TITLE PAGE

Title
Diabetes Prevention in the Real World: Effectiveness of Pragmatic Lifestyle Interventions for the Prevention of Type 2 Diabetes and of the Impact of Adherence to Guideline Recommendations. A Systematic Review and Meta-analysis.

Short Running Title
Systematic Review Pragmatic Diabetes Prevention

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ABSTRACT (222 words)

Objective:

To summarise the evidence on effectiveness of translational diabetes prevention programmes, based on promoting lifestyle change to prevent type-2-diabetes in real world settings; to examine whether adherence to international guideline recommendations is associated with effectiveness.

Research Design and Methods:

Bibliographic databases were searched up to July 2012. Included studies had a follow-up of ≥12-months and outcomes comparing change in body composition, glycaemic control, or progression to diabetes. Lifestyle interventions aimed to translate evidence from previous efficacy trials of diabetes prevention into 'real world' intervention programmes. Data were combined using random effects meta-analysis, and meta-regression considering the relationship between intervention effectiveness and adherence to guidelines.

Results:

25 studies met the inclusion criteria. The primary meta-analysis included 22 studies (24 study groups) with outcome data for weight loss at 12-months. The pooled result of the direct-pairwise meta-analysis shows that lifestyle interventions resulted in a mean weight loss of 2.32kg (95% CI: -2.92 to -1.72; I^2=93.3%). Adherence to guidelines was significantly associated with a greater weight loss (an increase of 0.4Kg per point increase on a 12-point guideline-adherence scale).

Conclusions:

Evidence suggests pragmatic diabetes prevention programmes are effective. Effectiveness varies substantially between programmes, but can be improved by maximising guideline adherence. However, more research is needed to establish optimal strategies for maximising both cost-effectiveness, and longer-term maintenance of weight loss and diabetes prevention effects.

INTRODUCTION

A major opportunity exists to drastically reduce the incidence of type 2 diabetes; a disease that has a huge impact on patients and health care systems worldwide. Large, high quality clinical trials (1-3) show that relatively modest changes in diet and physical activity reduce the incidence of type 2 diabetes by more than 50% for people with impaired glucose regulation. Impaired glucose regulation is an intermediate condition between normal glucose regulation and type 2 diabetes, which confers an increased risk of progression to type 2 diabetes (4). Indeed, within-trial data show that the rate of progression to type 2 diabetes at seven years of follow up was reduced to almost zero for people who had succeeded in making five modest lifestyle changes (2). The main drivers of diabetes prevention appear to be weight loss and physical activity (5, 6). However, a substantial challenge remains in translating these findings into routine clinical practice. The intensive and prohibitively expensive interventions used in clinical trials, to ensure lifestyle change, need to be translated into practical affordable interventions that are deliverable in real world health care systems and which, nevertheless, retain a reasonable degree of effectiveness (7).

Since the publication of the original diabetes prevention clinical trials between 1996 and 2001, a number of translational or “real world” diabetes prevention programmes (8, 9) have aimed to translate the evidence (1, 10-12). A meta-analysis of the evidence on translational interventions was published in 2010 (9). Although this review excluded 15 studies that were conducted in non-health care settings. A more recent meta-analysis was published in 2012 (13). However, the authors only focused on translation of evidence from the US Diabetes Prevention Programme and also included studies where up to half of the population already had diabetes. Other systematic reviews of diabetes prevention interventions have either not included a

meta-analysis (6, 8, 14-17) or have not focused on translational studies (3, 6, 15, 16, 18-22). Overall, the systematic reviews conducted to date indicate that real-world diabetes prevention programmes vary widely in their effectiveness, although most produce lower levels of weight loss than the more intensive interventions used in the clinical efficacy trials (9). Explaining this variation is important. If we can identify the components of lifestyle interventions that are reliably associated with increased effectiveness, this will inform the design of more efficient (cost-effective) diabetes prevention programmes.

Recently published evidence based guidelines (23, 24) make distinct recommendations about which intervention components should be included to maximise the effectiveness of lifestyle interventions for diabetes prevention. Such recommendations include the use of group based interventions to minimise cost and the use of specific behaviour change strategies that are associated with increased effectiveness. These recommendations come from systematic reviews of the wider literature on supporting changes in diet and physical activity in a range of populations (25, 26). Lifestyle interventions for diabetes prevention vary in their content, however, whether closer adherence to the guideline recommendations might improve the performance of real-world diabetes prevention interventions remains unclear. To consolidate the evidence, we undertook a systematic review of studies considering the effectiveness of translational interventions for prevention of type 2 diabetes in high risk populations. The primary aim was to conduct a meta-analysis of the effectiveness of pragmatic interventions on weight loss, and conduct a meta-regression to examine whether closer adherence to guideline recommendations for diabetes prevention improves the effectiveness of real world interventions. If

sufficient data were available, a secondary aim was to consider other diabetes risk factors using similar methods.

METHODS

Search strategy and study selection

We included experimental and observational studies that considered the effectiveness of a lifestyle intervention (diet and/or exercise), alone or compared to control; where the stated aim of the intervention was diabetes risk reduction or prevention of type 2 diabetes; where the focus of the study was to translate evidence from previous diabetes efficacy trials into routine healthcare, or a community setting. For studies to be eligible for inclusion, we required them to include adults (≥18 years old) identified as being at high risk of developing type 2 diabetes (for example, obese, sedentary lifestyle, family history of diabetes, older age, metabolic syndrome, impaired glucose regulation, pre-diabetes, or elevated diabetes risk score) (24); have a minimum follow-up of 52 weeks; and have an outcome relating to diabetes risk, as measured by a change in body composition or a change in glycaemic control, or report progression to diabetes (incidence or prevalence). The focus of the review was primary prevention, therefore, we excluded trials where >10% of the population had established diabetes. We included only studies published in English language and as full-length articles.

We searched EMBASE, MEDLINE and The Cochrane Library (Issue 7, 2012), using a combination of MeSH terms and keywords which were tailored to individual bibliographic databases. We restricted searches to articles published after January 1998; the starting point of 1998 was chosen to facilitate the identification of studies that were informed by or translating evidence from previous diabetes prevention efficacy trials (1, 10-12). In order to avoid missing papers the final search strategy included only terms related to the intervention and the study design. An example

search strategy (MEDLINE) is outlined in Supplemental Table S1. We combined the results of an initial search and an updated supplementary search, which together identified papers up to the end of July 2012.

Two reviewers independently assessed abstracts and titles for eligibility and retrieved potentially relevant articles, with differences resolved by a third reviewer where necessary. Where studies appeared to meet all the inclusion criteria but data were incomplete, we contacted authors for additional data and/or clarification. In an attempt to identify further papers not identified through electronic searching, we examined the reference lists of included papers and relevant reviews.

Data extraction and quality assessment

Data were extracted by one reviewer and a second reviewer subsequently checked for consistency. We extracted data on sample size, population demographics, intervention details and length of follow-up. Where available, we recorded outcome data for the mean change from baseline to 12-months follow-up for the following outcomes: weight, body mass index (BMI), waist circumference, fasting glucose, 2-hour glucose, glycated haemaglobin (HbA1c), total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure (BP), and diastolic BP. Incidence of type 2 diabetes was also recorded. We retrieved all papers relating to a particular study, including those on design and methodology (if reported separately), and any supplementary online material.

We assessed the quality of selected studies according to the UK's National Institute for Health and Clinical Excellence (NICE) quality appraisal checklist for quantitative

intervention studies (27). The checklist includes criteria for assessing the internal and external validity of experimental and observational quantitative studies (randomized controlled trials (RCTs), non-randomised controlled trials, before and after studies) and allows assignment of an overall quality grade (categories ++, + or -).

Coding of intervention content

We coded intervention content (see Supplemental Tables S2 and S3), in relation to the recommendations for lifestyle interventions for the prevention of diabetes provided by both the IMAGE project (Development and **Im**plementation of **a** European **G**uidelin**e** and Training Standards for Diabetes prevention) (23) and NICE (24). Where a study intervention was inadequately described, we requested further details from the authors. If available information was insufficient to allow coding, we coded data as missing; where an intervention appeared to be well described but a particular component (e.g. engaging social support) was not mentioned or could not be implied from other text, we assumed that the component was not used. In the analysis, we assumed that missing values indicated that the guideline criterion was not met.

Data synthesis and analysis

We converted all values reported in imperial units, into metric units. Capillary blood glucose values were converted to plasma equivalent values (28). If studies did not directly report the mean and standard deviation (SD), for change from baseline to 12 months for the outcomes of interest, they were calculated. We calculated the mean change by subtracting the baseline mean value from the mean at 12-months. We

calculated the SD from reported p-values or confidence interval (CI), as recommended by the Cochrane Collaboration (29). Where data were insufficient, to allow calculation of the SD, we imputed values for each outcome based on the correlation estimates from those studies that reported; for weight the correlation used in these imputations was 0.95 (30-34).

For the primary outcome of interest (weight), we conducted a direct-pairwise comparison meta-analyses to examine the effect size (change from baseline to 12-months), where data were available. Only intervention arms were included in the meta-analysis. This was because we were interested in whether adherence to guidelines improved weight loss; therefore, only arms in which people received an intervention were applicable. Meta-regression was used to assess the relationship between weight change at 12-months and the total IMAGE guidance score and the total NICE guidance score, as explanatory variables, in separate uni-variate analyses. We performed further meta-regression with the individual guideline components as the explanatory variables, where at least 3 studies fell into each category. We conducted similar analyses for the secondary outcomes of interest; however, as these outcomes were reported in fewer studies and to avoid multiple testing, meta-regression of individual guideline components against secondary outcomes was not performed. We performed sensitivity analyses for the primary outcome, weight, where missing guideline data were treated as unknown and a total guidance score was not given for those studies, and where we restricted the analysis to RCTs only.

We assessed publication bias using Egger's test and heterogeneity using the I^2 statistic. Due to high levels of heterogeneity, we used random effects models throughout to calculate effect sizes. We performed all analyses in Stata version 12.1 (StatCorp, College Station, Texas, US).

RESULTS

Identification of studies

Results relating to identification and selection of eligible trials are summarised in Figure 1. Searches yielded 6326 citations and 3872 unique titles and/or abstracts were screened for eligibility. Following full text retrieval of 114 potentially relevant papers, twenty additional papers were identified from reference lists making a total of 134. Authors for 13 studies were then contacted in order to clarify eligibility criteria and/or for additional outcome data. Replies were received for 12 studies, 10 of which were subsequently included in the 25 studies (30-54) (35 papers (30-64)) that met the review criteria.

Summary of included studies

The 25 studies (30-54) included in the systematic review are summarized in Table 1. Study interventions included either dietary intervention, physical activity intervention or both. Standard/brief advice on diet and/or exercise was considered to be comparable with usual care and not judged to be an active intervention. One study focused solely on the effectiveness of physical activity intervention (54), one combined dietary intervention and a supervised exercise programme (44), and 23 studies considered the effectiveness of combined dietary and physical activity intervention. Eleven of the studies were RCTs, 11 were before and after studies and the remaining studies included a matched cohort, a prospective cohort and a non-randomised controlled trial. All papers were published within the last 10 years.

Studies were conducted in the US (n = 11), Australia (n = 2), Europe (n = 11) and Japan (n = 1); however, ethnicity was poorly reported. The number of people who

were enrolled into the intervention arm in individual studies ranged from 8 to >2700 with 22 studies including at least 50 participants. The criteria used, alone or in combination, to identify high risk included: elevated BMI, elevated diabetes risk score (FINDRISC (65), ADA (66)), raised random, fasting or two-hour glucose (finger prick or venous sample); older age; ethnicity; family history of diabetes; previous medical history of cardiovascular disease, polycystic ovary syndrome, gestational diabetes, metabolic syndrome, elevated BP or lipids. Length of follow-up ranged from 12 months to around 4 years. The mean age and BMI of participants ranged from 38 - 65 years and 25 – 37 kg/m^2 respectively, and the proportion of males ranged from 7 – 66%.

Outcome data for change in weight were available for 24/25 studies (not Costa (39)); 22/25 studies reported weight at 12 months, see Supplemental Table S4. Additional 12 month data reported for 23 studies (Supplemental Tables S4 and S5) included change in BMI (18 studies), waist size (16), fasting glucose (15), 2 hour glucose (10) HbA1c (7), total cholesterol (13), LDL (7), HDL (12), triglycerides (10), systolic BP (13), diastolic BP (11), and the incidence of diabetes after 12-months (8). Outcome data for change in physical activity and diet were poorly reported. Overall, considerable heterogeneity was evident between studies in relation to several key characteristics including the setting, population, criteria used to identify diabetes risk, interventions and follow-up.

Study quality

A breakdown of study quality is presented in Supplemental Table S6. Most studies achieved a high quality grading for internal validity (19/25). However, details relating

to the source/eligible population and area, and the selected participants were less well reported; only 11 studies achieved a high quality score for external validity.

Scoring of intervention content

Details of coding scores for study interventions are presented in Supplemental Table S3. Fourteen of the 25 intervention groups included in the main meta-analysis attained an overall score of ≥9 out of a possible 12, in relation to meeting NICE guideline recommendations; 19 scored ≥7. For IMAGE guideline recommendations, an overall score of ≥5 out of a possible 6 was achieved by 12 study groups.

Meta-analysis

Twenty two studies involving 5500 participants (estimated 43% male), were included in the meta-analysis for mean weight change at 12-months One study was excluded from the primary meta-analysis as weight change was not recorded as a study outcome (39) and two studies were excluded from all analyses as they only reported 18-month data (45, 53). Two studies included in the meta-analysis had two intervention arms (43, 54), meaning that 24 study groups were analysed.

The pooled result of the direct-pairwise meta-analysis (Figure 2) shows that lifestyle interventions resulted in a mean weight loss of 2.32kg (95% CI: -2.92 to -1.72; I^2=93.3%). Supplemental Figures S1 and S2 show the meta-regression results for the NICE and IMAGE guidelines for weight, respectively. Greater adherence to guideline recommendations was significantly associated with greater weight loss for both sets of guidelines (Table 2). Adherence to individual guideline elements also tended to result in greater weight loss, some of which were statistically significant (Table 2).

Sensitivity analyses without imputed data are also shown in Table 2. This showed that, where data were complete, the effect sizes were generally larger for both NICE and IMAGE guidance, -0.52 kg per point increase on the 12-point adherence scale (95% CI: -0.95 to -0.10) and -0.77 kg per point increase on the 6-point adherence scale (95% CI: -1.28 to -0.26) respectively.

None of the study level co-variates (proportion of males, mean age, proportion of White European ethnicity) were significantly associated with the mean difference in weight change. Sensitivity analysis, restricted to RCTs only, indicated a mean weight change (-2.7kg; 95% CI: -4.2 to -1.2kg) that is similar to the overall result. Additional analysis comparing the difference in weight lost between the treatment and control arms, for RCTs only, suggests that on average the intervention arm lost an extra -1.93kg (95% CI -3.10 to -0.76kg; p=0.001). Furthermore, sensitivity analyses which included studies scoring ++ for external validity demonstrated a slightly greater weight loss in higher quality studies (-3.1kg; 95% CI: -4.6 to -1.6kg). Additionally, there was very limited evidence of publication bias (p=0.05, Egger's test).

All other outcomes showed an improvement at 12 months, see Supplemental Table S7, but not all of these reached statistical significance. Supplemental Table S8 shows the effect of adherence to NICE and IMAGE guidelines on the other outcomes. For both NICE and IMAGE guidelines respectively, greater adherence resulted in better outcomes for waist circumference (-0.52cm, p=0.007; -0.80cm, p=0.001) and triglycerides (-0.03mmol/l, p=0.016; -0.04mmol/l, 0.023). For BMI the improvements were only significant for adherence to NICE guidelines (-0.12kg/m^2, p=0.028). There was no effect on any of the other outcomes. Across the 8 studies

that reported incident diabetes, the pooled incidence rate was 34 cases per 1000 person-years (95% CI: 22 to 56), which gives the number needed to treat (NNT) as 29.

DISCUSSION

The 22 translational diabetes prevention programmes included in our meta-analysis significantly reduced weight in their intervention arms by a mean 2.3Kg at 12 months of follow up. Where data were available, we found significant reductions in other diabetes and cardiovascular risk factors, including blood glucose, blood pressure and some cholesterol measures. Adherence to guideline recommendations on intervention content and delivery was significantly associated with a greater weight loss such that, for each 1 point increase on the 12-point scale for adherence to NICE recommendations an additional 0.4Kg (p=0.008) of weight loss was achieved; furthermore, for waist size a significant reduction of 0.5cm was achieved for each point increase. The pooled diabetes incidence rate was 34 per 1000 person-years (NNT 29). Outcome data on changes in the key lifestyle behaviour targets (physical activity and diet) were poorly reported.

Relationship to other literature

The mean level of weight loss achieved was around a half to one third of the levels reported at the same time point within the intervention arms of clinical efficacy trials such as the US DPP (~6.7Kg) and the Finnish DPS (~4.2Kg) (1, 10). This is consistent with the findings of a meta-analytic systematic review published in 2010 by Cardona et al (9) which identified a mean net weight loss after 12 months of 1.82Kg (95%CI:-2.7 to -0.99 Kg). Cardona et al interpreted the lower level of weight loss and a lack of significant differences in fasting plasma glucose and 2 hour glucose, as meaning that the interventions “appear to be of limited clinical benefit”. Our view is that, despite the drop-off in intervention effectiveness in translational studies, the level of weight loss found in our analysis is still likely to have a clinically meaningful

effect on diabetes incidence. This is based on data from the US DPP study which show that each kilogram of mean weight loss is associated with a reduction of around 16% in future diabetes incidence (5). Furthermore, a recent meta-analysis, which included studies without an intervention in order to look at natural diabetes progression rates in high risk individuals, found progression rates to diabetes from IFG, IGT and both were 47, 56 and 76 per 1000 person-years respectively (67). The rate of 34 per 1000 person-years that we found suggests that the real world lifestyle interventions studied here did lower diabetes progression rates.

For our review, the mean proportion of weight lost (%) at 12 months follow-up was -2.6%. This amount was slightly lower than was demonstrated by a recent meta-analysis conducted by Ali et al, which considered translational studies aimed at populations with existing diabetes (≤50%) or at high future risk (13). They found a mean weight loss of −4.1% (95%CI: −5.9 to −2.4%) after at least 9 months of follow-up (13). This difference may in part be due to a lower mean BMI at baseline for studies included in our review, compared to the Ali et al review (range 25-36kg/m^2 and 31-40kg/m^2 respectively), and a slightly longer follow-up period (12 months vs. ≥9). Additionally, their review focused on interventions based only on the US Diabetes Prevention Programme where we considered a broader set of interventions.

Changes in the four key dietary and physical activity targets (≤30% energy from fat, ≤10% energy from saturated fat, fibre ≥15 g/1,000 kcal, ≥30 minutes moderate physical activity daily) have also been shown to have independent effects on diabetes risk reduction, irrespective of weight loss (5). However, few of the studies we examined provided data on dietary intake or physical activity, so we cannot be

sure whether diabetes prevention in these studies is driven by increased physical activity, dietary change or both.

The strong association between increased weight loss and increased adherence to guideline recommendations is of particular interest. Where complete data were available, the coefficients were larger: -0.52Kg per point increase (95% CI: -0.95 to -0.10) for adherence to NICE guidance, on a 12-point scale; -0.77 Kg per point increase (95% CI: -1.28 to -0.26) for adherence to IMAGE guidance, on a 6-point scale. This may reflect a reduction in the statistical 'noise' caused by missing data, or it may reflect the fact that studies that had a stronger behavioural science input were more likely to report the intervention content in detail (and were also more likely to be effective). Overall, these data suggest that a high proportion of the variation in weight loss could be explained by variations in intervention design. The implication is that a design based on guideline recommendations should lead to performance at the higher end of the range (4 Kg or more).

Strengths and Limitations

This study is novel in that it provides an updated meta-analysis of a global set of lifestyle interventions for diabetes prevention. Our study used comprehensive search criteria and focused on establishing the utility of pragmatic attempts to achieve diabetes prevention in real-world service delivery settings. It also provides novel data that appear to validate the usefulness of recent guideline based recommendations on the content of lifestyle interventions for diabetes prevention.

The study is limited in that there was insufficient data to analyse outcomes beyond 12 months; our findings may not translate into long-term therapeutic value due to uncertainty around sustaining outcomes, such as weight loss, in the longer term.(68) Furthermore, results in individual studies were not always reported on an intention-to-treat basis, leading to a likely overestimation of effect sizes. Assuming no change in weight for those with missing data, sensitivity analyses that we conducted suggest that weight loss could be up to 0.5kg less in practice than the figures reported in the studies.

Due to the nature of pragmatic implementation studies, which include a number of uncontrolled studies, our analysis was restricted to intervention arms only; however, sensitivity analysis, restricted to RCTs only, indicated a mean weight change (-2.7kg; 95% CI: -4.2 to -1.2kg) that is similar to the overall result. These findings suggest that the estimate based on intervention arms only is likely to be robust.

Implications for practice

Our review suggests that pragmatic lifestyle interventions are effective at promoting weight loss and could potentially lead to a reduced risk of developing diabetes and cardiovascular disease in the future. However, the difficulties in translating this evidence into practice and in delivering guideline-based interventions need to be overcome. The ability to implement these findings in practice may be further hampered by a lack of resource for service provision, the design of efficient risk identification systems, and engagement of politicians and health care organisations in funding national diabetes prevention programmes; diabetes prevention strategies require substantial up-front investment to accrue longer-term benefits (7).

Future directions

More research is needed to examine the longer-term effectiveness and cost-effectiveness of pragmatic lifestyle interventions for diabetes prevention, including diabetes incidence as well as weight loss outcomes. The practical value of diabetes prevention interventions would be much clearer if we had data on longer-term outcomes. Research is also needed to identify the role of different types of physical activity and dietary changes (6, 69) and on ways to increase effectiveness without increasing cost. Possible approaches might include the use of larger group sizes and substitution or supplementation of intervention techniques using self-delivered formats (e.g. internet, smart phone or workbook) (70).

Conclusion

Overall, the interventions were effective, but there was wide variation in effectiveness. Adherence to international guidelines on intervention content and delivery explained much of the variance in effectiveness, implying that effectiveness could be improved by maximising guideline adherence. However, more research is needed to establish optimal strategies for maximising both cost-effectiveness and longer-term maintenance of the lifestyle changes that these programmes can achieve.

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Author contributions:

A.J.D. Conceived the idea for the review, developed the search strategy, selected and retrieved relevant papers, made the final decisions regarding inclusion/exclusion of all papers, designed the data extraction tool, carried out extraction/checking of data and quality assessments, and wrote the manuscript. D.H.B. conducted the meta-analyses and meta-regression, and wrote the manuscript. C.J.G. conceived the idea for the review, coded interventions for adherence to guidelines, and wrote the manuscript. C.R. selected and retrieved relevant papers, carried out extraction/checking of data and quality assessments, and reviewed/edited the manuscript. T.Y. reviewed/edited the manuscript. M.J.D. reviewed/edited the manuscript. K.K. conceived the idea for the review, made the final decisions regarding inclusion/exclusion of all papers, and reviewed/edited the manuscript.

Guarantors name:

D.H.B. is the guarantor of this work on behalf of the authors and, as such, had full access to the data and takes responsibility for the integrity and the accuracy of the data analysis.

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Conflicts of interest:

C.J.G., K.K., M.J.D. and T.Y. were involved in the development of the NICE guidelines on diabetes prevention and C.J.G. was involved with development of the IMAGE guidelines. C.J.G. in the last 3 years has received payment from: (1) Weight Watchers to make a presentation to some of their UK staff, summarising evidence on weight loss interventions, the health /economic consequences of weight loss and the content of current NICE guidance; (2) Stanford Burgess Health for consultancy on the development of a website to support diabetes prevention; and (3) Novartis Pharma Service Inc for delivery of a workshop on supporting behaviour change at the Middle East Summit on Cardiovascular Management in October 2011. A.J.D., D.H.B. and C.R. have declared that no competing interests exist relevant to this article.

FIGURE LEGENDS

Figure 1: Flow chart of selection of studies from search to final inclusion

Figure 2. Forest plot showing mean weight change in each study and the overall pooled estimate

Boxes and horizontal lines represent mean weight change and 95% CI for each study. Size of box is proportional to weight of that study result. Diamonds represent the 95% CI for pooled estimates of effect and are centred on pooled mean weight change.

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Table 1: Characteristics of studies included in the systematic review

Author & Year	Study design	Study name	Definition of high risk of T2DM	Focus of Intervention(s)	№ recruited overall (& by group)	№ study groups	Follow-up (months)	Setting	Country	Ethnicity %	Age (mean)	Male (%)	BMI (mean kg/m$^{2)}$
Absetz 2007 (& 2009)	Before & after	GOAL	Aged 50-65 years; Any risk factor from obesity, ↑BP, ↑plasma glucose, ↑lipids; FINDRISC score ≥12	Lifestyle *(Diet & exercise)*	352	1	12 & 36	Primary care	Finland	N/R	58 (F); 59 (M)	25	33 (F); 32 (M)
Ackermann 2008 (& 2011)	RCT	DEPLOY	BMI ≥24 & ADA diabetes risk score ≥10; CBG random (110 – 199 mg/dl) or fasting (100 – 199 mg/dl)	Lifestyle *(Diet & exercise)*	92	2	12	Community (YMCA)	US	82% White, 3% Hisp, 12% Af-Am, 5% other	58	45	31
Almeida 2010	Matched cohort	KPCO	Existing IFG (110 – 125mg/dl) identified from medical records	Lifestyle *(Diet & exercise)*	1640 (1520 data available)	2	12	Integrated healthcare organisation	US	N/R	55	47	30
Boltri 2008	Before & after	DPP in faith based	ADA diabetes risk score ≥10; CBG fasting (100 – 125mg/dl)	Lifestyle *(Diet & supervised exercise)*	8	1	12	Community (Church)	US	Af-Am community	52*	42*	32
Costa 2012	Prospective cohort	DE-PLAN Spain	FINDRISC score ≥14 or 2hr OGTT (≥7.8 and <11.1mmol/l)	Lifestyle *(Diet & exercise)*	552 (219+333)	2	Median 4.2yrs	Primary care	Spain	White-European	62	32	31
Davis-Smith 2007	Before & after	N/R	ADA diabetes risk score ≥10; CBG fasting (100 – 125mg/dl)	Lifestyle *(Diet & exercise)*	11	1	12	Community (Church)	US	Af-Am community	N/R	27	36†
Faridi 2010	Non-randomised controlled trial	PREDICT	1 or more risk factor from BMI ≥25, FH diabetes, gestational diabetes	Lifestyle *(Diet & exercise)*	146	2	12	Community (Church)	US	Af-Am 100%	N/R	32	33

Author & Year	Study design	Study name	Definition of high risk of T2DM	Focus of Intervention(s)	№ recruited overall (& by group)	№ study groups	Follow-up (months)	Setting	Country	Ethnicity %	Age (mean)	Male (%)	BMI (mean kg/m$^{2)}$
Gilis-Januszewska 2011	Before & after	DE-PLAN Poland	FINDRISC score ≥14	Lifestyle *(Diet & exercise, optional supervised sessions)*	175	1	12	Primary care	Poland	NR	NR	22	32
Katula 2011	RCT	HELP PD	BMI ≥25 <40 & CBG random; FPG (95 - 125 mg/dl)	Lifestyle *(Diet & exercise)*	301 (151 + 150)	2	12	Community various venues	US	74% White, 25% Af-Am, 1% other	58	43	33
Kramer 2009	Before & after	GLB 2005 – 2008	BMI ≥25 & metabolic syndrome or CBG fasting (100 – 125mg/dl)	Lifestyle *(Diet & exercise)*	42	1	12	Primary care & university based support centre	US	White 100%	57	21	35
Kramer 2012	Before & after	GLB 2009	Fasting glucose 100 – 125mg/dl	Lifestyle *(Diet & exercise)*	60 (31+29)	2	12	Community (YMCA) and university	US	90% Caucasian	55	35	~36
Kulzer 2009	RCT	PREDIAS	FINDRISC score ≥10 or assessed as ↑risk diabetes by primary care physician	Lifestyle *(Diet & exercise)*	182 (91 + 91)	2	12	Outpatient setting	Germany	N/R	56	57	32
Laatikainen 2007 (& 2012)	Before & after	GGT study	FINDRISC score ≥12	Lifestyle *(Diet & exercise)*	311	1	12	Primary care	Australia	N/R	57	28	34
Makrilakis 2010	Before & after	DE-PLAN Greece	FINDRISC score ≥15	Lifestyle *(Diet & exercise)*	191	1	12	Primary care, workplace	Greece	NR	56	40	32

Author & Year	Study design	Study name	Definition of high risk of T2DM	Focus of Intervention(s)	№ recruited overall (& by group)	№ study groups	Follow-up (months)	Setting	Country	Ethnicity %	Age (mean)	Male (%)	BMI (mean kg/m$^{2)}$
Mensink 2003 (& 2003) (Roumen 2008 & 2011)	RCT	SLIM study	Aged >40 years & FH diabetes or BMI ≥25; IGT (OGTT 2hrG ≥7.8 & <12.5) & FPG <7.8	Lifestyle *(Diet & supervised exercise)*	114 (55 + 59)	2	12, 24, 36, 48 (Roumen)	unclear	Netherlands	White caucasian	57	56	30
Nilsen 2011	RCT	APHRODITE study	FINDRISC score ≥9	Lifestyle *(Diet & exercise)*	213 (104+109)	2	18	Primary care	Norway	NR	47	50	37
Ockene 2012	RCT	Lawrence Latino DPP	BMI≥24, >30% increased likelihood of diabetes over next 7.5 from validated risk algorithm	Lifestyle *(Diet & exercise)*	312 (150+162)	2	12	Community, family health centre	US	60% Dominican; 40% Puerto Rican	52	26	34
Parikh 2010	RCT	Project HEED	BMI ≥25 & pre-diabetes; CBG fasting <126mg/dl & 2hr CBG following 75g glucose	Lifestyle *(Diet & exercise)*	99 (50 + 49)	2	12	Community various venues	US	89% Hisp, 9% Af-Am	48	15	32
Payne 2008	Before & after	N/R	Aged ≥45 years or aged ≥35 Aboriginal, Torres Strait Islanders, Pacific Islanders, Indian, Chinese) & BMI ≥30 &/or ↑BP; Existing CVD, PCOS, gestational diabetes; 1st degree FH diabetes; IGT or IFG	Lifestyle *(Diet & exercise program)*	122 (62 + 60)	2	12	Outpatient facility	Australia	N/R	53	22	35
Penn 2009	RCT	N/R	BMI >25 & aged >40 years; IGT (OGTT 2hrG ≥7.8 & <11.1)	Lifestyle *(Diet & exercise)*	102 (51 + 51)	2	12 & 3.1 yrs mean	Outpatient setting	UK	N/R	57	40	34
Ruggiero 2011	Before & after	N/R	BMI≥24.9	Lifestyle *(Diet & exercise)*	69	1	12	Community various venues	US	Hispanic	38	7	31

Author & Year	Study design	Study name	Definition of high risk of T2DM	Focus of Intervention(s)	№ recruited overall (& by group)	№ study groups	Follow-up (months)	Setting	Country	Ethnicity %	Age (mean)	Male (%)	BMI (mean kg/m$^{2)}$
Saaristo 2010, (Rautio 2011 & 2012)	Before & after	FIN-D2D	FINDRISC score ≥15 or IFG or IGT or CVD event or gestational diabetes	Lifestyle *(Diet & exercise)*	2798	1	12	Primary care	Finland	NR	54	49	~31
Sakane 2011	RCT	N/R	IGT identified as follows: IFG ≥5.6 & <7.0; Random PG (≥7.8 <11.1 within 2 hrs of meal) or (≥6.1 & <7.8, ≥2 hrs after meal); IGT	Lifestyle *(Diet & exercise)*	296 (146 + 150)	2	12 & 36	Various: primary care, workplace, collaborative centre	Japan	N/R	51	51	25
Vermunt 2012 (& 2011)	RCT	N/R	FINDRISC score ≥13	Lifestyle *(Diet & exercise)*	925 (479+446)	2	18, 30	Primary care	Netherlands	NR	NR	NR	~29
Yates 2009 (& 2011)	RCT	PREPARE	BMI ≥25 (23 for SAs); Screened detected IGT	Lifestyle *(Exercise)*	98 (33+31+34)	3	12, 24	Outpatient setting	UK	75% † White, 24% SA, 1% Black	65†	66†	29.2†

**Boltri estimated from larger cohort (n = 26) who were screened with CBG; † given for completers. Payne randomily allocated to 2 exercise groups but most results presented overall*

Abbreviations: ADA, American Diabetes Association; Af-Am, African American; BP, blood pressure; BMI, body mass index; CBG, capillary blood glucose; CI, confidence interval; CVD, cardiovascular disease; F, female; FH, family history; FINDRISC, Finnish Diabetes Risk Score; FPG, fasting plasma glucose;HbA1c, glycated haemoglobin; HDL, high density lipoprotein; Hisp, Hispanic; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL, low density lipoprotein; M, male; N/R, not reported; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; PG, plasma glucose; SA, South Asian; T2DM, type 2 diabetes

Table 2. Meta-regression results for weight change from baseline to 12 months.

Explanatory variable	**Number of studies**	**Number of participants**	**Effect (95% CI), kg**	**P value**
NICE (continuous)	24	5500	-0.37 (-0.64, -0.11)	0.008
NICE without imputation (continuous)	17	4885	-0.52 (-0.95, -0.10)	0.020
IMAGE (continuous)	24	5500	-0.56 (-0.96, -0.17)	0.008
IMAGE without imputation (continuous)	18	4942	-0.77 (-1.28, -0.26)	0.006
IMAGE B (continuous)	24	5500	-0.61 (-0.99, -0.22)	0.004
IMAGE B without imputation (continuous)	18	4942	-0.78 (-1.26, -0.29)	0.004
Engage social support (yes vs no)	24	5500	-1.58 (-3.06, 0.10)	0.037
Number of contacts (freq)	23	5417	-0.09 (-0.13, -0.05)	<0.001
Contact time (hours)	23	5147	-0.15 (-0.21, -0.08)	<0.001
≥16 hours of contact time (yes vs no)	23	5147	-2.20 (-3.61, -0.79)	0.004
Self-regulatory techniques (yes vs no)	24	5500	-1.17 (-3.00, 0.66)	0.200
Empathy-building approach (yes vs no)	24	5500	0.86 (-0.71, 2.43)	0.269
Spread sessions over 9-18 months (yes vs no)	24	5500	-1.62 (-3.07, -0.18)	0.029
Motivation (yes vs no)	24	5500	-1.49 (-3.05, 0.07)	0.060
Gradual building of confidence (yes vs no)	24	5500	-0.58 (-2.24, 1.08)	0.477
Fidelity (yes vs no)	24	5500	-0.79 (-2.59, 1.02)	0.377
Additional physical activity sessions (yes vs no)	24	5500	-0.53 (-2.62, 1.56)	0.604

Abbreviations: CI, confidence interval; IMAGE, Development and **Im**plementation of **a** European **G**uideli**n**e and Training Standards for Diabetes prevention; NICE, National Institute for Health and Clinical Excellence (*Preventing type 2 diabetes: Risk identification and interventions for individuals at high risk)*.