Title: Impact of self-care programs in Type 2 Diabetes Mellitus population in primary health care. Systematic review and meta-analysis

Short running title

T2DM self-care programs in primary care

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Conflict of Interest Statement

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Authorship

All authors contributed to the drafting of the paper. JCB and JMMA developed the study design and contributed to data analysis, data interpretation, revisions and manuscript preparation; SGM, FVE, JCMH, SHU, AGG and ALC were involved in data acquisition and analysis, and manuscript revision. All authors approved the manuscript version submitted.

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Impact of self-care programs in Type 2 Diabetes Mellitus population in primary health care. Systematic review and meta-analysis

ABSTRACT

Aims and Objectives: To evaluate the effectiveness of self-care programs in type 2 diabetes mellitus (T2DM) population in primary health care.

Background: The impact of educational interventions on T2DM has been evaluated in various contexts, but there is uncertainty about their impact in that of primary care.

Design: Systematic review and meta-analysis.

Methods: A search was conducted in PubMed, CINAHL, WOS and Cochrane databases for randomised controlled trials carried out in the period January 2005-December 2017, including studies with at least one face-to-face educational interventions. The quality of the evidence for the primary outcome was evaluated using the GRADE System. A meta-analysis was used to determine the effect achieved although only the results classified as critical or important were taken into consideration. Checklist of Preferred Reporting Items for Systematic Reviews and Meta-analyses has been followed. PROSPERO registration Number**:** CRD42016038833.

Results: In total, 21 papers (20 studies) were analysed, representing a population of 12,018 persons with T2DM. For the primary outcome, HbA_1c, the overall reduction obtained was -0.29%, decreasing the effect in long-term follow-up. The quality of the evidence was low/very low due to very serious risk of bias, inconsistency and indirectness of results. Better results were obtained for individual randomized trials versus cluster designs and in those programs in which nurses leaded the interventions. The findings for other cardiovascular risk factors were inconsistent.

Conclusions Educational interventions in primary care addressing T2DM could be effective for metabolic control, but the low quality of the evidence and the lack of measurement of critical results generates uncertainty and highlights the need for high-quality trials.

Relevance to clinical practice: Most of self-care programs for T2DM in primary care are focused on metabolic control, while other cardiovascular profile variables with greater impact on mortality, or patient reported outcomes are less intensely addressed.

KEY WORDS

Type 2 Diabetes Mellitus, meta-analysis, primary health care, self-care, diabetes education

What does this paper contribute to the wider global clinical community?

- On the context of primary health care, educational programs on T2DM population have a very limited impact on HbA1c and other cardiovascular risk factors, a poor methodological quality and no long term follow-ups effects.
- In order to standardize the quality of the evidence assessment following the GRADE system, the algorithms developed in the study could improve decision-making by researchers.
- There is a poor description of the interventions in these studies, which creates uncertainty about their replicability in clinical practice.

1. INTRODUCTION

Diabetes mellitus (DM), one of the world's most prevalent non-transmissible diseases, has a major impact on public health. The International Diabetes Federation (IDF) estimated that in 2015, 415 million people (uncertainty interval: 340-536) aged 20-79 years had DM, and predicted that by 2040 this population would rise to 632 million (521-829), with a global prevalence of 8.8% and 10.4%, respectively (Ogurtsova et al., 2017). In 2014, it was estimated that the average global health care expense for a person with DM ranged from 1583-2842 US dollars, at an overall cost of $612-1099 billion (da Rocha Fernandes et al., 2016). Moreover, this disease has numerous associated complications (both macro- and microvascular) that require the development of diverse self-care skills; in T2DM these complications account for about 50% of the final cost (Zhuo, Zhang, & Hoerger, 2013).

Appropriate self-management of DM is not only associated with good metabolic control, but also with addressing cardiovascular risk factors (CVRF) such as hypertension or hyperlipidaemia, for which adequate therapeutic control is often not obtained, despite increasing pharmacological attention (Furler et al., 2013). Obesity, another risk factor that can be modified by the adoption of a healthy lifestyle, is present in 30-50% of people with T2DM, and is becoming even more prevalent, especially among persons aged over 45 years with abdominal obesity (Caspard et al., 2018).

The implementation of strategies to combat these factors has been considered in numerous systematic reviews, some focused on the form of intervention (group vs. individual) (Duke, Colagiuri, & Colagiuri, 2009; Odgers-Jewell et al., 2017) and others on the characteristics of the reference population (for example, analysing a population with poorer metabolic control) (Murphy et al., 2017).

Primary health care is the ideal setting to address barriers for the modification of lifestyles. To do so, clear responsibilities of stakeholders must be defined, given the usual absence of common objectives between clinicians and patients (Rushforth, McCrorie, Glidewell, Midgley, & Foy, 2016).

In this context, a number of factors have been associated with the success of programs aimed at promoting the self-management of T2DM. 1) Contact time, with better results being obtained from more intensive programs and when there is a shorter delay between the end of the programme and the measurement of results (Chrvala, Sherr, & Lipman, 2016). 2) The type of counselling provided. Thus, programs implemented by multidisciplinary teams, and

those based on peer counselling, are usually most successful in reducing levels of HbA_1c (Odgers-Jewell et al., 2017), while multidisciplinary teams led by nurses achieve significant reductions in mortality (He et al., 2017). 3) The characteristics of the educational programme; better results are obtained in patient-centred care programs, with interventions based on theoretical models and with an educational itinerary structured by a professional adviser (Zhao, Suhonen, Koskinen, & Leino-Kilpi, 2017).

Due to significant care pressure supported by primary health care and reflecting the rise of new technologies, many studies are now based on computer programs or telephone applications. However, these have achieved only limited results for metabolic control and to date there is little evidence of their effectiveness concerning depression, reduced quality of life or CVRF. The most promising area in this regard appears to be that of teleconsultation (Lee, Chan, Chua, & Chaiyakunapruk, 2017).

A recent systematic review that analysed the outcomes of diverse interventions (patient-centred, based on organisational changes, financially-oriented, etc.) for T2DM patients in primary care reported that the best results were achieved for persons with poor metabolic control (HbA_1c> 9.5%) (Murphy et al., 2017) . However, there is uncertainty in this context about the impact of face-to-face educational interventions, whether or not combined with other forms of health care, and the results reported are limited to certain minority groups (Ferguson, Swan, & Smaldone, 2015) . Equally uncertain is the extent to which the quality of the evidence currently available could generate uncertainty in the results obtained and if the impact of these programs is only limited to metabolic control or other outcomes could also benefited.

2. AIMS

The aim of this study was to evaluate the effectiveness of self-care programs in T2DM population, implemented in the context of primary health care.

3. METHODS

This review was planned and carried out in accordance with the checklist of Preferred Reporting Items for Systematic Reviews and Meta-analyses (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009) (See Supplementary File 1). The protocol is registered in the PROSPERO International Prospective Register of Systematic Reviews, as number CRD42016038833.

3.1. Study selection

Studies with the following inclusion criteria were included in the review: (1) Type of population: adults with T2DM (if the sample also included T1DM, the results should be differentiated by type); (2) Type of design: randomised controlled trials / randomised by cluster; (3) Type of intervention: diabetes education and support programs regarding T2DM, both in individual and group formats, and include at least one face-to-face session; (4) Context: primary health care and/or community setting (including attention in the patient's home); (5) Follow-up: minimum three months; (6) Language of publication: Spanish or English; (7) Type of results: clinical variables (HbA_1C, blood pressure, BMI, lipid profile, etc.) or patient-reported variables (quality of life, self-efficacy, diabetes-associated stress, self-care, etc.).

The following publication types were excluded: (1) Research protocols; (2) Pilot studies; (3) Quasi-experimental studies; (4) Programs in which no on-site educational interventions were made, or when they were provided exclusively online or as telemedicine; (5) Those focused on pre-diabetic populations, T1DM or non-DM; (6) Studies focused on hospital care or specialised regimens.

3.2. Search strategy

A search was carried out of the PubMed, CINAHL, Cochrane Central Register of Controlled Trials and Web of Science databases. Since the publication of scientific evidence on educational programs regarding new forms of health care has multiplied exponentially in recent years, we decided to include only studies published between January 2005 and December 2017. Subsequently, this was completed by a manual search of articles cited in the studies found (Montori, Swiontkowski, & Cook, 2003). The search strategy was based on the following MESH terms, among others: *type 2 diabetes, patient education, health promotion, counselling, health behaviour, self-care, primary health care* or *lifestyle modification* (the detailed search strategies are available in Supporting Information File S1).

3.3. Data extraction and quality assessment

Two authors (JCB, FVE), working independently, reviewed the titles, abstracts and full text articles that met the inclusion criteria. Any disagreement over the eligibility of certain studies was resolved by a third independent reviewer (JMMA), with extensive experience in this

field. All the texts examined were imported using Zotero 4.0.29.16 reference management software.

From the studies included in the review, descriptive information was obtained of each health care programme (type of design, country of origin, follow-up period), the population characteristics (average age, distribution by gender, baseline HbA_1c), type of intervention in the experimental group (individual, group or mixed), the health providers involved and the theoretical model used to design the programme. The primary and secondary outcomes assessed in studies were specified, together with a brief description of the intervention carried out. The authors were contacted when the researchers considered the description of the intervention to be inadequate or when results data were incomplete.

The methodological quality of each study was evaluated according to the criteria stipulated in The Cochrane Handbook (Higgins & Green, 2013), in each case classifying bias according to the level of risk, as "low", "high" or "unclear".

In order to obtain the best available evidence, the studies that complied with the randomised assignment criterion but failed to meet the other quality criteria were classed as "very poor methodological quality" and eliminated from the review.

3.4. Data synthesis and analysis

In order to analyse the most important results presented, in clinical terms, three team members (SGM, JCMH and SKU), working independently, scored each of the outcomes evaluated in the studies considered, using a Likert scale ranging from 1 (no importance) to 9 (very high importance). The results were classified according to the GRADE guidelines recommendations (median value), as 7-9 (of critical importance), 4-6 (important) or 1-3 (limited). For the purposes of the present review, only the results classified as critical or important were taken into consideration for meta-analysis (Supporting Information File S2).

The review results were grouped according to the follow-up period of each study: short (<6 months), mid (7-14 months) and long term (>14 months); the total effect of each result was also evaluated.

A meta-analysis was conducted of all the variables that were measured in at least three studies in the same follow-up period. Effect size was computed by weighted mean difference and their respective confidence intervals, using the random effects inverse variance method described by DerSimonian and Laird (DerSimonian & Laird, 2015). For studies that did not

provide information on standard deviations, these were determined according to the Cochrane recommendations (Higgins & Green, 2011). Not all variables were expressed in the same units of measurement, and so they were converted as follows: for HbA_1c, from mmol/L to %; for triglycerides and cholesterol profile, from mmol/L to mg/dL. Heterogeneity was analysed using the Cochrane's Q test, with $p<0.10$ as an indicator of heterogeneity. The degree of heterogeneity was quantified using the I2 statistic. Subgroup analyses were also carried out, taking into account: risk of bias (very serious, serious o no serious), design (RCT or cluster), mode of intervention (individual, group o mixed), health provider (nurse or others), and the existence of a theoretical framework supporting the intervention (with or without). . Moreover, meta-regression was carried out to explore the extent to which statistical heterogeneity could be due to the following characteristics of the studies: risk of bias, type of intervention (group or individual), and main provider. STATA 15 software (StataCorp., 2017) was used to perform the meta-analysis, together with GRADEPro GDT (Available from gradepro.org).

3.5. GRADE assessment

In addition to the above, we evaluated the quality of the evidence for the primary outcome of the studies included, using GRADE, the Grading of Recommendations, Assessment, Development and Evaluation. This measure reflects the overall level of bias, publication bias, inconsistency and imprecision and the existence or otherwise of indirect results (G. Guyatt et al., 2011). In order to maximise the objectivity of the GRADE evaluation obtained, the research team developed decision-making algorithms for this purpose.

1) Risk of bias (G. H. Guyatt, Oxman, Vist, et al., 2011): taking into account that studies in which educational interventions are analysed cannot be blinded to the participants, the types of bias encountered were segmented into two levels: a) essential (selection bias and control of confounders, via randomisation and concealment of the sequence); b) complementary (all others). As recommended by the authors of the GRADE System, we used a functional classification based on whether the level of bias was very serious, serious or not serious (Supporting Information File S3).

2) Publication bias: this criterion is usually considered to be present when asymmetry is observed in the funnel plots. However, this approach has limitations and it is considered important, in addition, to take into account the sample size of the studies included in the

review (small studies tend to overestimate the effect) and the funding provided by the industry (G. H. Guyatt, Oxman, Montori, et al., 2011).

3) Imprecision: in view of the limitations encountered in assessing precision by means of confidence intervals, and in response to the proposal made by Guyatt et al., we decided to evaluate this factor in terms of the optimal information size (OIS) (G. H. Guyatt, Oxman, Kunz, Brozek, et al., 2011). Accordingly, we calculated the sample size that each study would have needed to obtain sufficient statistical power (>80%), considering the effect actually achieved in the primary outcome, not that of the initial estimate. The recommendation for systematic reviews is that if the OIS is not met, the result is considered imprecise, unless the sample size for that result is high (4000 patients). If it is met, the reviewer should examine whether or not the confidence intervals exclude the desired effect.

4) Inconsistency: three criteria were assessed; a) the heterogeneity of the studies, considering I^2<40% to be low and 40-60% to be moderate values, together with a non-significant test value (>0.10) as positive indicators; b) the homogeneity of the confidence intervals; c) the homogeneity of the effect/outcome obtained (G. H. Guyatt, Oxman, Kunz, Woodcock, et al., 2011). This was classified as very serious (when two or more criteria were not met), serious (when one was not met) or not serious (when all three criteria were met) (Supporting Information File S4).

5) Indirectness: this criterion takes into account the population of interest (in terms of applicability), the intervention performed, the existence of surrogate results and, finally, whether indirect comparisons were made.

4. RESULTS

In all, 734 references were obtained, of which 269 were repeated among the different databases. After reviewing the abstracts, 375 studies were excluded and the full texts of 90 were then read. Finally, 21 papers (20 studies; DESMOND study had two manuscripts with respective 12- and 36-months follow-up periods) were included in the review (Figure 1). The following main reasons for exclusion were applied: study not consisting of a randomised clinical trial (n=188), absence of educational intervention (n=90) or study population not consisting of persons with T2DM (n=61) (Supporting Information File S5).

4.1. Characteristics of studies included

The 20 studies that met the inclusion criteria were performed in the USA (seven), UK and Sweden (three), and Japan, the Netherlands, South Africa, Thailand, Spain, Brazil and Austria (one each). In all cases, the study design was that of a randomised controlled trial, although in seven of them the randomisation was by clusters, usually taking a primary health care centre as the unit of assignment.

A total of 12,018 persons with T2DM were included, of whom 5,893 were in the intervention group (IG) and 6,125 in the control group (CG), with an average age of 59.88 years (59.76 and 60, respectively). The mean baseline HbA_1c was 7.83%, this value being the primary outcome in all cases (Adachi et al., 2010; Adolfsson, Walker-Engström, Smide, & Wikblad, 2007; Clancy, Huang, Okonofua, Yeager, & Magruder, 2007; Davies et al., 2008; Deakin, Cade, Williams, & Greenwood, 2006; DePue et al., 2013; D'Eramo Melkus et al., 2010; Gregg, Callaghan, Hayes, & Glenn-Lawson, 2007; Grillo et al., 2016; Hörnsten, Lundman, Stenlund, & Sandström, 2005; Houweling et al., 2011; Jutterström, Hörnsten, Sandström, Stenlund, & Isaksson, 2016; Khunti et al., 2012; Mash et al., 2014; Salinero-Fort et al., 2011; Sönnichsen et al., 2010a; Sturt et al., 2008; Thom et al., 2013a; Wattana, Srisuphan, Pothiban, & Upchurch, 2007; Welch et al., 2011) except the Look AHEAD Study (Redmon et al., 2010), in which it was the weight loss achieved. The follow-up periods ranged from 3 to 36 months, the most common being 12-14 months (13 studies).

The type of intervention was group format in nine cases, individual in six and a combination of the two forms in the remaining five, in every case with at least one face-to-face session. Only nine intervention programs were based on a theoretical model, the most common being that of self-efficacy (used in five studies). A variety of health providers were responsible for the intervention, but in the majority of cases (13) the programs were implemented by nurses. Primary and community health care centres, including the home of the person with T2DM, have been the more frequent contexts of care.

Although the content of the self-care programs was reported in a heterogeneous way, various key components were repeated in the different studies: 1) training in self-care skills and the promotion of healthy lifestyles (such as physical activity, nutrition, medication and smoking cessation,...); 2) training in coping through empowerment and awareness of the disease (managing stress and depression, improving knowledge or self-efficacy…); and 3) prevention and management of complications (foot and eye care, CVRF,…) (Table 1).

4.2. Quality of the studies included

The methodological quality of the studies included was medium-low. In 75%, detection bias was present, as the assessors were not blinded to the outcomes. Moreover, due to the inherent nature of these studies, there was no blinding of participants or programme providers. In over 75% of the studies there was either a high risk of other biases being present or doubts in this respect, the most common such occurrences being the presence of recruitment bias in trials that were randomised by clusters (Adachi et al., 2010; Mash et al., 2014; Sönnichsen et al., 2010a; Wattana et al., 2007) or the existence of contamination between participants in IG and CG (Sturt et al., 2008; Wattana et al., 2007). However, less than 25% of the studies presented a high risk of attrition or reporting bias (Figures 2 and 3).

4.3. Effects of self-care programs in T2DM

Not all of the results considered were suitable for meta-analysis, either due to the heterogeneity of the evaluation methods employed, as in the studies focused on health-related quality of life, cardiovascular risk, self-efficacy, stress or level of nutritional adherence, or because the outcome in question was measured in fewer than three studies, as was the case of studies of diabetes affecting the foot, or those seeking to determine levels of physical activity. Long-term subgroup analysis was not possible in all variables due to the lack of studies with this follow-up period.

4.3.1. Results of meta-analysis for metabolic control (HbA1c)

Metabolic control is the main outcome usually targeted in primary health care. Thus, all the studies measured HbA_1c over a follow-up period for a total T2DM population of 5,075 people in the IG and 5,325 in the CG. Overall, the reduction in HbA_1c obtained was significantly greater in the IG: mean difference (MD) -0.29% (95%CI: -0.45.% to -0.14%), although there was a large degree of heterogeneity, I-squared=89.5%. By duration of follow-up, the intervention had a significant impact in the short term (<6 months), MD: -0.27% (95%CI: -0.48% to -0.07%) I-squared=48.3%, and in the mid-term (7-14 months), MD: -0.31% (95%CI: -0.53% to -0.08%), I-squared=94.2%. In the long term, the effect was diluted: MD: -0.24% (95%CI: -0.63% to 0.15%), I-squared=64.8% (Figure 4).

Subgroup analysis

Several additional analyses were carried out for HbA_1c, obtaining better results for studies with a RCT design (vs. clusters), at short term MD -0.46% (95%CI: -0.68% to -0.25%) vs. -

0.05% (95%CI: -0.29% to 0.20%) and mid-term MD -0.39% (95%CI: -0.69% to -0.10%) vs. -0.09% (95%CI: -0.34% to 0.17%). Programs in which nurses participated in the intervention also achieved better results (vs. programs without nurses participating), at short-term MD -0.32% (95%CI: -0.57% to -0.07%) vs. -0.25% (95%CI: -0.60% to 0.11%) and mid-term MD -0.38% (95%CI: -0.74% to -0.02%) vs. -0.20% (95%CI: -0.54% to 0.13%). Studies at higher risk of bias (ROB) consistently showed a greater reduction in HbA1c in any follow-up period.

No differences were found in programs based on a theoretical model, nor on the basis of the modality of intervention (individual, group or mixed) (Supporting Information File S6).

4.3.2. Results of meta-analysis for blood pressure

Twelve studies measured SBP (Adachi et al., 2010; Deakin et al., 2006; Grillo et al., 2016; Houweling et al., 2011; Jutterström et al., 2016; Khunti et al., 2012; Mash et al., 2014; Redmon et al., 2010; Salinero-Fort et al., 2011; Sönnichsen et al., 2010a; Thom et al., 2013b; Welch et al., 2011), spanning a population of 4,454 persons in IG and 4,624 in CG. Overall, there were no differences between groups, with a MD of -1.34 mmHg (95%CI: -2.86 to 0.17) I-squared=70.6%. By follow-up period, only at mid-term (7-14 months) were results favourable to the intervention, with a MD of -2.27 mmHg (95%CI: -4.34 to -0.21) (Supporting Information File S7).

DBP was determined in eleven studies (same studies of SBP except Thom et al.) (4,332 persons in IG and 4,510 in CG). No significant differences between the groups were recorded: MD -0.21 mmHg (95%CI: -1.09 to 0.67) I-squared=71.6%. Moreover, for DBP, there was no effect favourable to intervention for any follow-up period (Supporting Information File S8).

4.3.3. Results of meta-analysis for lipid profile

Four variables were measured to evaluate this result: HDL-cholesterol (HDL-c) (Adachi et al., 2010; Deakin et al., 2006; Grillo et al., 2016; Hörnsten et al., 2005; Jutterström et al., 2016; Khunti et al., 2012; Redmon et al., 2010; Salinero-Fort et al., 2011; Sönnichsen et al., 2010b) and LDL-cholesterol (LDL-c) (Adachi et al., 2010; Deakin et al., 2006; Grillo et al., 2016; Jutterström et al., 2016; Khunti et al., 2012; Redmon et al., 2010; Salinero-Fort et al., 2011; Sönnichsen et al., 2010a; Thom et al., 2013b) in nine studies (3,733/3,857 persons in IG and 3,752/3,861 in CG, respectively), total cholesterol (TC) in seven (Deakin et al., 2006; Grillo et al., 2016; Houweling et al., 2011; Jutterström et al., 2016; Khunti et al., 2012;

Salinero-Fort et al., 2011; Sönnichsen et al., 2010a) (1,651 in IG and 1,757 in CG) and triglycerides (TG) in eight (Adachi et al., 2010; Deakin et al., 2006; Hörnsten et al., 2005; Jutterström et al., 2016; Khunti et al., 2012; Mash et al., 2014; Redmon et al., 2010; Sönnichsen et al., 2010a) (3,822 in IG and 4,029 in CG).

Overall significant differences favourable to the intervention were not found: for HDL-c, MD 0.63 mg/dl (95%CI: -0.42 to 1.69), I-squared=51.2%; for LDL-c, MD -0.58 mg/dl (95%CI: -1.99 to 0.82), I-squared=0%; for TC, MD 0.89 mg/dl (95%CI: -1.43 to 3.21), I-squared=0%, and for TG, MD -2.70 mg/dl (95%CI: -11.62 to 6.21), I-squared=71%.

The only benefits observed were mid-term positive increases for HDL-c, MD 1.23 mg/dL (95%CI: 0.04 to 2.43) I-squared=49.9%. (Supporting Information File S9).

4.3.4. Results of meta-analysis for Body Mass Index

Thirteen of the studies (Adachi et al., 2010; Adolfsson et al., 2007; Deakin et al., 2006; Grillo et al., 2016; Hörnsten et al., 2005; Houweling et al., 2011; Jutterström et al., 2016; Khunti et al., 2012; Redmon et al., 2010; Salinero-Fort et al., 2011; Sönnichsen et al., 2010a; Thom et al., 2013b; Welch et al., 2011) took the BMI as the anthropometric value, for an overall population of 4,151 persons in IG and 4,252 in CG. Neither at the global level, MD -0.03 kg/m^2 (95%CI: -0.85 to 0.79), I-squared=95.3%, nor in any of the follow-up periods were results favourable to the intervention (Supporting Information File S10).

Meta-regression showed no statistical association of effect sizes due to risk of bias, type of intervention (group or individual), or main provider, except for blood pressure. Those studies where the intervention was conducted in a group modality, and with a nurse as the main provider SBP decreased significantly.

4.4. GRADE assessment

For the purposes of this review, HbA_1c was selected as the primary study outcome in applying the GRADE quality assessment.

Risk of bias. The risk of bias was very serious in all the study periods, according to the decision-making algorithm used for this classification. Only two studies (X-PERT Programme (Deakin et al., 2006) and DESMOND (Davies et al., 2008; Khunti et al., 2012) could be classed as non-serious bias risk (Supporting Information File S11).

Inconsistency. The heterogeneity of the studies ranged from moderate (short-term) to high (mid and long-term, and overall), in every case with $p<0.10$. The confidence intervals had

some overlap and the effect obtained was favourable, in the short and mid-term, and overall. According to the algorithm applied (Supporting Information File S4), the inconsistency was considered to be serious for all periods except the long-term, for which it was classed as very serious.

Indirectness. Classification of this parameter was reduced by one level because although the results obtained were applicable (in terms of population of interest and of the intervention), HbA_1c was evaluated as a surrogate variable of the impact of the educational programs.

Imprecision. Hardly any of the studies complied with an adequate power for the obtained results, with the only exceptions being the Look Ahead Study (Redmon et al., 2010) and Horsten and colleagues (Hörnsten et al., 2005). Consequently, optimal information size (OIS) for a power of 80% was insufficient for all the follow-up periods. Thus, real power obtained in individual studies ranged from 8.7% for the long-term, through around 25-27% at short-mid-term. At overall evaluation, the highest power obtained was to 45%. Both at 7-14 months and overall, imprecision was classed as "not serious", and no reduction was made to the level of quality, because although an adequate OIS was not obtained, the sample size was >4000 participants and the effect obtained was significant (Supporting Information File S12).

Publication bias. The funnel plots were asymmetric in all follow-up periods and also overall (Supporting Information File S13). For each follow-up period, there were several studies with a small sample size, which might lead to the results being overestimated. Only one study (Clancy et al., 2007) declared a conflict of interest, acknowledging a relation with the pharmaceutical industry. Accordingly, the risk of publication bias for all periods was classified as "serious".

Final rating of quality. The quality of the evidence on the effectiveness of educational interventions in T2DM with respect to HbA1c was considered to be very low for the short and long-term follow-up, being mainly associated with the presence of a high risk of bias in the studies included, the inconsistency of the results presented (high levels of heterogeneity and a lack of homogeneity regarding the amplitude of the CI and the effect obtained) and unacceptable imprecision (the absence of the required OIS after obtaining the results). Only the evaluation at the mid follow-up level (7-14 months) and the overall evaluation of the studies for any follow-up period obtained a quality rating of "low" (Table 2).

5. DISCUSSION

In this review, we show that the T2DM population could benefit from educational interventions aimed at self-care in the context of primary health care. Our meta-analysis reflected the significant overall effect obtained on HbA1c and at different follow-up periods, up to 14 months. Others CVRF were also analysed, and a favourable impact on the intervention for SBP and HDL-c was only obtained in the mid-term (7-14 months). In no case, these CVRF (BP, lipids or BMI) yielded an overall significant difference favourable to the intervention. None of the patient-reported outcomes (PROs) used were meta-analysed, due to the use of different measurement scales (which evaluated different constructs) or because non-validated instruments were applied to the reference population.

Regarding metabolic control, the results of our review show a slightly lower impact than those reported in a comparable review based on an exclusively Latino population (Ferguson et al., 2015). About CVRF, similar results have been described previously in primary health context, with no impact on BP values and the lipid profile after implementing educational interventions (Dambha-Miller, Cooper, Kinmonth, & Griffin, 2017).

Although it is known that adopting a Mediterranean diet improves the lipid profile, it is not easy to modify the lifestyle in the long-term (Neuenschwander, Hoffmann, Schwingshackl, & Schlesinger, 2019). A similar situation occurs with the promotion of physical activity: the combination of aerobic and resistance exercises improves metabolic control (Pan et al., 2018), but its implementation in the primary health care setting is subject to difficulties which have been associated to diabetes complications (Sina, Graffy, & Simmons, 2018).

Primary health care is the ideal setting for the development of educational programs aimed at promoting self-care for persons with T2DM. Such programs should be person- centred, with agreed goals based on shared decision making, and oriented towards the modification of lifestyles (Reusch & Manson, 2017). However, certain segments of the population are not regular users of primary health care and it is difficult to improve their health outcomes. On the other hand, the accessibility to Primary Health Care services is not guaranteed in some countries or population groups (socioeconomically disadvantaged people) (Figueira, Silva & Silva, 2018; Ford, Wong, Jones & Steel, 2016). Alternatives such as the use of tele-coaching (Yu-Mei Chen, Wu, Chan, & Goh, 2019), or mobile phone text messages (Haider, Sudini, Chow, & Cheung, 2019) for improving metabolic and CVRF control have shown hopeful results, although they are not available in all health care systems.

Among the main contributions of this review is the evaluation made of the quality of the evidence of this type of intervention, using the GRADE system, and the use of criteria that facilitate decision making throughout the process. To do so, we focused on HbA_1c, a variable which was the primary outcome in most of the studies in our analysis (19/20) and was measured in all of them. Previous analyses, too, have attempted to make this process objective (Pollock et al., 2016); they used an exploratory approach based on four criteria: the number of participants (imprecision if ≤200), the risk of trial bias (serious limitations if >75% of participants present risk of bias), heterogeneity (inconsistency if I^2 >75%) and quality of the review (AMSTAR quality assessment tool).

Our method strictly follows the GRADE series recommendations made by Guyatt et al., in order to reduce the diversity of criteria used to classify the research evidence. In our review, the quality of the evidence was found to be low to very low, as a result of the important methodological limitations observed regarding the risk of bias, and the inconsistency and imprecision of the findings obtained. With respect to the assessment of possible bias, the criterion applied was specifically designed for studies in which the intervention could not be masked (as is the case with educational programs), an approach that differs from and improves upon previous methods employed in this field (Higgins & Green, 2011).

The studies analysed were considered to present a "very serious" or "serious" risk of inconsistency, for all follow-up periods, mainly due to the high levels of heterogeneity observed, which were not alleviated in the subgroup analysis. This problem could arise from the fact that the studies included were conducted in countries where primary care had developed to different levels and where levels of accessibility differed. The complexity of the interventions made (different providers, numbers of sessions, research methods, contact times, etc.) may also have played a significant role in this outcome. Although the content of self-care programs is moderately well defined, there is a high heterogeneity in terms of terminology used. The same interventions/activities are described in many different ways, which hinder their clinical replicability.

There is evidence that educational programs for persons T2DM, based on solid theoretical models, can improve HbA1c status (Zhao et al., 2017). In our review this result was not observed. This finding leads us to believe that self-care programs should be tightly focused on patients' needs, in which professionals receive specific training that facilitates the understanding and implementation of the models proposed.

Although it is well established that small studies tend to overestimate the intervention effect obtained, and that this has obvious consequences in terms of imprecision, our review followed the recommendations of Guyatt et al., in calculating the OIS from the post-intervention result, an approach providing greater methodological rigour.

Methodological innovations have been introduced that may be useful with the present review but this one also reveals certain limitations. HbA_1c continues to be the primary outcome in the vast majority of studies but growing numbers of researchers are downplaying the clinical scope of this factor. A recent study reported that, among the T2DM population, giving up smoking, lowering blood pressure or improving the lipid profile can all reduce mortality and associated complications more than strict glycaemic control (Erlich, Slawson, & Shaughnessy, 2014). Although the United Kingdom Prospective Diabetes Study (UKPDS) established that a 1% reduction in HbA_1c has an important impact on macrocomplications (14% reduction in acute myocardial infarction) and microvascular complications (37% reduction), hardly any RCT has achieved these figures; the benefits would appear to be restricted, fundamentally, to persons recently diagnosed and without comorbidities (Keeble, Farland, & Eaddy, 2014).

Furthermore, in this review we were unable to analyse results considered "critical" (such as the incidence of diabetic foot, quality of life or numbers of hospital admissions), a problem that is aggravated by the absence of published clinical trials that measure the long-term impact, a situation that seems unlikely to be resolved in the near future (Gandhi et al., 2008). Neither was it possible to meta-analyse PROs, which limits our understanding of patients' views on the attention received. This question remains to be addressed in future research, with the application of qualitative methods (Rushforth et al., 2016).

6. CONCLUSION

In this meta-analysis, self-care programs have achieved significant results in terms of metabolic control (an overall reduction of 0.29% for HbA_1c). These outcomes are far from the target set by the UKPDS (1% reduction), which substantially reduces micro and macrovascular complications. HbA1c is the most common clinical target for primary health care teams.

In turn, other variables which produce a higher impact on mortality (blood pressure or lipid profile), have obtained inconsistent results. Moreover, the low quality of the evidence, and

the lack of measurement of critical results generates uncertainty and highlights the need for high-quality trials.

7. RELEVANCE TO CLINICAL PRACTICE

Most of self-care programs for type 2 diabetes mellitus in primary health care are focused on metabolic control, while other cardiovascular profile variables with greater impact on mortality, or patient reported outcomes are less intensely addressed.

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TABLES

Table 1 Characteristics of studies included in the systematic review

Study and country	Design and follow-up	Theoretical framework	Participants	Outcomes and providers	Intervention type and description	Control
Adachi et al. 2013 Japan	Cluster randomised controlled trial 6 months	None	IG: 100 (60.4 years, female: 55%) HbA_1c: 7.6% CG: 93 (62.3 years, female: 58%) HbA_1c: 7.3%	Primary endpoint: HbA1c Secondary endpoint: blood pressure, BMI and lipid profile Dietitians	Individual Education programme focused on food intake distribution, structured in four steps: "Basic information on glycaemic control", "Actions for glycaemic control", "Daily activities for glycaemic control" and "Management of stress for glycaemic control"	Information about food intake using FFQW82 and general advice on glycaemic control
Adolfsson et al. 2007 Sweden	Randomised controlled trial 12 months	Empowerment model	IG: 50 (62.4 years, female: 43%) HbA_1c: 7.4% CG: 51 (63.7 years, female: 39%) HbA_1c: 7.1%	Primary endpoint: HbA1c Secondary endpoints: BMI. Physicians and specialist diabetes nurses	Group 4-5 empowerment education sessions focused on confidence in diabetes knowledge, self-efficacy and satisfaction with daily life, BMI and glycaemic control. The sessions were directed by physicians and 12 diabetes specialist nurses, who volunteered to receive training to become facilitators	Regular diabetes care consisting of at least one annual visit by the doctor and one by the nurse. Receiving advice on the basis of biochemical results and glycaemic self-control
Clancy et al. 2007 USA	Randomised controlled trial 12 months	None	IG: 98 (55 years, female: 74%) HbA_1c: 9.3% CG: 90 (57 years, female: 70%) HbA_1c: 8.9%	Primary endpoint: HbA1c Internal medicine physicians and registered nurses	Individual / Group Twelve two-hour educational group sessions (one per month) were given to the IG. All had the following structure: 10-15 minutes for "warm-up" and socialisation, 30-45 minutes for an interactive discussion of a health-related topic such as foot care or health eating strategies, and 60 minutes for one-on-one consultations with the physician	Usual care
			IG: 437 (60 years,		Group	

Davies et al. 2008 (DESMOND STUDY) UK	Multicentre cluster randomised controlled trial 12 months	Self-efficacy theories	female: 41%) HbA_1c: 8.3% CG: 387 (59 years, female: 40%) HbA_1c: 7.9%	Primary endpoint: HbA1c Secondary endpoints: blood pressure, blood lipid levels, etc. Health care professionals, educators	A structured education programme based on the diabetes education and self-management for ongoing and newly diagnosed (DESMOND) for six hours. Most of the curriculum was focused on lifestyle factors, such as food choices, physical activity and cardiovascular risk factors Group	Usual care
Khunti et al. 2012† (DESMOND STUDY)	36 months	Self-efficacy theories	Same population	Same endpoints and providers	DESMOND Study. Same structured intervention programme as in Davies et al. 2008	Usual care

Table 1 (continued)

Study and country	Design and follow-up	Theoretical framework	Participants	Outcomes and providers	Intervention type and description	Control
De Pue et al. 2013 USA	Randomised controlled trial 12 months	Chronic care model	IG: 164 (56 years, female: 56%) HbA_1c: 9.6% CG: 104 (54 years, female: 54%) HbA_1c: 10%	Primary endpoint: HbA1c Nurses and community health workers	Individual / Group Each session content was guided by both patient risk and self-selected goals from a menu of the following eight topics: diabetes introduction; healthy eating; being active; using medication; monitoring (understanding and using information from BG and BP measurement, tracking progress); reducing risk (preventing complications, standards of care, visits and laboratory measurements, smoking, alcohol, foot care); healthy coping (managing stress and depression); and problem solving	Usual care, but were placed in a wait-list for at least one year until they started the programme

Deakin et al. 2006 UK	Randomised controlled trial 14 months	Empowerment model	IG: 157 (61.3 years, female: 61.3%) HbA_1c: 7.7% CG: 157 (61.8 years, female: 61.8%) HbA_1c: 7.7%	Primary endpoint: HbA1c Secondary endpoints: BMI, blood pressure, blood lipids, self-care behaviour. Dieticians, practice nurses and general practitioners	Group Six two-hour weekly sessions of the X-PERT Programme, which aimed to develop skills and build confidence, and to enable patients to make informed decisions regarding their diabetes self-care	Diabetes education with individual appointments
D'Eramo Melkus et al. 2010 USA	Randomised controlled trial 24 months	Social learning theory	Black American women 100% IG: 57 (45 years) HbA_1c: 8% CG: 52 (47 years) HbA_1c: 8.3%	Primary endpoint: HbA1c Nurses	Group 11 weekly group sessions. The first 6 sessions (each 2 hr in duration) provided culturally relevant cognitive behavioural diabetes self-management training based on American Association of Diabetes Educators' Self-Care Behaviour standards, supported by culturally specific cookbooks and videos. The remaining 5 group sessions (each 1 hr in duration) comprised the coping skills training portion of the intervention	Group diabetes education classes and group follow-up question and answer sessions delivered over 10 consecutive weeks
Gregg et al. 2007 USA	Randomised controlled trial 3 months	None	IG: 43 (51.9 years, female: 48.8%) HbA_1c: 8.17% CG: 38(49.8 years, female: 57.9%) HbA_1c: 8.21%	Primary endpoint: HbA1c -	Group Participants of the IG were given a 4 hour workshop based on an Acceptance and Commitment Therapy manual that covered each of the above educational topics in an abbreviated form, plus mindfulness and acceptance training regarding difficult thoughts and feelings about diabetes, exploration of personal values related to diabetes, and a focus on the ability to act in a valued direction while contacting difficult experiences	7-hour workshop that followed a patient education manual based on ADA diabetes education principles

Table 1 (continued)

Study and country	Design and follow-up	Theoretical framework	Participants	Outcomes and providers	Intervention type and description	Control
Grillo et al. 2016 Brazil	Randomised controlled trial 12 months	None	IG: 69 (61.7 years, female: 71%) HbA_1c: 8.8% CG: 68 (63.2 years, female: 56%) HbA_1c: 9.1%	Primary endpoint: HbA1c Secondary endpoints: BMI, blood pressure, lipid levels, waist circumference, cholesterol, triglycerides Nurses	Group A structured diabetes self-management education course (weekly 2-hour meetings for 5 weeks and reinforcement meetings every 4 months for one year). The content included: identification of modifiable risk factors for type 2 diabetes mellitus, non-pharmacological treatment, emphasising diet and exercise, pharmacological therapy, an overview of chronic diabetes complications and foot care.	Usual care
Hornsten et al. 2005 Sweden	Randomised controlled trial 12 months	None	IG: 44 (63.6 years, female: 48%) HbA_1c: 5.7% CG: 60 (63.4 years, female: 45%) HbA_1c: 5.8%	Primary endpoint: HbA1c Secondary endpoints: blood lipids and BMI Diabetes nurses	Group 1-2 visits per year by a nurse, who was encouraged to put more emphasis on the patients' understanding of their illness, than on transferring their own professional knowledge during the consultations. Also, they attended 10 group sessions (of 2 h each), addressing themes related to the patients' personal understanding of their illness.	Usual care
Houweling et al. 2012 The Netherlands	Randomised controlled trial 14 months	None	IG: 102 (67.1 years, female: 47.1%) HbA_1c: 7.6% CG: 104 (69.5 years,	Primary endpoint: HbA1c Secondary endpoints: Blood pressure, cholesterol and BMI	Individual The patients in the IG were treated by two trained practice nurses following a detailed treatment and management protocol based on the guidelines published by the Dutch College of General Practitioners and on those from the	Usual care with general practitioners

			female: 57.7%) HbA_1c: 7.4%	Practice nurses	Dutch Diabetes Federation aimed at optimising glucose, blood pressure and lipid profile regulation and eye and foot care in patients with diabetes. Practice nurses were allowed to prescribe 14 different medications and adjust dosages for a further 30. They were also allowed to order laboratory tests. The PNs were specifically not permitted to prescribe insulin, but were able to adjust the dosage.	
Jutterström et al. 2016 Sweden	Randomised controlled trial 12 months	Self-efficacy theories	IG: 59 (64 years, female: 31.7%) HbA_1c: 6.7% CG: 47 (66.2 years, female: 37.3%) HbA_1c: 6.5%	Primary endpoint: HbA1c Secondary endpoints: BMI, waist circumference, cholesterol, lipid levels, triglycerides and blood pressure Diabetes specialist nurses	Individual / Group The intervention consisted either of discussions in groups or individual conversations with the nurse, depending on the intervention group. During the six sessions, the participants were free to discuss issues they considered important in relation to their experiences with the disease. The IG_2 participants met the local diabetes nurse one-on-one, while the IG_1 participants met in groups where the diabetes nurse acted as a moderator.	Usual care

Table 1 (continued)

Study and country	Design and follow-up	Theoretical framework	Participants	Outcomes and providers	Intervention type and description	Control
Mash et al. 2014 South Africa	Pragmatic clustered randomised controlled trial	None	IG: 710 (56.4 years, female: 75.7%). HbA_1c: 8.9% CG: 860 (55.8 years, female: 71.5%) HbA_1c: 9.3%	Primary endpoints: HbA1c and self-care activities Secondary endpoints: blood pressure and	Group 60-minute group sessions that focused on understanding diabetes, living a healthy lifestyle, understanding the medication and avoiding complications. Health promoters' communication style was based on motivational	Usual care

	12 months			triglycerides Health promoters	interviewing principles and skills	
					Individual / Group	
Redmon et al. 2010 (The Look Ahead Research Group) USA	Multicentre randomised controlled trial 12 months	None	IG: 2496 (59 years, female: 59%) HbA_1c: 7.3% CG: 2502 (59 years, female: 60%) HbA_1c: 7.3%	Primary endpoint: weight loss (BMI) Secondary endpoints: HbA1c, blood pressure, and blood lipid Dietititians, phychologists and exercise specialists	A programme of diet, behaviour modification and increased physical activity, with goals of a minimum weight loss of 7% of initial body weight and at least 175 min/week of moderate physical activity. The initial year included frequent individual and group meetings. To assist participants in reducing caloric intake, participants were prescribed portion-controlled diets that included the use of meal-replacement products. Dietary counselling included information on healthy diet composition	Three additional diabetes education sessions during the first year.
					Individual	
Salinero et al. 2011 Spain	Cluster randomised controlled trial 24 months	PRECEDE Model	IG: 300 (66.06 years, female: 53.8%) HbA_1c: 7.05% CG: 300 (67.28 years, female: 49.3%) HbA_1c: 7.36%	Primary endpoint: HbA1c Secondary endpoints: blood pressure, blood lipids and BMI Nurses	The model was based on the following aspects: self-monitoring of glycaemic control (patients were encouraged to monitor their blood glucose levels, to record these values and bring a record book to all subsequent appointments); physical exercise (this involved initiation of an exercise plan that could be incorporated into the patient's daily schedule, after taking into consideration their level of fitness, e.g. 1-h walk daily); diet (the patient was assisted with the identification of dietary behaviour that adversely influences blood glucose control, lipid levels, weight management, medication adherence; and smoking cessation	Conventional health promotion education
					Group	

Sönnichsen et al.2010 Austria	Cluster randomised controlled trial 12 months	None	IG: 649 (65.4 years, female: 49%) HbA_1c: 7.46% CG: 840 (65.5 years,	Primary endpoint: HbA1c Secondary endpoints: improvement in systolic or diastolic blood pressure, lipids, and body	"Therapie aktiv" intervention included the following components: - A mandatory 10-hour face to face training course for physicians, designed by the Austrian Diabetes Association (ÖDG), the Austrian Medical College (Ärztekammer), and the Austrian Society for General	Usual care

Table 1 (continued)

Study and country	Design and follow-up	Theoretical framework	Participants	Outcomes and providers	Intervention type and description	Control
Sönnichsen et al.2010 Austria	Cluster randomised controlled trial 12 months	None	female: 46.9%) HbA_1c: 7.34%	mass index. GPs and internists	Practice (ÖGAM) consisting of an update in diabetes care, current guidelines of the ÖDG, and practice management training. - Nine hours of patient-education in 4 modules with a group size of 3 to 12 patients. Patient education was organised by the Working Group for Preventive Medicine Salzburg (AVOS) using the "Düsseldorfer Modell" curriculum. - Standardised documentation of physical examination, laboratory findings and diabetes complications in a DMP-form once a year. - Structured interdisciplinary care according to the guidelines of the Austrian Diabetes Association (ÖDG). - Agreement on therapeutic goals in a shared patient physician decision-making process.	
Sturt et al. 2008.	Cluster randomised	Self-efficacy theories	IG: 114 (62 years, female: 39%) HbA_1c: 8.9%	Primary endpoint: HbA1c, Secondary endpoint:	Individual A 15-min face-to-face consultation with the nurse to introduce the 12-week Diabetes Manual programme.	Usual care

UK	controlled trial 6 months (26 weeks)		CG: 131 (62 years, female: 40%) HbA_1c: 8.7%	diabetes-related distress, measured with the Problem Areas in Diabetes Scale (PAID) Nurses	Patients worked independently through the Diabetes Manual workbook, which was underpinned by self-efficacy theory with component parts designed to develop confidence for self-care and reduce diabetes-related distress. Nurse telephone support was provided in weeks 1, 5 and 11.	
Thom et al. 2013 USA	Randomised controlled trial 6 months	None	IG: 148 (54 years, female: 51.4%) HbA_1c: 10.05% CG: 151 (56 years, female: 53%) HbA_1c: 9.85%	Primary endpoint: HbA1c. Secondary endpoints: LDL-C levels, systolic blood pressure and BMI Peer coaches	Individual Potential peer coaches were trained over 8 weeks using a curriculum(http://familymedicine.medschool.ucsf.edu/cepc/pdf/ HealthCoachTrainingCurriculumMay08.pdf) that included instruction in using active listening and non-judgmental communication, helping with diabetes self-management skills, providing social and emotional support, assisting with lifestyle change, facilitating medication understanding and adherence, navigating the clinic, and accessing community resources. Peer coaches interacted by telephone or during a clinic visit; target goals for coaching sessions were telephone contact at least twice a month and 2 or more in-person contacts over 6 months. Coaches helped patients design action plans to achieve goals chosen by the patient.	Usual care: access to a nutritionist and diabetes educator through referral from their primary care clinician

Table 1 (continued)

Study and country	Design and follow-up	Theoretical framework	Participants	Outcomes and providers	Intervention type and description	Control
			IG: 75 (58 years,			

Wattana et al. 2007 Thailand	Randomised controlled trial 6 months	Self-efficacy theories	female: 52%) HbA_1c: 8.08% CG: 72 (55 years, female: 69%) HbA_1c: 8.09%	Primary endpoint: HbA1c Nurses	Individual / Group One small-group diabetes education class (120 min), four small-group discussions (90 min/group), two individual home visit sessions from the researcher (45 min), and a patient education manual	Usual care including physical examination and individual health education from a registered nurse and/or other health-care provider.
Welch et al. 2011 USA	Randomised controlled trial 12 months	None	IG: 21 (54 years, female: 62%) HbA_1c: 9% CG: 18 (57 years, female: 68%) HbA_1c: 8.5%	Primary endpoint: HbA1c Secondary endpoints: blood pressure and BMI Diabetes nurses and dietician team	Individual Seven 1-hour visits over the follow-up period to review a set of diabetes education booklets with the AC patients (i.e., information on diet, medication, exercise, blood glucose monitoring, eye and foot care) that are published by the American Diabetes Association. The importance of culturally competent diabetes interventions has been established, and cultural sensitivity was an important element of this intervention. During the sessions, dietary education focused on portion size, food selection, and cooking techniques for foods preferred by the local Hispanic population.	The CG interventionists encouraged patients to formulate diabetes-related questions for discussion with their primary care provider at the next scheduled primary care visit.

† Khunti et al. 2012 is the same research as that of Davies et al. 2008, but with a 3-year follow-up. IG: Intervention group, CG: Control group, BMI: Body Mass Index

Table 2 GRADE evidence profile: effect on HbA_1 in T2DM (educational studies vs. usual care; setting: primary health care)

Quality assessment							No. of patients		Effect		Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Education	Usual care	Relative (95% CI)	Absolute MD (95% CI)	
Hb1Ac- <6 months (Short-term)											
9	RCT	Very serious†	Serious‡	Serious§	Very serious¶	Serious¥	1085	1005	-	-0.27 (-0.48 to -0.07)	⊕◯◯◯ VERY LOW
Hb1Ac- 7 to 14 months (Mid-term)											
13	RCT	Very serious†	Serious ‡	Serious§	Not serious¶	Serious¥	4311	4566	-	-0.31 (-0.53 to -0.08)	⊕⊕◯◯ LOW
Hb1Ac- >14 months (Long-term)											
3	RCT	Very serious†	Very serious‡	Serious§	Very serious¶	Serious¥	661	601	-	-0.24 (-0.63 to 0.15)	⊕◯◯◯ VERY LOW
Hb1Ac- TOTAL											
20	RCT	Very serious†	Serious ‡	Serious§	Not serious¶	Serious¥	5075	5325	-	-0.29 (-0.45 to -0.14)	⊕⊕◯◯ LOW

Abbreviations: RCT: Randomised controlled trial or clustered. CI: Confidence interval ; MD: Mean difference

†All studies, except Davies et al. and Khunti et al. (DESMOND Study) and Deakin et al. (X-Pert Program), presented risk of serious or very serious bias associated with the absence of concealment in the allocation and/or absence of blinding of participants or outcome assessors (performance and detection bias).

‡Considerable heterogeneity, disparity of effects and different amplitudes of 95% CI. Reduced by only one level at short and mid-term, and overall; because the CIs were homogeneous with positive effects, although with moderate-high heterogeneity.

§Reduced by one level (Serious) because HbA_1c was considered a surrogate result.

¶Sample size below OIS. Only two studies featured an adequate sample size after testing the hypotheses (Hörnsten et al., 2005; Redmon et al., 2010). In both cases, the CI included potential reductions. At Mid-term and total, imprecision was considered "not serious" because population was higher of 4000 subjects.

¥Funnel plot symmetry and sample size were considered. Only one study (Clancy et al.) declared a conflict of interest with the industry.

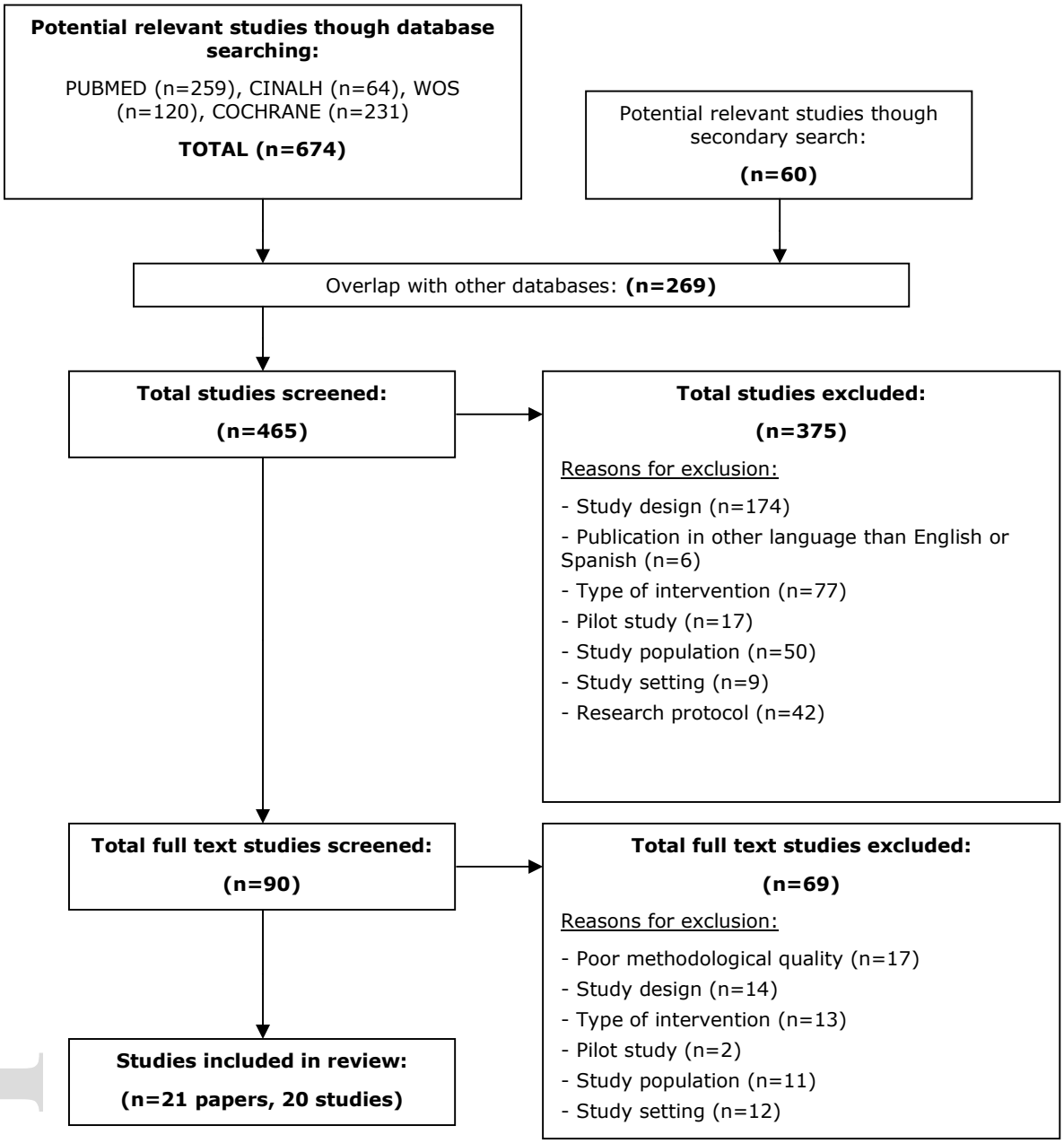
FIGURE LEGENDS

Figure 1. Flow chart of selected studies (PRISMA flow diagram).

Figure 2. Summary of risk of bias.

Figure 3. Risk of bias of the studies included.

Figure 4. Forest plot on HbA_1c. Meta-analysis that includes total effect and follow-up periods.



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