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Effectiveness of disease-management programs for improving diabetes care: a meta-analysis

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Abstract

Background: We conducted a meta-analysis of randomized controlled trials to assess the effectiveness of disease-management programs for improving glycemic control in adults with diabetes mellitus and to study which components of programs are associated with their effectiveness.

Methods: We searched several databases for studies published up to December 2009. We included randomized controlled trials involving adults with type 1 or 2 diabetes that evaluated the effect of disease-management programs on glycated hemoglobin (hemoglobin A_{1C}) concentrations. We performed a meta-regression analysis to determine the effective components of the programs.

Results: We included 41 randomized controlled trials in our review. Across these trials, disease-management programs resulted in a significant reduction in hemoglobin A_{1C} levels (pooled standardized mean difference between intervention and control groups –0.38 [95% confidence interval –0.47 to –0.29], which corresponds to an absolute mean difference of 0.51%). The finding was robust in the sensitivity analyses based on quality assessment. Programs in which the disease manager was able to start or modify treatment with or without prior approval from the primary care physician resulted in a greater improvement in hemoglobin A_{1C} levels (standardized mean difference –0.60 v. –0.28 in trials with no approval to do so; $p < 0.001$). Programs with a moderate or high frequency of contact reported a significant reduction in hemoglobin A_{1C} levels compared with usual care; nevertheless, only programs with a high frequency of contact led to a significantly greater reduction compared with low-frequency contact programs (standardized mean difference –0.56 v. –0.30, $p = 0.03$).

Interpretation: Disease-management programs had a clinically moderate but significant impact on hemoglobin A_{1C} levels among adults with diabetes. Effective components of programs were a high frequency of patient contact and the ability for disease managers to adjust treatment with or without prior physician approval.

Despite well-established recommendations for diabetes care,[1–3] quality of care still needs to be improved. Although many nonpharmacologic strategies (patient education, psychological intervention, dietary education, self-monitoring and telemedicine) have been developed, their effectiveness is still unclear.[4–6] "Disease management" is a structured, multifaceted intervention that includes several of the above-mentioned components. In two recent meta-analyses, disease management was associated with an improvement in glycemic control, as assessed by a mean reduction in hemoglobin A_{1C} concentration of 0.52% and 0.81%.[7,8] Disease management seems to be more effective than single strategies such as clinician education, patient education or promotion of self-management.[7]

Because disease-management programs are heterogeneous, the effective components need to be identified to improve program implementation. Previous studies have evaluated the efficacy of some program components.[7,8] Independent medication changes by the disease manager appear to be particularly effective.[7] However, other important factors such as the intensity of the intervention have not been previously evaluated.

We conducted a meta-analysis of randomized controlled trials (RCTs) involving adults with type 1 or 2 diabetes mellitus that evaluated the effect of disease-management programs on hemoglobin A_{1C} levels. We determined the effective components of the programs, considering both the type of component and the intensity of the intervention.

Methods

Definition of disease management

There is no consensual definition of disease management. According to the Care Continuum Alliance (formerly the Disease Management Association of America), disease management "supports the physician or practitioner/patient relationship and plan of care; emphasizes prevention of exacerbations and complications utilizing evidence-based practice guidelines and patient empowerment strategies; and evaluates clinical, humanistic, and economic outcomes on an on-going basis with the goal of improving overall health" (www.carecontinuum.org/dm_definition.asp). To identify relevant studies for our meta-analysis, we adopted an operational definition based on the above definition, literature review and expert opinion.

We defined disease management as ongoing and proactive follow-up of patients that includes at least two of the following five components: patient education (dietary and exercise counselling, self-monitoring, and knowledge of disease and medication); coaching (the disease manager encourages the patient to overcome psychological or social barriers that impede autonomy or improvement in medication compliance); treatment adjust-

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ment (the disease manager is able to start or modify treatment with or without prior approval from the primary care physician); monitoring (the disease manager gets medical data from the patient); and care coordination (the disease manager reminds the patient about upcoming appointments or important aspects of self-care and informs the primary care physician about complications, treatment adjustment or therapeutic recommendations).

Literature search

We searched the following computerized databases: MEDLINE (1966 to December 2009), Scopus (1960 to December 2009), Web of Science (1975 to December 2009) and the Cochrane Library (1993 to 2009 [issue 4]) The complete MEDLINE search strategy is presented in Appendix 1 (available at www.cmaj.ca/cgi/content/full/cmaj.091786/DC1). In an attempt to minimize the omission of potentially relevant trials, we also searched the reference lists of included studies. We used the terms "patient care team," "disease management," "case management," "managed care programs," "home-based intervention" and "patient care management" to cover the inconsistency in the definition of disease management; we also used the terms "diabetes mellitus," "HbA_{1C}" and "glycated hemoglobin."

Two of us (C.P. and C.H.) first reviewed the titles and abstracts of identified articles and then examined the full-text version of selected articles further to assess relevance to the research topic. Only RCTs were included, because this study design supports maximum validity and causal inference.[9] The search was limited to English-language publications. We restricted inclusion to studies that reported hemoglobin A_{1C} levels, which is an index of the mean blood glucose concentration of the preceding 8–12 weeks.[10] In addition to our operational definition of disease management, we defined the following inclusion criteria: the study had to involve adults with type 1 or 2 diabetes; it had to report both pre- and postintervention hemoglobin A_{1C} levels; and postintervention hemoglobin A_{1C} levels had to be assessed after at least 12 weeks of follow-up.

We excluded trials in which the intervention did not involve direct contact between the disease manager and the patient or was unclear, unspecified or exclusively based on contact by Internet or mail.

Data extraction

Two of us (C.P. and C.H.) evaluated each study separately and extracted data. To assess outcome, hemoglobin A_{1C} levels before and after the intervention were extracted. In the event of several postintervention values, only the first one was considered. Other data extracted were as follows: characteristics of the participants (percentage of women, mean age), sample size, number of dropouts, intervention mode (one-to-one session, phone contact or both), type of program components (patient education, psychological coaching, monitoring, feedback of initial evaluation to primary care physician, treatment adjustment), length of intervention, frequency of contact, interval between pre- and postintervention hemoglobin A_{1C} assessments, and adverse events (hypoglycemic episodes, hospital admission and death).

Frequency of contact was estimated on the basis of the reported intervention protocol and, when available, the results. We classified the frequency into three levels: low (less than one contact monthly per patient), moderate (one contact monthly per patient) and high (several contacts monthly per patient). In the event of discrepancies in the classification of contact frequency, data were reviewed by another one of us (M.L.G.), and a consensus was reached.

When data were missing, the original authors of the article were contacted by email.

Statistical analysis

To account for differences in baseline hemoglobin A_{1C} levels between the studies, we calculated the mean difference between pre- and postintervention hemoglobin A_{1C} levels for the intervention and control groups, and the standard deviation (SD) of each difference. Thus, our outcome corresponds to the improvement in glycemic control in the intervention group between baseline and postintervention hemoglobin A_{1C} levels compared with the control group. We used the imputation method according to baseline values for missing SDs (we imputed missing SDs according to the pre-intervention values). Owing to significant heterogeneity, we used a random-effects model to calculate the pooled standardized mean difference in hemoglobin A_{1C} levels between the intervention and control groups, along with the 95% confidence interval (CI).[11] Heterogeneity was quantified by using I^2 and τ^2 (study variance) values.[12,13]

We used meta-regression analysis to determine what part of between-study variance was explained by patient characteristics (mean hemoglobin A_{1C} level, age, sex) and components of the disease-management programs (length of intervention, treatment adjustment, mode of patient education, frequency of contact, feedback of initial evaluation to primary care physician, and mode of intervention). Results are expressed as standardized mean changes in the hemoglobin A_{1C} level. Explained heterogeneity was expressed as a percentage change of τ^2 (between-study variance).

Because quality assessment in meta-analysis is controversial,[14] we performed three sensitivity analyses based on key components of internal validity to test the robustness of our results.[15] In the first sensitivity analysis, we excluded trials that had a dropout rate of 20% or more and trials without dropout information. In the second analysis, we excluded trials in which the difference in dropout rates between study groups was 7% or more (highest quintile) and trials without dropout information. In the third analysis, we excluded trials with unclear information about allocation concealment.[16]

For all analyses, a p value of 0.05 or less was considered to be statistically significant.

Results

Study characteristics

The selection of studies for our review is summarized in Figure 1.[17] The initial search strategy identified 2148 citations, and 135 full-text articles were reviewed. Forty-four studies met our inclusion criteria. Three studies were excluded because of missing data on hemoglobin A_{1C} levels at baseline, even after contacting the authors.[18–20] Thus, we included 41 RCTs published between 1990 and 2009 that enrolled a total of 7013 adults with type 1 or 2 diabetes.[21–61]

The main features of the 41 RCTs are shown in Table 1 (at the end of the article). Twenty-six trials were conducted in the United States, five in Canada, three in Europe and seven in Asia. Sample sizes ranged from 31 to 1665. The length of the intervention ranged from 1.5 to 48 months. In most trials, the length of intervention and the length of follow-up were similar, with only five trials reporting a few months' difference between the end of the intervention and hemoglobin A_{1C} assessment.[21,23,29,39,49] Most of the studies (29 trials) focused solely on type 2 diabetes, 9 included patients with either type 1 or 2 diabetes, and 3 trials focused on type 1 diabetes. The mean age of the participants was 57.6 years (SD 7.3); 46.0% were men. The mean hemoglobin A_{1C} concentration at baseline was 8.5% (SD 1.4%).

Effect of intervention on glycemic control

The impact of the disease-management programs on changes in hemoglobin A_{1C} concentrations in the intervention and control groups is presented in Figure 2. In the random-effects model, the pooled standardized mean difference in levels between the intervention and control groups was –0.38 (95% CI –0.47 to –0.29; $p < 0.001$), favouring disease management over usual care. This standardized mean difference corresponds to an absolute mean difference in hemoglobin A_{1C} levels of 0.51% between the intervention and control groups. None of the studies reported a significant change in hemoglobin A_{1C} in favour of usual care. There was significant heterogeneity among the trials regarding changes in hemoglobin A_{1C} ($I^2 = 66\%$).[62]

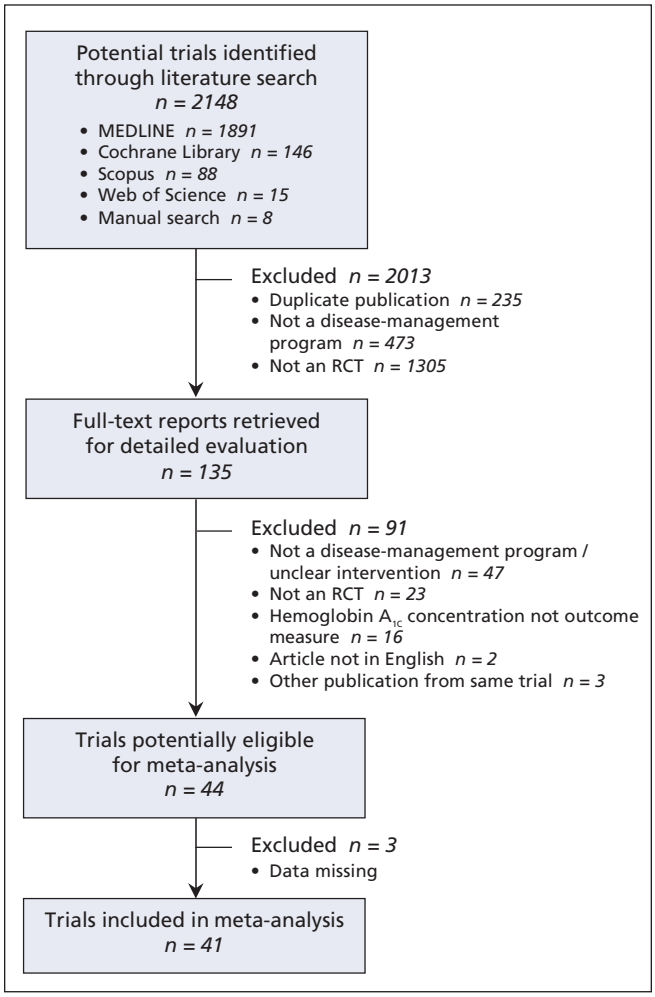

Figure 1: Selection of randomized controlled trials (RCTs) for the meta-analysis.

Meta-regression and subgroup analyses

Results of univariable meta-regression analyses, stratified by patient characteristics and components of the disease-management programs, are shown in Table 2. Of the patient characteristics analyzed, age and sex were not associated with between-group differences in hemoglobin A_{1C} outcomes. The reduction in hemoglobin A_{1C} levels was significantly greater among patients with a baseline hemoglobin A_{1C} level of 8.0% or higher (standardized mean difference –0.45) than among those with a baseline level of less than 8.0% (standardized mean difference –0.14) ($p = 0.003$). About 33% of the variance between trials could be explained by mean hemoglobin A_{1C} values at baseline.

Two components of the disease-management programs led to greater improvements in glycemic control (Table 2). First, programs in which the disease manager was able to start or modify treatment with or without prior approval from the primary care physician resulted in a significantly greater reduction in hemoglobin A_{1C} levels (standardized mean difference –0.60 v. –0.28 in trials with no approval to do so; $p < 0.001$). Second, among the 36 trials that reported sufficient information to allow classification of the frequency of patient contact (Table 1), programs with a moderate or high frequency of contact (28 trials) reported a significant reduction in hemoglobin A_{1C} levels compared with usual care (standardized mean difference –0.56 for high frequency and –0.24 for moderate frequency). Nevertheless, only programs with a high frequency of contact led to a significantly greater reduction in hemoglobin A_{1C} levels compared with programs with a low frequency of contact (standardized mean difference –0.56 v. –0.30, $p = 0.03$).

In the random-effects subgroup analyses, none of the other program components modified the effectiveness of the intervention on hemoglobin A_{1C} levels. Two components explained a large part of the variance between trials: 31.9% was explained by mode of education and 39.2% by treatment adjustment. Trials in which the disease manager was able to start or modify treatment with or without prior approval of the physician, trials with face-to-face sessions and trials with a moderate frequency of patient contact each showed a low level of heterogeneity ($I^2 < 50\%$).

Sensitivity analyses

Our primary findings did not change after we excluded trials with dropout rates of 20% or more and trials without dropout information (Table 3). The same was true after we excluded trials with a between-group difference in dropout rates of 7% or more and trials without dropout information, and after we excluded trials with unclear allocation concealment (Table 3).

Adverse events

Hypoglycemic episodes were not systematically assessed. Only 9 of the 41 studies reported this information separately for intervention and control groups, but with varied definitions of

hypoglycemic episodes.[22,25,27,31,40,43,45–47] No difference in hypoglycemic episodes between study groups was reported in six of the nine trials. In two of the three trials that reported a difference, the adverse event occurred more frequently in the control groups than in the intervention groups.[31,45] Twenty studies reported deaths over the follow-up period; no overall difference in mortality between groups was found (p = 0.18). Hospital admissions were not clearly or systematically reported.

Interpretation

Our meta-analysis suggests that disease-management programs have a favourable effect on improving glycemic control, with a pooled standardized mean reduction of 0.38 (corresponding to a pooled absolute mean reduction of 0.51%) in hemoglobin A_{1C} levels compared with usual care. This finding was robust in sensitivity analyses based on quality assessment. The United

Study	Mean change in HbA_{1c}, %		Standardized mean difference between groups (95% CI)
	Intervention	Control	
Ahring et al.[22]	–1.4	–1.0	–0.17 (–0.81 to 0.47)
Choe et al.[44]	–2.1	–0.9	–0.52 (–1.02 to –0.02)
Dale et al.[58]	–0.9	–0.8	–0.07 (–0.46 to 0.32)
Doucette et al.[59]	–0.3	0.1	–0.27 (–0.76 to 0.21)
Estey et al.[21]	–0.7	–0.3	–0.49 (–1.03 to 0.06)
Farmer et al.[45]	–0.6	–0.4	–0.16 (–0.60 to 0.28)
Franz et al.[23]	–1.1	–0.8	–0.20 (–0.49 to 0.09)
Fukuda et al.[26]	–0.2	–0.2	0.00 (–0.55 to 0.55)
Gabbay et al.[50]	–0.1	0.0	–0.03 (–0.25 to 0.18)
Gaede et al.[27]	–0.8	0.2	–0.57 (–0.89 to –0.24)
Gary et al.[38]	–1.0	–0.2	–0.79 (–1.28 to –0.30)
Goudswaard et al.[39]	–1.0	–0.4	–0.47 (–1.01 to 0.07)
Hiss et al.[32]	–0.3	–0.2	–0.08 (–0.32 to 0.16)
Hiss et al.[54]	–0.4	–0.2	–0.14 (–0.44 to 0.17)
Jaber et al.[25]	–2.2	–0.1	–0.73 (–1.38 to –0.07)
CMD Study[40]	–1.9	–1.2	–0.50 (–0.72 to –0.27)
Kim et al.[60]	–1.3	–0.4	–0.66 (–1.11 to –0.21)
Ko et al.[41]	–0.5	–0.2	–0.24 (–0.53 to 0.06)
Ko et al.[55]	–1.5	–0.5	–0.80 (–1.03 to –0.57)
Krein et al.[42]	0.0	0.0	0.00 (–0.27 to 0.27)
Litaker et al.[34]	–0.6	–0.1	–0.39 (–0.71 to –0.07)
McMahon et al.[47]	–1.6	–1.2	–0.28 (–0.71 to 0.14)
Montori et al.[43]	–1.3	–0.6	–0.59 (–1.35 to 0.17)
Ménard et al.[46]	–1.6	–0.7	–0.71 (–1.20 to –0.22)
Oh et al.[35]	–1.2	0.6	–1.26 (–1.96 to –0.56)
Piette et al.[33]	–0.6	–0.3	–0.30 (–0.57 to –0.03)
Piette et al.[31]	–0.1	0.1	–0.13 (–0.37 to 0.11)
Polonsky et al.[36]	–2.3	–1.7	–0.30 (–0.66 to 0.07)
Ridgeway et al.[28]	–0.8	–0.7	–0.04 (–0.67 to 0.60)
Rothman et al.[48]	–2.5	–1.6	–0.45 (–0.73 to –0.16)
Sadur et al.[29]	–1.2	–0.3	–0.69 (–1.01 to –0.37)
Samuel-Hodge et al.[61]	–0.3	–0.2	–0.08 (–0.39 to 0.22)
Scott et al.[51]	–1.7	–0.7	–0.99 (–1.36 to –0.63)
Shea et al.[52]	–0.4	–0.2	–0.13 (–0.23 to 0.04)
Shibayama et al.[53]	–0.1	0.0	–0.08 (–0.26 to 0.42)
Sun et al.[57]	–0.8	–0.1	–0.54 (–0.89 to –0.19)
Taylor et al.[37]	–1.1	–0.3	–0.66 (–1.02 to –0.30)
Taylor et al.[49]	–0.3	0.7	–0.70 (–1.35 to –0.05)
Thompson et al.[30]	–1.8	–0.5	–0.98 (–1.59 to –0.37)
Wattana et al.[56]	–0.7	–0.1	–0.50 (–0.83 to –0.17)
Weinberger et al.[24]	–0.2	0.4	–0.30 (–0.59 to –0.01)
Overall (I^2 = 66%)	–0.62	–0.25	–0.38 (–0.47 to –0.29)

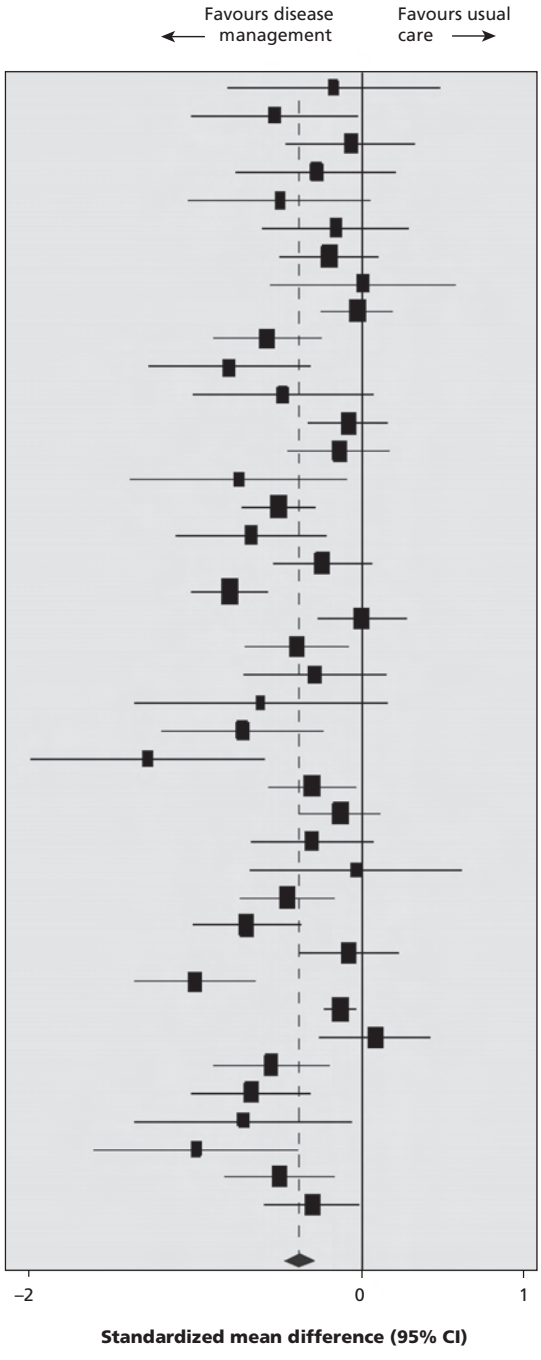

Figure 2: Estimated differences in hemoglobin A_{1C} level before and after intervention of disease management for improved glycemic control in adults with type 1 or 2 diabetes mellitus. Standardized mean differences between intervention and control groups of less than zero indicate an effect in favour of disease-management programs. CI = confidence interval, CMD study = California Medi-Cal Type 2 Diabetes Study.

Kingdom Prospective Diabetes Study showed that each 1% reduction in hemoglobin A_{1C} level was associated with a 37% decrease in the risk of microvascular complications and a 21% decrease in the risk of death related to diabetes, with no evidence of a threshold.[63] Therefore, the absolute reduction of 0.51% in hemoglobin A_{1C} level in our study appears to be clinically significant. Moreover, this finding is probably largely underestimated, because the usual care provided in control groups in RCTs is often better than that provided in clinical practice. Indeed, there was a significant standardized mean reduction in hemoglobin A_{1C} levels of −0.25 in the control groups, which corresponds to an absolute mean reduction of 0.40%. Some studies included in our meta-analysis permitted patients in the control group to contact the medical team or be contacted by them during follow-up in addition to usual care.[23,43,55] Also, patients received structured individual education before randomization in some trials.[21,23]

Our findings suggest that disease-management programs are more effective for patients who have poor glycemic control (mean hemoglobin $A_{1C} \geq 8.0\%$ at baseline) than for those with better glycemic control. This is concordant with results among patients starting insulin therapy.[64] Thus, disease management could be particularly effective if targeted at patients with nonstabilized diabetes. Moreover, such patients have a higher risk of complications and so would probably derive greater long-term benefit from disease management.

Table 2: Effect of patient characteristics and components of disease-management programs on changes in hemoglobin A_{1c} concentration

Variable	No. of studies	Standardized mean difference in change of hemoglobin A_{1c} between intervention and control groups (95% CI)	*p* value for difference in effect*	Heterogeneity,† I^2 (95% CI), %	Variance between studies explained by variable, %
Patient characteristic					
Mean HbA_{1c} level at baseline	40‡				32.7
< 8.0%	11	–0.14 (–0.25 to –0.05)		25 (0 to 63)	
≥ 8.0%	29	–0.45 (–0.56 to –0.34)	0.003	59 (38 to 73)	
Age	36‡	0.01 (–0.01 to 0.02)	0.23		22.2
Sex	39‡	0.00 (–0.01 to 0.01)	0.30		4.6
Component of disease-management program					
Treatment adjustment	41				39.2
No (ref)	28	–0.28 (–0.37 to –0.18)		60 (39 to 73)	
Yes	13	–0.60 (–0.73 to –0.47)	< 0.001	28 (0 to 63)	
Patient education	39‡				31.9
Individual (ref)	31	–0.32 (–0.41 to –0.23)		54 (31 to 69)	
Group + individual	8	–0.48 (–0.68 to –0.28)	0.11	65 (25 to 84)	
Intervention mode	41				10.7
Phone (ref)	10	–0.27 (–0.42 to –0.12)		53 (5 to 77)	
Face to face + phone	18	–0.47 (–0.63 to –0.32)	0.12	71 (54 to 82)	
Face to face	13	–0.30 (–0.43 to –0.16)	0.90	39 (0 to 68)	
Length of intervention, mo	41				7.5
< 12 (ref)	19	–0.48 (–0.63 to –0.33)		53 (21 to 72)	
≥ 12	22	–0.31 (–0.42 to –0.20)	0.08	69 (52 to 80)	
Frequency of contact	36‡				6.1
Low (ref)	8	–0.30 (–0.54 to 0.06)		80 (62 to 90)	
Moderate	12	–0.24 (–0.37 to –0.12)	0.73	33 (0 to 66)	
High	16	–0.56 (–0.72 to –0.40)	0.033	52 (14 to 73)	
Feedback of initial evaluation to primary care physician	41				3.4
Yes (ref)	21	–0.33 (–0.44 to –0.22)		67 (49 to 79)	
No	20	–0.44 (–0.59 to –0.29)	0.26	58 (31 to 74)	

Note: CI = confidence interval, ref = reference group.
*p values refer to meta-regression analysis. For each variable, the p value compares the effect of each category compared with the reference category.
†Values of < 50% represent a low level of heterogeneity, ≥ 50% to < 75% a moderate level of heterogeneity and ≥ 75% a high level of heterogeneity.
‡Number of trials does not total 41 because trials with missing data for the variable specified were excluded.

Table 3: Components of quality assessment that were considered for the sensitivity analyses

Study	Dropout rate, %	Difference in dropout rates between study groups, %	Allocation concealment
Estey et al.[21]	11.7	NA	B
Ahring et al.[22]	9.5	2.1	B
Franz et al.[23]	27.5	NA	B
Weinberger et al.[24]	8.7	3.4	B
Jaber et al.[25]	13.3	26.1	B
Fukuda et al.[26]	3.8	3.0	B
Gaede et al.[27]	6.9	3.7	A
Ridgeway et al.[28]	32.1	7.1	B
Sadur et al.[29]	15.7	4.4	B
Thompson et al.[30]	0	0	A
Piette et al.[31]	11.4	3.8	A
Hiss et al.[32]	27.4	3.7	B
Piette et al.[33]	6.2	5.5	A
Litaker et al.[34]	NA	NA	B
Oh et al.[35]	24.0	8.0	B
Polonsky et al.[36]	39.8	13.5	B
Taylor et al[37]	24.8	5.0	B
Gary et al.[38]	23.9	1.0	A
Goudswaard et al.[39]	13.8	1.0	A
CMD Study[40]	12.4	7.0	A
Ko et al.[41]	1.1	2.2	B
Krein et al.[42]	15.0	2.3	B
Montori et al.[43]	9.7	7.1	A
Choe et al.[44]	18.7	13.4	B
Farmer et al.[45]	12.9	8.9	A
Ménard et al.[46]	4.2	2.8	A
McMahon et al.[47]	19.2	7.7	A
Rothman et al.[48]	10.6	2.1	A
Taylor et al.[49]	2.5	0.05	B
Gabbay et al.[50]	NA	NA	B
Scott et al.[51]	12.1	12.8	B
Shea et al.[52]	14.9	4.4	B
Shibayama et al.[53]	10.4	3.0	B
Hiss et al.[54]	16.7	3.9	B
Ko et al.[55]	29.5	5.2	A
Wattana et al.[56]	6.4	2.6	B
Sun et al.[57]	2.7	0.0	B
Dale et al.[58]	12.8	4.6	A
Doucette et al.[59]	15.4	2.8	B
Kim et al.[60]	4.8	2.3	B
Samuel-Hodge et al.[61]	15.4	4.2	A

Note: A = adequate, B = unclear, CMD Study = California Medi-Cal Type 2 Diabetes Study, NA = not available.

We found that the ability of disease managers to start or modify medical treatment was an effective feature of disease-management programs. This confirms the findings of Shojania and colleagues, who evaluated the ability to adjust treatment without prior physician agreement.[7] However, we found that the ability to adjust treatment was an effective feature both with and without prior physician agreement, which is more relevant for physicians, nurses and pharmacists in clinical practice. This has important implications, because nonadherence to medical treatment is a significant predictor of all-cause mortality and hospital admission among patients with diabetes.[65]

Despite its relevance for clinicians and policy-makers, the intensity of disease-management programs has not been investigated in previous reviews. Program intensity depends on the frequency of patient contacts, their duration and the length of the program. Because the duration of contact was not reported in most of the studies included in our review, we were not able to explore it. However, we explored frequency of contact and length of intervention. We did not find any significant difference associated with length of intervention, despite a nonsignificant improvement observed with shorter interventions. Frequency of contact proved to be a key feature of the effectiveness of disease-management programs. There was substantial discrepancy in frequency across trials, ranging from "counseling by telephone every week if necessary"[22] to "at least five visits by the nurse within a study period of one year."[41] For our analysis, frequency of contact was estimated on the basis of the intervention protocol reported and, when available, the results. Although the reported intervention protocol probably overestimated the real frequency of contact, frequency was evaluated on the basis of results in 12 studies and was consequently found to be an effective measure. Our findings are consistent with those from a recent large controlled trial, although it showed a nonsignificant trend toward better glycemic control with more intensive intervention.[20] The greater effectiveness associated with a high frequency of patient contact suggests that only disease-management programs with intensive interventions should be implemented, perhaps by targeting patients at high risk of diabetes complications.

Patient education is the cornerstone of diabetes care. An overall beneficial effect of education among patients with diabetes has already been shown in several studies.[66,67] We did not find any difference in effectiveness between individual education and a combination of individual and group education. This finding suggests that a combination of group and individual education could be a solution to cope with the lack of medical providers and the time-consuming aspect of individual education. Surprisingly, neither the mode of contact nor feedback of the initial evaluation to the primary care physician were discriminatory components. However, we cannot rule out the possibility of incorrect classification of feedback as a program component, because it was taken for granted that such feedback would be provided systematically, so this step was not stipulated formally in the protocol.

Strengths and limitations

The strengths of the study include a comprehensive systematic review of the literature, with a large number of studies included. We used a broad search strategy to capture all relevant informa-

tion. Our work confirms the findings of previous reviews, with a mean difference in hemoglobin A_{1C} level similar to that observed in previous studies.[7,8,68,69] However, we included only RCTs and several more recent studies, with thus a larger sample size. Therefore, our estimate is probably more precise than that in previous studies.

Our study has limitations. Our analyses were based on results from randomized controlled trials, and adjustment was not done at an individual patient level. By including only studies published in English, we may have missed other relevant studies. The weak description of the intervention strategy in most studies precluded the analysis of some potentially relevant components. Notably, we were unable to study the effect of the degree of the primary care physician's involvement in these programs, which is an essential aspect for implementation. For some components, such as frequency of patient contact, we contacted the authors for more details. However, because some trials were performed several years ago, no supplementary information was available. Another limitation was the short follow-up in many of the trials, even though we excluded trials with less than 12 weeks of follow-up. Because only five trials continued for more than 12 months, we were unable to capture the long-term effects of disease-management programs. However, outcomes such as long-term diabetes complications, especially vascular complications, have not yet been examined in studies of disease management for improved diabetes care. In some trials, the length of the intervention was very short (less than six months in six trials) and thus may have been too short to produce any clinical benefits.

We noted heterogeneity in the overall effect estimate and performed a meta-regression analysis to determine potential sources. The two components of disease-management programs that led to significantly greater improvements in glycemic control accounted for 6.1% (frequency of contact) and 39.2% (treatment adjustment) of the variance between studies. We did not identify all sources of variance among trials, but a meta-analysis of summary data from reported studies has little capacity to do so.

Although a recurrent problem in meta-analyses is publication bias, application of asymmetry tests seemed inappropriate owing to the presence of heterogeneity.[70] A previous meta-analysis reported a larger effect estimate for small studies.[7] Because a higher intensity of intervention appears to be an important feature underpinning the efficacy of disease-management programs, this "size trial effect" could be due to a higher intensity of intervention in small studies. Indeed, of the 16 studies with a high frequency of patient contact in our analysis, 11 (69%) were relatively small, with samples smaller than the median for the studies included (117 patients). This more intensive intervention in small studies, rather than publication bias, could explain the greater improvement in glycemic control.

Conclusion

Disease-management programs had a clinically moderate but significant impact on hemoglobin A_{1C} levels among adults with diabetes. Effective components of the programs were a high frequency of patient contact and the ability for disease managers to adjust treatment with or without prior physician approval. Our findings have important implications for both the current policy on the delivery of diabetes care and the direction of future research. Our work delineates a general framework with core features for effective programs for disease management. Priority should be given to programs with intensive and proactive follow-up that target patients at high risk of diabetes complications rather than to programs with low frequency of contact that target the overall population of patients with diabetes. In addition, disease managers should be allowed to start or modify medical treatment proactively.

More research is needed concerning the long-term impact of disease-management programs on glycemic control, microvascular and macrovascular complications, admission to hospital and mortality. Further research should also determine whether, in addition to patients with nonstabilized diabetes, other groups of patients with diabetes would benefit from disease management. Lastly, high-quality cost-effectiveness studies of disease-management programs are needed to direct care providers and policy-makers in the allocation of health care resources.

This article has been peer reviewed.

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Contributors: Clément Pimouguet and Catherine Helmer designed the study, completed the literature search, extracted the data and drafted the manuscript. Mélanie Le Goff contributed to the data extraction, performed the data analysis and helped with the revision of the manuscript. Rodolphe Thiébaut helped with the interpretation of the results, and the consolidation and revision of the manuscript. Jean François Dartigues assisted with the design of the study, contributed to the interpretation of the results and helped with the consolidation and revision of the last draft of the manuscript. All of the authors approved the final version of the manuscript.

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Table 1: Details of randomized controlled trials of disease-management programs included in the meta-analysis (part 1 of 3)

Study (country)	No. of patients, intervention/ control	Main inclusion criteria	Treatment in control group	Length of intervention, maximum no. of months	Modes of intervention	Frequency of contact	Team	Intervention component					
								Individual education	Group education	Coaching	Monitoring	PCP feedback information	Treatment adjustment
Estey et al.[21] (Canada)	30/30	Type 2 diabetes	3-day education program	2.5	Face to face, phone	High	Nurse	X		X			
Ahring et al.[22] (Canada)	22/20	Type 1 diabetes; $HbA_{1c} \geq 7\%$; age 15–65 yr	Usual care	3	Phone	High	NA	X		X			X
Franz et al.[23] (USA)	94/85	Type 2 diabetes; age 38–76 yr	One visit with dietitian	1.5	Face to face	Moderate	Dietitian	X		X	X	X	
Weinberger et al.[24] (USA)	204/71	Type 2 diabetes; age at onset of diabetes ≥ 40 yr	Usual care	12	Phone	Moderate	Nurse	X		X	X	X	
Jaber et al.[25] (USA)	23/22	Type 2 diabetes; African-American people	Usual care	4	Face to face	High	Pharmacist	X		X	X		X
Fukuda et al.[26] (Japan)	27/25	Type 2 diabetes or IGT but no drug therapy for diabetes; $HbA_{1c} < 8\%$; age 40–70 yr	Usual care	6	Face to face, phone	Moderate	Nurse	X	X	X	X		
Gaede et al.[27] (Denmark)	80/80	Type 2 diabetes; AER ≥ 30 mg/24 h; age 40–65 yr	Usual care	48	Face to face	NA	Nurse, dietitian, doctor	X			X		X
Ridgeway et al.[28] (USA)	28/28	Type 2 diabetes; age ≥ 15–65 yr; ≥ 20% over ideal weight; fasting blood glucose > 150 mg/dL; $HbA_{1c} > 6\%$	Usual care	12	Face to face	Moderate	Nurse, dietitian		X	X	X		
Sadur et al.[29] (USA)	97/88	Type 1 or 2 diabetes; age 16–75 yr; $HbA_{1c} > 8.5\%$ or no HbA_{1c} measure during previous yr	Usual care	6	Face to face, phone	High	Nurse, dietitian, diabetologist, behaviourist, pharmacist	X	X		X	X	
Thompson et al.[30] (Canada)	23/23	Type 1 or 2 diabetes; insulin treatment; $HbA_{1c} > 8.5\%$	Usual care	6	Phone	High	Nurse	X			X		X
Piette et al.[31] (USA)	124/124	Type 1 or 2 diabetes; age < 75 yr	Usual care	12	Phone	High	Nurse	X		X	X	X	
Hiss et al.[32] (USA)	186/190	Type 2 diabetes	Usual care	12	Face to face	Low	Nurse	X		X	X	X	
Piette et al.[33] (USA)	146/146	Type 1 or 2 diabetes; age < 75 yr	Usual care	12	Phone	Moderate	Nurse	X		X	X	X	
Litaker et al.[34] (USA)	79/78	Type 2 diabetes; mild or moderate hypertension	Usual care	12	Face to face, phone	NA	Nurse	X		X	X	X	
Oh et al.[35] (South Korea)	25/25	Type 2 diabetes; $HbA_{1c} \geq 7\%$	Usual care	3	Phone	High	Dietitian, researcher	X		X	X		X

Table 1: Details of randomized controlled trials of disease-management programs included in the meta-analysis (part 2 of 3)

Study (country)	No. of patients, intervention/ control	Main inclusion criteria	Treatment in control group	Length of intervention, maximum no. of months	Modes of intervention	Frequency of contact	Team	Intervention component					
								Individual education	Group education	Coaching	Monitoring	PCP feedback information	Treatment adjustment
Polonsky et al.[36] (USA)	89/78	Type 1 or 2 diabetes; $HbA_{1c} \geq 8.5\%$	Quarterly educational mailings	6	Face to face, phone	Low	Nurse, physician, dietitian, exercise physiologist	X	X	X	X		X
Taylor et al.[37] (USA)	84/85	Type 1 or 2 diabetes; $HbA_{1c} > 10\%$	Usual care	12	Face to face, phone	Moderate	Nurse	X	X	X	X	X	X
Gary et al.[38] (USA)	NA	Type 2 diabetes; age 35–75 yr	Informational mailings every 3–4 mo	24	Face to face, phone	Low	Nurse, community health worker	X		X	X	X	
Goudswaard et al.[39] (Netherlands)	28/30	Type 2 diabetes; $HbA_{1c} \geq 7\%$; age ≤ 75 yr	Usual care	6	Face to face	Moderate	Nurse	X		X			
CMD Study[40] (USA)	186/172	Type 2 diabetes; $HbA_{1c} \geq 7.5\%$	Usual care	36	Face to face, phone	NA	Nurse, dietitian	X		X	X	X	X
Ko et al.[41] (China)	90/88	Type 2 diabetes; HbA_{1c} 8%–11%; age 75–70 yr	Usual care	12	Face to face	Low	Nurse	X		X	X		
Krein et al.[42] (USA)	123/123	Type 2 diabetes; $HbA_{1c} \geq 8.5\%$	Usual care	18	Face to face, phone	Low	Nurse	X		X	X	X	
Montori et al.[43] (USA)	15/16	Type 1 diabetes; $HbA_{1c} \geq 7.8\%$	Control patients could contact study nurse if necessary	6	Face to face, phone	High	Nurse, endocrinologist	X			X		
Choe et al.[44] (USA)	41/39	Type 2 diabetes; $HbA_{1c} \geq 8\%$; age ≤ 70 yr	Usual care	12	Face to face, phone	Moderate	Pharmacist	X		X	X	X	X
Farmer et al.[45] (UK)	47/46	Type 1 diabetes; HbA_{1c} 8–11; age 18–30 yr	Minimal feedback of blood glucose	9	Phone	High	Nurse	X		X	X		
Ménard et al.[46] (Canada)	36/36	Type 2 diabetes; $HbA_{1c} \geq 8\%$; age 30–70 yr	Usual care	12	Face to face, phone	High	NA	X		X	X		X
McMahon et al.[47] (USA)	52/52	Type 1 or 2 diabetes; $HbA_{1c} \geq 9\%$	Usual care	12	Web, phone	NA	Nurse	X		X	X	X	
Rothman et al.[48] (USA)	112/105	Type 2 diabetes; $HbA_{1c} \geq 8\%$	Usual care	12	Face to face, phone	High	Pharmacist, diabetes care coordinator	X		X	X	X	X
Taylor et al.[49] (Canada)	20/19	Type 2 diabetes	Usual care	3	Face to face	High	Nurse, dietitian, sport coach	X		X	X	X	
Gabbay et al.[50] (USA)	150/182	Type 1 or 2 diabetes; age ≥ 18 yr	Usual care	12	Face to face, phone	Low	Nurse	X		X	X	X	

Table 1: Details of randomized controlled trials of disease-management programs included in the meta-analysis (part 3 of 3)

Study (country)	No. of patients, intervention/ control	Main inclusion criteria	Treatment in control group	Length of intervention, maximum no. of months	Modes of intervention	Frequency of contact	Team	Intervention component					
								Individual education	Group education	Coaching	Monitoring	PCP feedback information	Treatment adjustment
Scott et al.[51] (USA)	76/73	Type 2 diabetes; age ≥ 18 yr	Usual care	9	Face to face, phone	High	Nurse, pharmacist		X	X	X	X	X
Shea et al.[52] (USA)	844/821	Type 1 or 2 diabetes; age ≥ 55 yr	Usual care	12	Phone	NA	Nurse, endocrinologist	X			X	X	
Shibayama et al.[53] (Japan)	67/67	Type 2 diabetes; age 20–75 yr; HbA_{1c} 6.5%–8.5%	Usual care	12	Face to face	Moderate	Nurse	X		X			
Hiss et al.[54] (USA)	95/102	Type 2 diabetes	Feedback of initial evaluation to primary care physician	6	Face to face	Moderate	Nurse	X		X	X	X	
Ko et al.[55] (South Korea)	219/218	Type 2 diabetes; age ≤ 70 yr	Follow up every 3 mo; focused on blood glucose and drug adjustment	48	Face to face, phone	Low	Nurse, dietician, pharmacist, general practitioner, endocrinologist	X	X	X	X		
Wattana et al.[56] (Thailand)	75/72	Type 2 diabetes; age ≥ 35 yr; fasting blood glucose > 140 mg for ≥ two follow-up visits	Usual care	6	Face to face	Moderate	Nurse	X	X	X			
Sun et al.[57] (China)	100/50	Type 2 diabetes; age 18–70 yr; BMI ≥ 23 kg/m^2	Diet and physical instruction	6	Face to face	High	Dietician, physician	X	X	X			X
Dale et al.[58] (United Kingdom)	44/97	Type 2 diabetes; HbA_{1c} > 8%	Usual care	6	Phone	Moderate	Nurse	X		X			
Doucette et al.[59] (USA)	36/42	Type 2 diabetes; HbA_{1c} ≥ 7%	Usual care	12	Face to face	Low	Pharmacist	X		X	X	X	
Kim et al.[60] (USA)	40/39	Type 2 diabetes; age ≥ 30 yr; HbA_{1c} ≥ 7.5%	Usual care	7.5	Face to face, phone	High	Nurse	X	X	X	X		
Samuel-Hodge et al.[61] (USA)	117/84	Type 2 diabetes	Mailing to participants of 2 pamphlets and 3 monthly newsletters	12	Face to face, phone	High	Dietician, health professional, peer counsellor	X	X	X	X		

Note: AER = urinary albumin excretion rate, BMI = body mass index, CMD Study = California Medi-Cal Type 2 Diabetes Study, IGT = impaired glucose tolerance, NA = not available, PCP = primary care physician.