change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al.*,[33] we have recalculated their results for systolic blood pressure according to the methodology applied by the other studies.

The study by Webb *et al.*[43] had an intervention duration of one year and the study by Griffin *et al.*[46] had a duration of five years. This study combined the five-year intervention data from all four Addition studies (Addition-Denmark, Addition-Netherlands, Addition-Cambridge, and Addition-Leicester), including the five-year data from Webb et al. (Addition-Leicester).[43]

The study by Olivarius *et al.*[41] had an intervention duration of six years.

Supplementary Figure S5

BMI

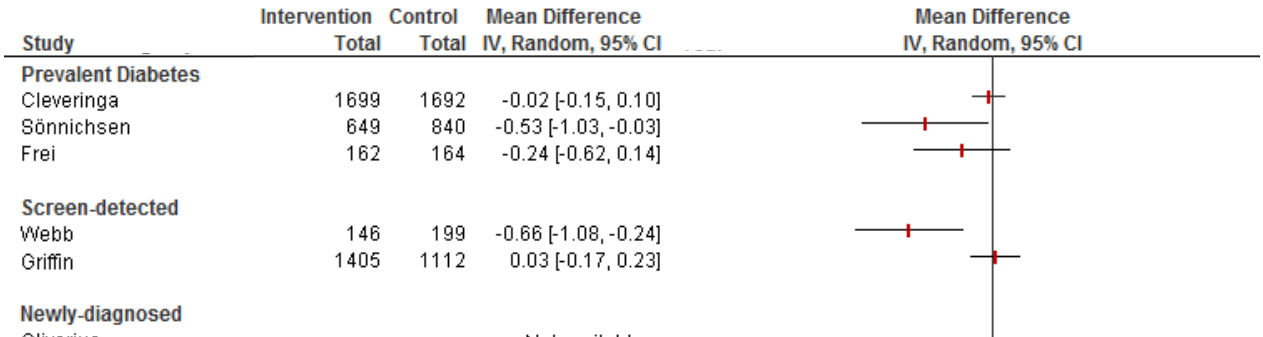

Figure S5: Overview of the mean differences in change (95% confidence interval) between intervention and control groups in BMI (kg/m^2) after multifaceted care. Results are stratified by type of diabetes patient.

IV; generic inverse variance method, CI: confidence interval

The studies by Cleveringa[33], Sönnichsen[45], and Frei[44] *et al*. had an intervention duration of one year. The methodology for calculating the difference in change between intervention and control group that Cleveringa[33] *et al* have used (subtracting the mean difference in change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the mean difference in change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al.*,[33] we have recalculated their results for BMI according to the methodology applied by the other studies.

The study by Webb *et al.*[43] had an intervention duration of one year and the study by Griffin *et al.*[46] had a duration of five years. This study combined the five-year intervention data from all four Addition studies (Addition-Denmark, Addition-Netherlands, Addition-Cambridge, and Addition-Leicester), including the five-year data from Webb et al. (Addition-Leicester).[43]

The study by Olivarius *et al.*[41] had an intervention duration of six years.

Supplementary Figure S6

Fasting glucose (mmol/l)

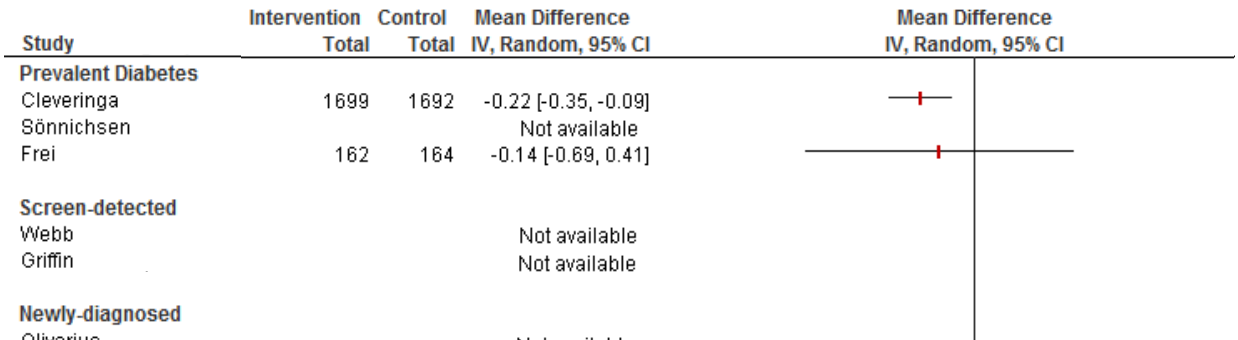

Figure S6: Overview of the mean differences in change (95% confidence interval) between intervention and control groups in fasting glucose concentrations (mmol/l) after multifaceted care. Results are stratified by type of diabetes patient.

IV; generic inverse variance method, CI: confidence interval

The studies by Cleveringa[33], Sönnichsen[45], and Frei[44] *et al*. had an intervention duration of one year. The methodology for calculating the difference in change between intervention and control group that Cleveringa[33] *et al* have used (subtracting the mean difference in change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the mean difference in change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al.*,[33] we have recalculated their results for fasting glucose levels according to the methodology applied by the other studies.

The study by Webb *et al.*[43] had an intervention duration of one year and the study by Griffin *et al.*[46] had a duration of five years. This study combined the five-year intervention data from all four Addition studies (Addition-Denmark, Addition-Netherlands, Addition-Cambridge, and Addition-Leicester), including the five-year data from Webb et al. (Addition-Leicester).[43]

The study by Olivarius *et al.*[41] had an intervention duration of six years.

Supplementary Figure S7

Triglycerides (mmol/l)

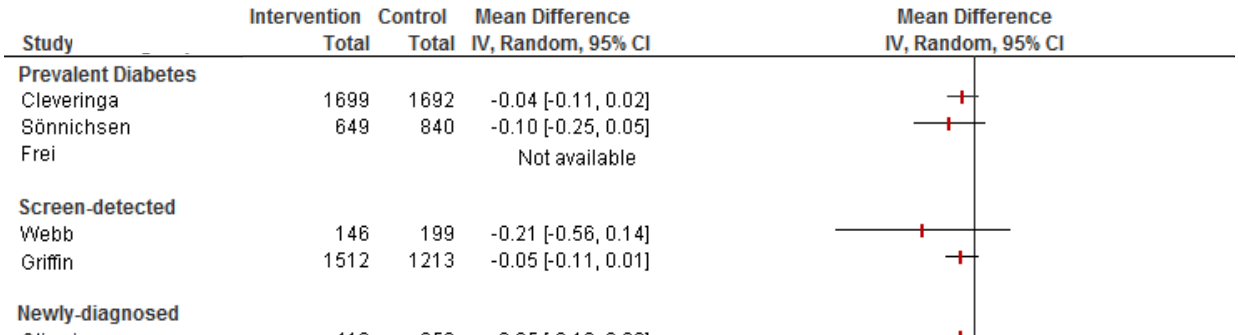

Figure S7: Overview of the mean differences in change (95% confidence interval) between intervention and control groups in triglyceride levels (mmol/l) after multifaceted care. Results are stratified by type of diabetes patient.

IV; generic inverse variance method, CI: confidence interval

The studies by Cleveringa[33], Sönnichsen[45], and Frei[44] *et al*. had an intervention duration of one year. The methodology for calculating the difference in change between intervention and control group that Cleveringa[33] *et al* have used (subtracting the mean difference in change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the mean difference in change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al.*,[33] we have recalculated their results for triglyceride levels according to the methodology applied by the other studies.

The study by Webb *et al.*[43] had an intervention duration of one year and the study by Griffin *et al.*[46] had a duration of five years. This study combined the five-year intervention data from all four Addition studies (Addition-Denmark, Addition-Netherlands, Addition-Cambridge, and Addition-Leicester), including the five-year data from Webb et al. (Addition-Leicester).[43]

The study by Olivarius *et al.*[41] had an intervention duration of six years.

Supplementary Figure S8

Creatinine (umol/l)

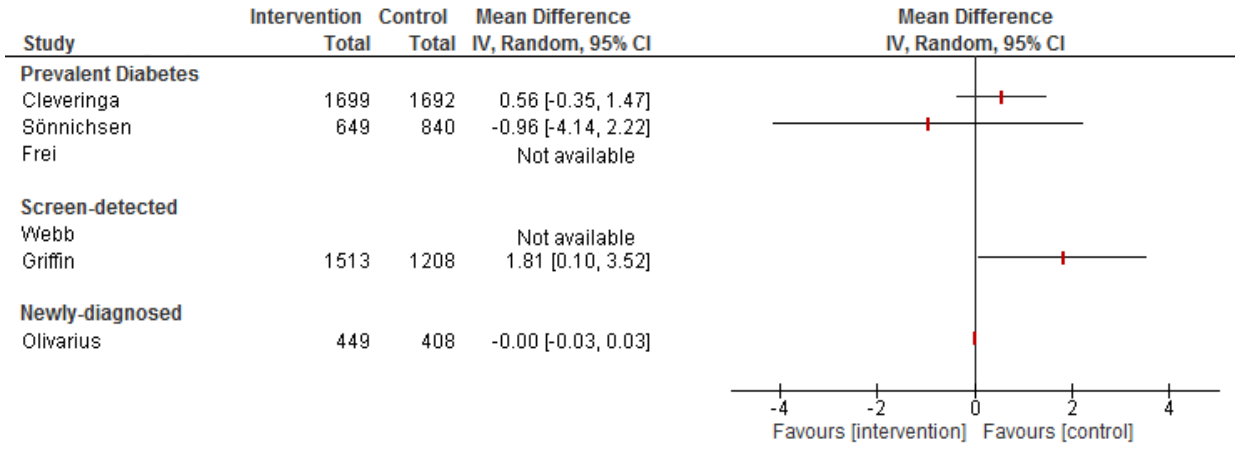

Figure S8: Overview of the mean differences in change (95% confidence interval) between intervention and control groups in creatinine levels (umol/l) after multifaceted care. Results are stratified by type of diabetes patient.

IV; generic inverse variance method, CI: confidence interval

The studies by Cleveringa[33], Sönnichsen[45], and Frei[44] *et al*. had an intervention duration of one year. The methodology for calculating the difference in change between intervention and control group that Cleveringa[33] *et al* have used (subtracting the mean difference in change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the mean difference in change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al.*,[33] we have recalculated their results for creatinine levels according to the methodology applied by the other studies.

The study by Webb *et al.*[43] had an intervention duration of one year and the study by Griffin *et al.*[46] had a duration of five years. This study combined the five-year intervention data from all four Addition studies (Addition-Denmark, Addition-Netherlands, Addition-Cambridge, and Addition-Leicester), including the five-year data from Webb et al. (Addition-Leicester).[43]

The study by Olivarius *et al.*[41] had an intervention duration of six years.