A lifestyle intervention (with or without lay volunteers) to prevent Type 2 diabetes in people with impaired fasting glucose and/or non-diabetic hyperglycemia : a randomized clinical trial.

Subtitle : The Norfolk Diabetes Prevention Study (NDPS)

Michael Sampson, MD [1,4] , Allan Clark, PhD [4] , Max Bachmann, PhD [4], Nikki Garner, MPhil [1] , Lisa Irvine, PhD [4], Amanda Howe, MD [4] , Colin Greaves, PhD [5,6] , Sara Auckland, PhD [1] , Jane Smith, PhD [4,6] , Jeremy Turner, MPhil [1] , Dave Rea [1] ,Gerry Rayman, MD [3], Ketan Dhatariya, PhD [1], W. Garry John, PhD [2], Garry Barton, PhD [4] , Rebecca Usher, MSc [1] , Clare Ferns [1], Melanie Pascale , PhD [1] on behalf of the NDPS group.

[1] Elsie Bertram Diabetes Centre, Department of Diabetes and Endocrinology, Norfolk and Norwich University Hospital NHS Trust, Norwich, UK.

[2] Department Clinical Biochemistry, Norfolk and Norwich University Hospital NHS Trust, Norwich, UK.

[3] Department of Diabetes and Endocrinology, Ipswich General Hospital, Ipswich, UK.

[4] Norwich Medical School, University of East Anglia, Norwich, UK.

[5] School of Sport, Exercise & Rehabilitation Sciences, University of Birmingham, Birmingham, UK

[6] University of Exeter Medical School, College of Medicine & Health, University of Exeter, Exeter, UK.

Corresponding author: Professor Michael J Sampson, Elsie Bertram Diabetes Centre, Norfolk and Norwich University Hospital NHS Trust, Colney Lane, Norwich, UK. NR4 7UY mike.sampson@nnuh.nhs.uk

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Key points

Question Does our group-based lifestyle intervention (with or without trained volunteers with Type 2 diabetes) reduce the risk of Type 2 diabetes in people with the current high risk intermediate glycemic categories of impaired fasting glucose or non-diabetic hyperglycemia

Finding In this trial of 1,028 participants with high risk intermediate glycemic categories , the intervention significantly reduced the 2 year risk of Type 2 diabetes by 40–47%, although lay volunteer support did not reduce the risk further. For every 11 participants treated, one diabetes diagnosis was prevented.

Meaning Nearly half the adult population have diabetes or a high risk glycemic category, and this low-cost group - delivered intervention significantly reduced the risk of diabetes.

Abstract

Importance Nearly half the older adult population have diabetes or a high risk intermediate glycemic category , but we still lack trial evidence for effective Type 2 diabetes prevention interventions in most of these current high-risk glycemic categories.

Objective To determine whether our group-based lifestyle intervention (with or without trained volunteers with Type 2 diabetes) reduced the risk of progression to Type 2 diabetes in populations with a high risk glycemic category

Design A parallel, three-arm, group-based, randomized controlled trial, up to 46 month follow–up (2011-2019; Norfolk Diabetes Prevention Study; NDPS).

Setting 135 primary care practices, and 8 intervention sites in the East of England.

Participants We identified 141,973 people at increased risk of Type 2 diabetes, screened 12,778 (9.0%) and randomized those with a high risk glycemic category : *either* an elevated fasting plasma glucose alone (≥ 110 and < 126mg/dl) or an elevated glycated hemoglobin (HbA1c; non-diabetic hyperglycemia; NDH; HbA1c ≥ 6.0 – <6.5%) with an elevated fasting plasma glucose ≥100–< 110 mg/dl),

Intervention A control arm receiving usual care (CON), a theory based lifestyle intervention arm of 6 core and up to 15 maintenance sessions (INT), or the same intervention with support from diabetes prevention mentors, trained volunteers with Type 2 diabetes (INT- DPM).

Main outcome Type 2 diabetes incidence between arms

Results We randomized 1,028 participants (INT:424, INT-DPM:426;CON:178) between January, 1st 2011 and and February 24th 2017. Mean age (SD) was 65.3 (10) years, mean body mass index 31.2 (5) kg/m^2 and mean follow-up 24.7 months. 156 participants progressed to Type 2 diabetes: 39/171 (22.8%; CON), 55/403 (13.7%; INT) and 62/414 (15.0%; INT-DPM). There was no significant difference between intervention arms in primary outcome (OR: 1.14; CI 0.77 to 1.7; p=0.51), but each intervention arm had a significantly lower odds of Type 2 diabetes INT: OR 0.54 (CI 0.34-0.85; p=0.008), INT–DPM: OR 0.61(CI 0.39-0.96; p=0.033), combined: OR 0.57 (CI 0.38–0.87; p=0.008). Effect size was similar in all glycemic, age, and social deprivation groups and intervention costs per participant were low at $153 (£122)

Conclusion The NDPS lifestyle intervention reduced the risk of Type 2 diabetes in current high risk glycemic categories. Enhancing the intervention with DPM did not further reduce diabetes risk. These translatable results are relevant for current diabetes prevention efforts.

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Introduction

The world diabetes population quadrupled between 1980 and 2014 to 422 million,[1] matched by what has been described as a worldwide epidemic of the intermediate glycemic categories that carry a high risk of Type 2 diabetes .[2,3] Nearly half of the older USA and UK population now have Type 2 diabetes or a high risk intermediate glycemic category,[4,5,6] as do a third of young obese adults.[7] There is an urgent need for effective and affordable diabetes prevention strategies [1,8,9] and national diabetes prevention programs are now operating in the USA,[10,11] UK,[12] and elsewhere. These offer a lifestyle intervention to people with a high risk score, or a high risk intermediate glycemic category, with a plasma glucose or glycated hemoglobin (HbA1c), or both that are elevated, but not into the diagnostic range for diabetes.[10-12] In the UK, entry to the national programme[12], and general recommendations for lifestyle intervention,[13] are targeted at people with a high risk elevated glycated hemoglobin of ≥ 6.0 – < 6.5% (non-diabetic hyperglycemia; NDH) or an elevated fasting plasma glucose ≥ 100 - < 126mg/dl (impaired fasting glucose; IFG).[14-16] Early observational outcomes are encouraging, [10-12] although clinician understanding of diabetes prevention remains poor.[17]

One critically important issue is that the trial evidence for Type 2 diabetes prevention in the now commonly used high risk glycemic categories of IFG or NDH is in fact very limited, and this lack of evidence in the current high risk phenotypes has been emphasised recently.[18] The early landmark prevention trials (used as the evidence base for current prevention programs), were mostly in populations defined as high risk based on an impaired glucose tolerance (IGT) category in a 2 - hour oral glucose tolerance test, rather than a fasting plasma glucose and IFG.[19-22] The shift to HbA1c criteria , for both categorising risk and diagnosing Type 2 diabetes[14-16] then created new large at risk NDH populations. There is as yet no substantial trial evidence for benefit from a lifestyle intervention in people with high risk impaired fasting glucose (IFG) and/or NDH. [18-23] No prevention trial of more than 2 years duration has used HbA1c as the diabetes diagnostic primary end-point, in line with modern diagnostic practice, so the prevention evidence base does not align with current diagnostic approaches.[18-22] We cannot assume outcomes of earlier trials (in different high risk glycemic populations with IGT), are simply translatable to populations with current high risk intermediate glycemic categories , who differ in pathophysiology, progression rates, and vascular risk.[24-27]

The diabetes prevention benefit found in the earlier high intensity landmark trials [19-22] has been much less marked in 'real world' pragmatic interventions.[28,29] This means that although there is a need for lower cost, more pragmatic intervention models, the current evidence to support their effectiveness is limited.[10-12, 18-23, 28-29] One attractive option is to include volunteer lay workers, who can support a diabetes prevention intervention alongside healthcare professionals to co-deliver an intervention at potentially lower cost.[30-34] People with Type 2 diabetes themselves are an appealing choice for this role, as they share similar lifestyle challenges to the target group. No large controlled trial has tested a diabetes prevention intervention supported by trained lay volunteers with Type 2 diabetes , compared to a standard intervention.

In the Norfolk Diabetes Prevention Study (NDPS) we tested the effectiveness of a pragmatic group - based lifestyle intervention, supported by diabetes prevention mentors (trained volunteers with Type 2 diabetes) in reducing the incidence of Type 2 diabetes in people with current prediabetes glycemic categories.

Study design

NDPS was a seven year research programme (UK National Institute for Health Research NIHR RP PG 0109 – 10013). The NDPS protocol [35] and baseline publications [35 - 38] summarise NDPS sample sizes, recruitment plans, training materials, and screening data. NDPS identified people with high risk intermediate glycemic categories in the East of England,[35] and eligible participants entered a randomized controlled three-arm parallel group trial, with up to 46-month follow-up, testing a group-delivered, theory based, lifestyle intervention, with or without the support of trained lay volunteers (diabetes prevention mentors ; DPM) with Type 2 diabetes.[35,37]

Screening Potential participants were screened with fasting plasma glucose, venous HbA1c, and biometric and clinical data collection.[35] Participants with an eligible glycemic high risk category on initial testing had repeat testing a median 40 days (interquartile range 27 - 69 days) later.[35,36] Trial randomization was offered if paired baseline tests were concordant for a high risk intermediate glycemic category. The first screening appointment was August, 22nd, 2011 and last March , 24th , 2017. Protocol driven screening was undertaken by NDPS program staff in eight screening sites across the East of England. [35]

Inclusion criteria

Non-diabetic hyperglycemia (NDH) was defined as an HbA1c ≥ 6.0 to < 6.5% [14-16] and impaired fasting glucose (IFG) as a fasting plasma glucose (FPG) ≥ 100 – < 126 mg/dl. [14-16] We defined two study populations with a high risk intermediate glycemic category, based on then current glycemic definitions [14-16] . We randomized participants if they had paired baseline isolated IFG range FPG measurements of ≥ 110 – < 126 mg/dl, *or* if they had NDH HbA1c combined with IFG FPG ≥ 100 – < 110 mg/dl. [14-16] Initial recruitment (2011-) into trial was for participants with isolated IFG ≥ 110 – < 126 mg/dl. In light of international changes in diabetes diagnostic criteria during the program, the new definition of high risk NDH, and UK national policy changes [14-16] we also then randomized those with NDH *and* a lower range IFG (≥ 100 – < 110 mg/dl) [14-16] from May, 6th , 2014. and also accepted paired HbA1c ≥ 6.5% as a primary end point (as well as paired FPG ≥ 126 mg/dl) for the diagnosis of Type 2 diabetes.[14-16,35] IGT during an oral glucose tolerance test was not used to randomise participants.[14-16,35] To identify high risk participants we contacted 194 primary care practices in the East of England and 135 (70%) collaborated. We invited all individuals without known diabetes in these practices who were a) age ≥ 40 years with a body mass index (BMI) ≥ 30 kg/m^2 or b) age ≥ 40 years and BMI ≥ 25 kg/m^2 with

a recorded first degree family history of Type 2 diabetes, a history of coronary artery disease, or gestational diabetes or c) any previous high risk glycemic category diagnosis by recorded category or biochemical range.[35] Ethnicity was participant defined, and this data was collected as important in Type 2 diabetes risk assessment.

Randomization and consent We used a rolling recruitment methodology to randomize participants in parallel to the screening programme. Participant screening, recruitment, and randomization spanned the study duration and continued from August 2011, up until March 24th 2017 and allowed each participant to reach at least the six - month time point follow - up appointment , and up to 46 months maximum. Eligible participants were randomized into a control arm (CON) who received no trial intervention, an intervention arm (INT) who received a lifestyle intervention (INT), or into an intervention arm who received the same intervention, but with additional telephone support from lay diabetes prevention mentors (INT-DPM). Randomization was conducted automatically using a dedicated function in the trial data management system. The randomization mechanism consisted of a pre-prepared random list of codes (for the Intervention and control groups) stored in the trial database. To reduce the risk of predicting the next allocation while maintaining a reasonable even spread of intervention and control patients, the list was constructed of blocks of 17 codes (3 CON, 7 INT, and 7 INT-DPM) to approximate the proportions of 170:390:390 respectively. Randomization policies are described in *Supplement :erandomization* and published.[35] Randomization was asymmetric between groups to maximize sample size and power for comparisons between the intervention groups. Ethical approval was obtained from the National Research Ethics Service (NRES), Essex 1 Research Ethics Committee (10/H0301/55; January, 13th .2011) and all participants gave written informed consent. There was no significant clinical trial evidence for diabetes prevention benefit with a structured lifestyle intervention in IFG or NDH subjects at NDPS inception, and no UK national prevention programme, and it was ethical to have a control group who received then standard best care.

Interventions The intervention was delivered by trained healthcare professionals alone (diabetes prevention facilitators; DPF), or delivered jointly by DPF and DPM.[35,37] The intervention theory aimed to support maintenance of changes in physical activity and diet, using patient centred counselling techniques to encourage decision making about behavior change, increase motivation to change, engage social support, aid individually tailored goal setting, action planning and self-monitoring, and support problem solving.[35,37] Behavior change targets were set by participants, who were encouraged to think about (and presented with the health benefits of) 7% weight loss if BMI was > 30 kg/m^2, achieving 150 minutes per week of moderate intensity physical activity over 5 days or more, 2-3 sessions of muscle-strengthening exercise per week, and reducing intake of total and saturated fat. The intervention comprised six 2 -hour educational group sessions of varying content for 12 weeks, followed by up to 15 maintenance sessions eight weeks apart from month 4. Maintenance sessions were discussion based and followed the same format, including a 50 minute supervised physical activity /muscle-strengthening exercise session. Sessions contained no more than 15 participants.

The maximum contact time per participant was 49.5 hours. Participants randomized to the INT – DPM arm received additional individual motivational telephone calls between sessions.[35,37] DPMs were assigned up to seven participants and telephone contacts were monthly for the first 3 months and then every 2 months. During these contacts, the DPM and participants discussed progress, goal achievement, action planning, and barriers to coping. INT – DPM participants therefore received a contact from the study at least every four weeks. Control participants (CON) received written information and discussion about the risk of diabetes, and the impact of lifestyle modification on reducing this risk in line with then current local NHS clinical policy. This was delivered in a single 2-hour session delivered by a DPF.[35,37]

Materials and methods. Fasting plasma glucose was measured by a hexokinase/G-6-PDH method (Architect c8000: Abbott, Maidenhead, UK). HbA1c was measured using Affinity high performance liquid chromatography (Hb9210: Menarini Diagnostics Ltd., Wokingham, UK). Additional detail on our methods and materials [38-42] are published [35] and described in detail in *Online Supplement : emethods,* which includes a fuller description of measurement of physical activity, homeostasis model assessment (HOMA) of insulin sensitivity and beta cell function, and social deprivation scores.

Outcomes. The primary outcome was the development of Type 2 diabetes based on paired HbA1c data both ≥ 6.5%, or paired fasting glucose both ≥ 126 mg/dl. Pre specified secondary outcomes are described [35] and in *Supplement : emethods.*

Statistical analysis plan and power estimates The assumed power calculations and sample size estimates are summarised in Supplementary material e: statistical analysis plan, The primary statistical analysis compared the proportions of participants in each group who progressed to Type 2 diabetes, independent of duration of follow-up. We used an intention-to-treat approach to analysis. For binary outcomes we used the chi-squared test, and logistic regression for adjustment for baseline imbalances. For continuous outcomes we used the *t*-test for comparison of two arms, or analysis of covariance for comparison of all three, and linear regression for adjustment for baseline imbalances. The primary outcome measure was progression to T2DM by study exit, analysed using a logistic regression model including a covariate to account for the different potential follow-up times at baseline. The full statistical analysis plan, power estimates, sample size, and attained power are published [35] and summarised in *Supplement e:Statistical analysis plan.* We also analysed and present the main outcome data using a proportional hazards model as a secondary analysis.

Health economic analysis

A within-trial analysis was conducted to estimate the cost-effectiveness of the intervention (with and without DPM), compared to usual care. [35] These methods are summarised briefly in Supplement e Health Economic Analysis, but the full analysis will be published separately.

Results

We invited 141,973 people at increased risk of Type 2 diabetes to participate, and 12,778 (9.0 %) were screened. Between Oct 1st 2011 and June 1st 2017 we randomized 424 eligible participants into the standard INT arm, 426 into the INT – DPM arm, and 178 into the control arm (CON). Baseline characteristics and flow through the trial are shown (Table 1; Figure 1). Mean follow up was 742 days (24.7 months), and by arm were 727 (CON), 744 (INT), and 746 daysn(INT – DPM). Between 75% and 78% were followed up for at least 12 months in a rolling recruitment until the end of the recruitment period (Figure 1). There were no significant differences between arms in baseline age (p = 0.87) or BMI (p = 0.80) in those who withdrew from intervention.

Of those who attended at least one intervention session,during follow up, 156 participants progressed to Type 2 diabetes, 39/171 CON arm (22.8 %; estimated adjusted annual incidence 11.0%), 55/403 INT arm (13.7%; estimated adjusted annual incidence : 6.4%) , and 62/414 INT–DPM arm (15.0%; estimated adjusted annual incidence adjusted for follow up 7.1%; *Supplement : eTable e1*). There was no significant difference between intervention arms (INT vs INT – DPM) in the primary outcome (Odds Ratio OR 1.14; 95% CI 0.77 – 1.70; p = 0.51; Table 2; Figure 2).

There were highly significant reductions in the primary end-point between each intervention arm compared to CON, and between a combined intervention group compared to CON (Tables 2; Figure 2). INT: OR 0.54 (95% CI 0.34 – 0.85; p= 0.008), INT – DPM: OR 0.61 (95% CI 0.39 – 0.96; p = 0.033), combined INT and INT–DPM : OR 0.57 (95% CI 0.38 – 0.87; p = 0.008). The fully adjusted effect size was between a 36 and 42% reduction in the odds of Type 2 diabetes (Table 2) depending on arm. These data are shown for our primary analysis using a logistic regression model (Table 2) and also a proportional hazards model as a secondary analysis (Table 2)

Estimates of differences for the primary outcome of Type 2 diabetes by subgroup showed no significant interactions with age band, sex, deprivation score, body mass index (BMI), or initial diagnostic category (NDH or IFG) in the risk of developing Type 2 diabetes in any arm or the combined group (Table 3). Broadly, one participant was prevented from developing diabetes for every 11 intervention participants.

At 12 months the combined intervention group showed significantly lower baseline- adjusted weight (-1.76kg ; 95% CI -2.55 to - 0.97; p = 0.01), waist circumference (-2.48 cm, 95% CI -3.67 to -1.29 ; p = < 0.01), BMI (- 0.59 kg/m^2 ; 95% CI -0.86 to -0.31; p = < 0.01) and greater physical activity (MET mins per week p=0.008) compared to controls (*Supplement: eTable e2*), with no significant changes in self-reported dietary measures. These differences were apparent for each intervention arm compared to the CON arm. At 24

months, lower mean adjusted weight loss in the combined intervention group was maintained (– 1.47 kg ; -2.64 to –0.30; p = < 0.01) with highly significant differences in adjusted physical activity compared to controls (*Supplement: eTable e3*). Within the intervention arms, weight loss was particularly marked in the intervention subgroup attained a 'high dose' of the intervention compared to those with a low dose at 24 months (INT : -3.29 ; - -4.97,-1.62; p < 0.001; INT – DPM : - 3.65kg ; -5.99, -1.32; p = 0.002; *Supplement: eTable e4*). The data on 'dose response' effects, unadjusted data, and descriptive data at each time point, are further described and shown in *Supplement :eResults and Supplement: eTables e5 – e8).* Mean intervention costs per participant were estimated as $153 (£122) in the INT arm and $301 (£241) in the INT-DPM arm. The full Health Economic Analysis will be published separately.

Discussion. In this trial, people with a current high risk intermediate glycemic category of IFG and /or NDH were 40 – 47% less likely to develop Type 2 diabetes in the intervention groups compared to controls, over an average 24 months. Broadly, one person was prevented from developing Type 2 diabetes for every eleven who received the intervention. The enhanced intervention with trained Type 2 diabetes volunteers (DPM) did not further reduce the risk of Type 2 diabetes. These findings are relevant to normal clinical practice, as nearly half the older adult population now have a high risk glycemic category or diabetes,[4 – 6, 36] as do one- third of obese young adults, with IFG constituting the largest element.[4 - 7]

NDPS is the largest Type 2 diabetes prevention trial since the US DPP more than 20 years ago [19 - 22] and now extends the prevention evidence base to the contemporary high risk glycemic categories. Nearly all of the earlier landmark trial evidence on diabetes prevention is drawn from people categorised as IGT using an oral glucose tolerance test. [19-22] The assumption that this earlier evidence can simply be translated with similar expected benefit to IFG or NDH populations with a different phenotype may not be valid.[18-23] NDPS now provides the reassurance that a low-cost group-based lifestyle intervention in these high risk groups does have a substantial impact in preventing Type 2 diabetes.[19 -22] The glycemic criteria we used are those now recognised as identifying high risk of diabetes individuals in UK prevention policy, in the NHS England diabetes prevention programme, and in USA prevention programs.[10-13] Our results are therefore translatable to the current clinical and policy context.

Meta - analysis of 11 similar trials with a diet and physical activity intervention of more than 2 years in high risk glycemic categories ,[20] described a similar composite effect size of RR 0.57 (CI 0.5 to 0.64; $p < 0.00001$). In that analysis, nine trials [20] exclusively randomized based on oral glucose tolerance test data, one included IFG or IGT, and one included people with a fasting glucose 95 – 124 mg/dl.[20,23] None used NDH –IFG as the primary entry criteria to trial, or HbA1c as primary end point, in line with current international practice, although the US DPP program did analyse HbA1c as a secondary outcome. [43] NDPS effect size did not differ significantly in subgroups defined by glycemic category, BMI, age or social deprivation. The only other comparable UK clinical trial used oral glucose tolerance testing as entry criteria and primary end point, and found no overall diabetes prevention benefit other than in a subgroup attaining a higher intervention dose.[44,45] Our full within - trial economic analysis will be published separately, and the high costs of the intense interventions in the early landmark research trials are well recognised [46], although intervention models translated into clinical settings may be deliverable at lower cost.[45,47-49]

The combined intervention group at 12 months had a significantly lower mean weight (-1.76kg), waist circumference (-2.48 cm) and body mass index. Despite relatively low levels of weight loss, compared with the landmark studies in the field, the maintenance of behaviour changes or “area under the curve” generated may be partly responsible for the high level of impact on diabetes incidence. For the subgroup who attained a high intervention dose, weight loss was significant even at two years into the programme (- 3.47 kg) compared to those attaining a low dose. These weight changes are similar to that seen in systematic analysis of weight loss

in intervention arms in both translational and controlled trial prevention studies.[28] It is also similar to the observed mean weight loss in high attenders the NHS England diabetes prevention Program (DPP).[12] The longer term legacy effect of the NDPS intervention on Type 2 diabetes incidence and maintained weight loss is of course unknown, but some short term regain of lost weight after an intensive lifestyle intervention is a common observation in people with obesity, Type 2 diabetes, or high risk glycemic categories, particularly in those with least initial weight loss.[49-52] We also observed a significant increase in energy expenditure in the intervention groups (e Supplementary material Table 3 – 7). There is a direct consistent association between reduced Type 2 diabetes risk and an increase in almost all type of physical activity and energy expenditure, which is only in part mediated through changes in adiposity.[53]

The DPM supplemented intervention group (INT – DPM) did not differ significantly from the standard intervention group (INT) in the risk of Type 2 diabetes, any secondary outcome, or in participant adherence to intervention. The use of lay volunteer health workers to deliver lifestyle modification interventions for people at high risk of Type 2 diabetes, or with established type 2 diabetes, is well recognised [30-32] but our model did not add value. [30-32,37] Only one other study has used people with Type 2 diabetes in this role to prevent diabetes [53] with significant improvement in risk markers, although it is unknown if this translated into a lower Type 2 diabetes incidence. The impact of lay or peer volunteers on Type 2 diabetes prevention in high risk groups has been reviewed, with 30 studies (including 10 randomised controlled trials), largely delivered in high income countries to largely non - white minority populations, and studies of between 20 and 2,369 participants. [30] None of these reported a diabetes prevention benefit with diabetes as an endpoint, or were powered to detect such an outcome, although there were commonly improvements in surrogate markers for diabetes risk [30] Cluster randomised controlled trials in high risk groups using generic lay trainer programmes to support or deliver the intervention have also shown no significant impact in diabetes prevention in community or primary care settings.[32] The NDPS DPM training, levels of retention in programme, responsibilities, and level of contact would be regarded as moderate to high compared to other models [30,37]. A telephone delivered intervention as we used is as acceptable to participants with NDH as more complex digitally enabled health coaching [54] and as effective in risk marker reduction as face to face interventions in people with intermediate high risk of diabetes categories. [33,34,55] There is evidence that more frequent contact by telephone peer contact has a greater value in reducing Type 2 diabetes risk. [56] In established T2DM the frequency of peer contact is a key feature of effectiveness in terms of glycemic change.[57] The framework in which the NDPS DPM operated was also highly supportive and structured within a multidisciplinary diabetes prevention team, one of the more effective ways to use lay volunteers.[30,36] We do not think therefore that the the lack of effect our DPM model is due to low intensity DPM training, a short duration of intervention, or an unsupportive framework.[30,36] It is possible that more intensive contact from the DPM and higher frequency telephone contact may have been more effective. [32,33,55,56] It is also quite possible that the lack of DPM effect could be due to the already large prevention effect size already attained with the standard intervention alone. The use of lay trainers (with or without Type 2 diabetes) in diabetes prevention remains an attractive model, but the most effective model

remains to be determined, and future trials should test different levels of contact intensity, compare efficacy of different lay groups, and using DPM as the primary intervention team.

The progression incidence to Type 2 diabetes in the control arm was an adjusted annual 11.9%. This is a high incidence for these glycemic categories, where very broadly an annual rate of 5 – 11% has been described over 5 years.[21] In the US DPP , mean follow up was 2.8 years, and crude incidence rates were 11.0 cases per 100 participant years in controls, and 4.8 in the lifestyle intervention group. [22] This high rate in NDPS reflects our inclusion criteria which were designed to identify and randomise those at highest risk. [35] We also excluded lower risk participants with an NDH range HbA1c and a normal fasting glucose < 100 mg/dl. [58] We also randomized only those with paired abnormal baseline data at lower risk of regression to normal glycemic status ,[35,56,59,60] and we used both HbA1c and fasting glucose-based definitions of diabetes for the end –point, in line with normal clinical practice. The high progression incidence when "high risk" is categorized this way validates the use of this approach in clinical guidelines and in the NHS England NDPP and confirm the importance of taking action in these high risk groups.[12,13]

At the start of NDPS there was no substantial trial evidence of outcomes benefit from an active lifestyle intervention in diabetes prevention in IFG or NDH populations, and NDPS antedated the UK national diabetes prevention programme [12] and UK national guidance on best practice in prevention of Type 2 diabetes [13] . During NDPS, the control participants received what was (and still is for much of the population) standard best practice UK NHS care for people with a higher risk intermediate glycaemic risk category, with a 2 hour education session with a diabetes prevention facilitator to discuss their risk of diabetes and then six month and annual review and monitoring. Lifestyle educators are not generally available in practices, and arguably the control group received a higher level of support than in normal clinical practice. The original age and BMI criteria for screening in NDPS were designed to be concordant with the the UK National Cardiovascular Risk Assessment primary care programme in England [61,62]. This programme started in 2009 , is one of the largest cardiovascular risk screening programs in the world, and aims to screen > 3M high risk individuals in primary care. There is a substantial glycemic element to the screening, and in 2011 we wished any positive outcomes from NDPS to be translatable to the large populations detected in this national programme, and to access participants selected in this way as part of normal clinical care.[61,62]

There are limitations in NDPS. The participants come from a largely white population, and results may not be translatable to more ethnically diverse populations, or other ethnicities with different patterns of glycemic risk.[11,12,51,52] This would also apply to adolescent and young adults with a high prevalence of high risk glycemic categories, but where there is no trial evidence for efficacy.[6] The attained power and effect size strongly support the view that our intervention is effective in diabetes prevention, and while power attained between intervention groups analysis was lower, rates of progression were very similar, and any difference is unlikely to be meaningful. More than 75% of participants were followed for at least 12 months, with prolonged follow up of participants recruited earliest, which added power to the study, and missing data levels were very low.[63] There is a more general observation, common to all similar trials, that wider population level approaches to

Type 2 diabetes prevention are needed.[64] However, NDPS now extends the diabetes prevention evidence base to the modern populations with an at risk glycemic category,[18] where trial evidence has been lacking, and with an impact on diabetes incidence close to that seen in high intensity clinical trials.[18-20] NDPS confirms that prevention efforts in these current high risk populations are effective, and brings the evidence base into line with current practice. The glycemic criteria we used are those now recognised as identifying high risk of diabetes individuals in UK prevention policy, in the NHS England diabetes prevention programme, in the UK national vascular screening program [62] and in USA prevention programs.[10-13] Our intervention materials and model are translatable and available to clinicians in practice, and suggest that a pragmatic group -based lifestyle intervention reduces the risk of Type 2 diabetes in these large populations currently being detected in primary care.

Full NDPS group Sara Auckland, Max Bachmann, Garry Barton, Allan Clark, Ketan Dhatariya, Clare Ferns, Nikki Garner, Colin Greaves, Andy Goldson, Martin Hadley-Brown, Amanda Howe, Lisa Irvine, Garry John, Melanie Pascale, David Rea, Jane Smith, Jeremy Turner Rebecca Usher, Tara Wallace.

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Data access, responsibility, and analysis. Three authors (MJS/MB/AC) had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests
We declare no competing interests for any author

Contributions to manuscript. **MS** (CI) led on study design, data interpretation, and manuscript writing. **AC** was co - investigator & trial statistician, led on the statistical analysis , the accuracy of the data analysis, data quality and contributed to trial design, data interpretation and writing. **MB** was co - investigator and contributed to trial design, data interpretation and writing.**NG** contributed to trial design, data interpretation, and writing **LI** led on health economic analysis, and on data interpretation and writing **AH** was a co - investigator and contributed to trial design, data interpretation and writing.**CG** was a collaborator and contributed to intervention design and delivery, data interpretation and writing **SA** contributed to intervention design, data interpretation and writing **JS** was a co - investigator and contributed to trial design, data interpretation and writing **JT** was a co - investigator and contributed to trial design, data interpretation and writing **DR** was a co - investigator and contributed to trial design, participant engagement, and writing **GR** was a collaborator and contributed to data collection, data interpretation, and writing **KD** was a co - investigator and contributed to trial design, data interpretation and writing **GJ** was a co - investigator and contributed to trial design, data interpretation and writing **GB** was a co - investigator and contributed to trial design, health economic analysis, data interpretation and writing **RU** contributed to data collection, intervention design, and writing **CF** contributed to data collection, analysis, and writing **MP** contributed to data analysis, data interpretation, and writing.

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Figure 1 Trial CONSORT profile (revised and now as a separate document)

Table 1. Baseline characteristics of control arm (CON) , standard intervention arm (INT) , and intervention arm with diabetes prevention mentors (INT-DPM).

		CON	INT	INT-DPM
n		178	424	426
Age, mean (SD) , years		65.3 (10.0)	66.5 (8.6)	66.7 (9.5)
Ethnicity White/South Asian/Black/Other (%)		96/1.7/0.6/1.7	97.1/1.7/0/1.2	97.1/1.2/0/1.7
Sex (n ;%)	**Female**	70 (39.3)	166 (39.2)	147 (34.5)
	Male	108 (60.7)	258 (60.8)	279 (65.5)
Family history Type 2 diabetes (n ; %)		67 (37.6)	173 (40.8)	167 (39.2)
Family history cardiovascular disease (n ; %)		22 (12.4)	63 (14.9)	57 (13.4)
Previous gestational diabetes (n; %) [a]		4 (5.7)	12 (7.2)	18 (12.2)
Social deprivation score, mean (SD) [b]		15.5 (10.6)	15.4 (10.2)	16.2 (10.7)
Weight, mean (SD), kg		90.5 (17.8)	90.2 (18.2)	89.8 (17.4)
Body mass index, mean (SD), kg/m^2		31.2 (5.0)	31.1 (5.6)	30.9 (5.6)
Waist circumference, mean (SD), cm		105.1 (13.1)	105.1 (13.5)	105.2 (13.0)
Body fat mass , mean (SD), kg [c]		35.2 (8.8)	34.0 (9.0)	33.6 (8.9)
Impaired fasting glucose (IFG), n (%) [d]		114 (64.0)	261 (61.6)	256 (60.1)
Non diabetic hyperglycemia (NDH), n (%) [d]		64 (36.0)	163 (38.4)	170 (39.9)
HbA1c, mean (SD), %		6.1 (0.3)	6.1 (0.3)	6.1 (0.3)
Fasting plasma glucose, mean (SD), mg/dl		112 (7.2)	112 (7.2)	113 (7.2)
Fasting HDL cholesterol, mean (SD), mg/dl		49.5 (13)	38.7 (13)	38.7 (13)
Fasting LDL cholesterol, mean (SD), mg/dl		119.1 (35)	117 (34)	118 (35)
Fasting plasma insulin, mean (SD), pmol/l)		108.3 (72.5)	95.7 (54.4)	91.0(57.1)
HOMA insulin sensitivity, mean (SD), (%) [e]		68.5 (41.9)	73.2 (51.5)	77.6 (47.2)
HOMA beta cell function, mean (SD), (%) [e]		98.1 (44.0)	90.6 (35.6)	88.2 (36.3)
Physical activity , mean (SD), MET minutes per week [f]		2507 (2761)	2701 (2640)	2660 (2748)
Physical activity, mean (SD), minutes sitting per week [f]		442 (269)	463 (263)	431 (241)
Low physical activity category, n (%) [f]		42 (32.3)	91 (29.4)	98 (32.3)
Dietary fat intake scale, mean (SD) [g]		2.3 (0.3)	2.3 (0.3)	2.3 (0.3)
Wellbeing score (W - BQ12), mean (SD) [h]		24.8 (6.1)	25.1 (6.5)	25.0 (6.1)
Health related quality of life score (EQ-5D) , mean (SD)[h]		0. 8 (0.2)	0.8 (0.2)	0.8 (0.2)

Data shown as mean and one standard deviation (SD) for continuous variables, or as n (%) for categorical variables. [a] Female participants, [b] IMD Social Deprivation score [30], Body fat by Tanita body composition analyser,[30] [d] Impaired fasting glucose (IFG: paired baseline fasting plasma glucose ≥ 110 – < 126 mg/dl. [d] Non - diabetic hyperglycemia (NDH) - paired baseline HbA1c ≥ 6.0 – < 6.5 % with IFG fasting plasma glucose ≥ 100 – < 110 mg/dl [e] Homeostasis model assessment (HOMA) of baseline insulin sensitivity (S) and beta cell function (B) expressed as % of standard reference range, from fasting plasma insulin and glucose data. [38] [f] Physical activity scales (energy expenditure during physical activity (metabolic equivalent of task (MET) minutes per week), low physical activity category, and sedentary time derived from international physical activity questionnaire IPAQ.[39,40] [g] Dietary fat and fiber scores based on self-reported Diet Behaviour Questionnaire (DBQ).[41] [h] Well - being score (WBQ-12) questionnaire, health related quality of life score (EQ-5D) questionnaire .[30,42-44] To convert conventional units to SI unit, for total, HDL and LDL cholesterol (mg/dl) multiply by 0.0259 (mmol/l), for plasma glucose (mg/dl) by 0.0555 (mmol/), and glycated hemoglobin (%) by 0.0915IFCC units (mmol/l) + 2.15.

Table 2 Estimates of difference between treatment arms in odds ratio of developing Type 2 diabetes shown as estimated value and 95% confidence interval and hazard ratio between treatment arms in time to developing Type 2 diabetes, shown as estimated value and 95% confidence interval in Cox regression models.

Analysis	INT – DPM vs INT	p	INT vs CON	p	INT- DPM vs CON	p	Combined intervention vs CON	p
Odds Ratio Unadjusted	1.11 (0.75, 1.65)	0.59	0.53 (0.34, 0.84)	0.007	0.60 (0.38,0.93)	0.024	0.57 (0.38, 0.85)	0.006
Odds ratio Adjusted [a]	1.12 (0.75,1.65)	0.59	0.54 (0.34, 0.85)	0.008	0.60 (0.38, 0.94)	0.024	0.57 (0.38, 0.85)	0.007
Odds ratio Adjusted [b]	1.14 (0.77,1.70)	0.51	0.54 (0.34, 0.85)	0.008	0.61 (0.39, 0.96)	0.033	0.57 (0.38, 0.87)	0.008
Hazard ratio Unadjusted	1.09 (0.76,1.57)	0.63	0.53 (0.35,0.80)	0.003	0.62 (0.41, 0.92)	0.019	0.57 (0.40,0.82)	0.002
Hazard ratio Adjusted [c]	1.13 (0.78,1.63)	0.51	0.53 (0.35,0.81)	0.003	0.64 (0.43,0.97)	0.033	0.58 (0.41,0.84)	0.004

INT : Standard intervention group ; INT – DPM : intervention group with diabetes prevention mentors (DPM) ; COMBINED Intervention is both intervention groups (INT – DPM and INT) combined for comparison against CON; CON : control arm without trial intervention. [a] adjusted for duration of follow up [b] adjusted for follow up length and age, BMI and fasting plasma glucose levels at baseline. [c] Adjusted at baseline for age, BMI and fpg levels. Please note the primary analysis in NDPS was a logistic regression model with data presented as odds ratios (above). A secondary analysis using a proportional hazard model is also shown with hazard ratios (above).

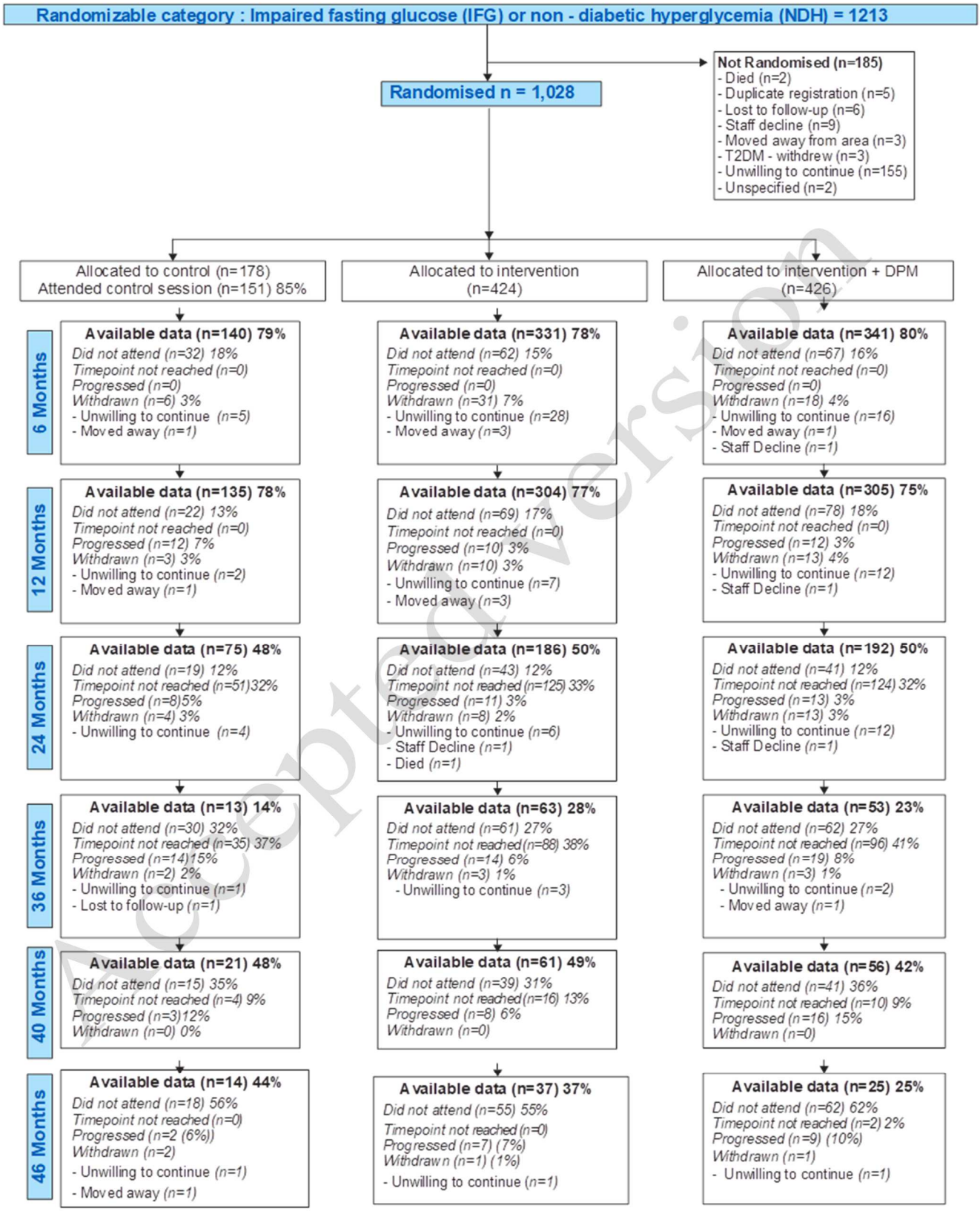
Table 3. Estimated odds ratio between treatment arms of developing Type 2 diabetes by sub groups : age, sex, deprivation score, body mass index, and diagnostic category shown as odds ratios and 95% confidence interval: logistic regression models.

	INT – DPM vs INT	Inter action p	INT vs CON	Inter action p	INT- DPM vs CON	Inter action p	Combined intervention vs CON	Inter action p
Male	1.07 (0.66, 1.73)	0.83	0.50 (0.28, 0.87)	0.68	0.53 (0.31, 0.92)	0.54	0.51 (0.31, 0.85)	0.58
Female	1.17 (0.59, 2.34)		0.61 (0.89, 1.35)		0.72 (0.32, 1.57)		0.66 (0.32, 1.34)	
Age < 65 years	1.34 (0.71, 2.51)	0.46	0.47 (0.23, 0.96)	0.63	0.63 (0.31, 1.25)	0.87	0.55 (0.29, 1.03),	0.88
Age ≥ 65 years	0.99 (0.60, 1.63)		0.59 (0.33, 1.06)		0.58 (0.32, 1.05)		0.58 (0.34, 1.00)	
Deprivation quartile 1 (low) [a]	1.49 (0.62, 3.57)	0.53	0.54 (0.20, 1.47)	0.13	0.80 (0.31, 2.09)	0.11	0.66 (0.28, 1.59)	0.08
Deprivation quartile 2	0.71 (0.35, 1.46)		0.87 (0.34, 2.21)		0.62 (0.24, 1.59)		0.73 (0.31, 1.73)	
Deprivation quartile 3	1.40 (0.63, 3.09)		0.80 (0.30, 2.15)		1.11 (0.42, 2.93),		0.94 (0.39, 2.31)	
Deprivation quartile 4 (high)	1.14 (0.51, 2.50)		0.23 (0.09, 0.53)		0.26 (0.11, 0.59)		0.24 (0.11, 0.51)	
BMI quartile 1 [b]	1.63 (0.72, 3.73)	0.15	0.42 (0.15, 1.14)	0.94	0.67 (0.27, 1.71)	0.45	0.55 (0.23, 1.32)	0.89
BMI quartile 2	1.03 (0.48, 2.21),		0.62 (0.25, 1.49)		0.63 (0.26, 1.54)		0.62 (0.28, 1.39)	
BMI quartile 3	0.54 (0.24, 1.22)		0.59 (0.26, 1.37),		0.32 (0.13, 0.80)		0.45 (0.21, 0.97)	
BMI quartile 4 (high)	1.78 (0.79, 3.99)		0.50 (0.19, 1.31)		0.88 (0.36, 2.17)		0.69 (0.30, 1.57)	
Impaired fasting glucose (IFG) [c]	0.92 (0.53, 1.61)	0.35	0.55 (0.29, 1.05)	0.89	0.51 (0.26, 0.97)	0.50	0.53 (0.29, 0.95)	0.76
Non-diabetic Hyperglycemia (NDH) [d]	1.34 (0.77, 2.32)		0.52 (0.27, 0.98)		0.69 (0.37, 1.28)		0.60 (0.34, 1.06)	

p value for interaction within each subgroup by arm comparison (INT : Standard intervention ; INT – DPM : intervention with diabetes prevention mentors (DPM) ; CON: control arm ; COMBINED Intervention is both intervention groups (INT – DPM and INT) combined for comparison against CON; . [b] IMD Deprivation scores [30] [b] Body mass index (BMI) quartile values are 1: 19 – 27 kg/m^2 , 2: 27 to 30.37 kg/m^2, 3: 30.38 to 33.83 kg/m^2, 4: 33.86 to 57.65 kg/m^2 [c] Impaired fasting glucose (IFG: paired baseline fasting plasma glucose ≥ 110 – < 126 mg/dl. [d] Non - diabetic hyperglycemia (NDH) - paired baseline HbA1c ≥ 6.0 – < 6.5 % with IFG fasting plasma glucose ≥ 100 – < 110 mg/dl

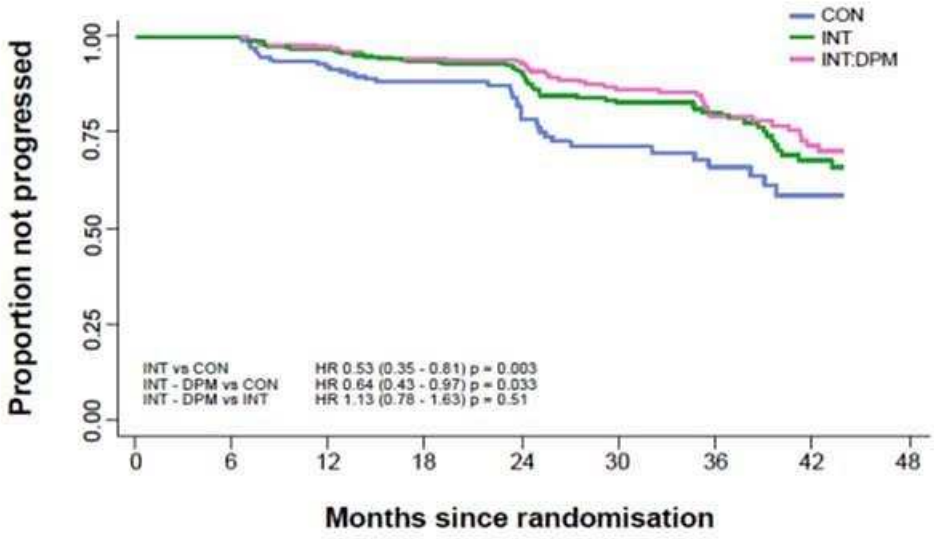
Figure 2. Kaplan-Meier estimate of time to progression by treatment trial arm.

Figure 1 Trial CONSORT profile



N.B. 'Time point not reached' refers to the number of participants randomised as planned, but not at a point during rolling recruitment that provided planned data collection at that later time point.

Figure 2. Kaplan-Meier estimate of time to progression by treatment trial arm.



Number at risk						
Control	178	170	148	82	38	7
Intervention	424	389	342	202	114	24
Intervention - DPM	426	403	355	210	105	27

Online Supplementary Material **A lifestyle intervention (with or without lay volunteers) to prevent Type 2 diabetes in people with impaired fasting glucose and/or non-diabetic hyperglycemia : a randomized clinical trial. (Sampson MJ et al.)**

Summary of content in the Online Only Supplement

1) **e Methods** : detailed summary of methods and secondary analyses.
2) **e Statistical analysis plan** : detail for statistical analysis plan and power estimates
3) **e Intervention** : detail on intervention and intervention fidelity
4) **e Health Economic methods** – summary of approach
5). **e Randomization** : randomization methodology
6) **e Results** : results for additional subgroup analysis by dose adherence
7) **e Data Tables** : unadjusted data, and absolute values, in line with CONSORT requirements.

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eTable 2	Adjusted mean differences (95% CI) between trial arms at 12 months: linear regression models
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8) **e References :** additional references for online only material. Please note some of these references duplicate the main reference manuscript list.

1) e Methods

Fasting plasma insulin was measured on the Siemens Immulite 2000 XPI (Siemens Healthcare Ltd, Sir William Siemens Square, Frimley, Camberley, Surrey. GU16 8QD), and homeostasis model assessment (HOMA) of insulin sensitivity and beta cell function calculated. [1] Physical activity as an outcome measure was measured by gathering responses via questionnaire to capture not only participants aerobic physical activity but also their resistance activity. Aerobic physical activity was measured using the short form IPAQ (International Physical Activity Questionnaire [2,3] which gathers information on the intensity of the activity being engaged in (vigorous, moderate or light), for how long and on how many days of the week, steps walked and on how may days , and also the amount of sedentary activity measured in hours each day. These data were converted to METS or Metabolic Equivalents to express the intensity of physical activity [2,3]. Resistance activity was measured by self-report via questionnaire specifically measuring mode and duration of training on how many days of the week. Questionnaire measures were administered at follow up time point assessments (0, 6, 12, 24,36, 40 months). In addition to physical activity as an outcome measure, participants attended physical activity circuit sessions as part of their maintenance sessions within the intervention. These sessions were 50 minutes duration and covered both aerobic and resistance exercises and were delivered by a physical activity facilitator (PAF). Participants moved around a circuit of 'stations', with each having a set exercise to perform and up to a choice of 4 levels at which to perform at. The levels represented the intensity of that exercise, allowing participants the opportunity to increase and improve on their performance as their intervention progressed. Participants in the two intervention groups were additionally given a pedometer which showed daily step count. The pedometer was intended as a motivational tool to encourage an increase in activity. Pedometers were given at the first Education session and were retained throughout the study. The data from pedometers was not collected for analysis. As part of the Education phase of the intervention, two sessions focused specifically on physical activity and part of those session involved the review of a physical activity diary completed by participants over the previous 7 days. This data was not included for analysis but again, allowed the participants to monitor and self-regulate their exercise behaviour. Finally, physical activity levels were discussed as part of participants progress review section within the intervention sessions and DPM telephone calls. Physical activity was outputs were reported in categories (low, moderate, high activity levels) or as a continuous variable describing the amount of energy expenditure during physical activity (metabolic equivalent of task [MET] minutes per week), as well as the purpose-made questionnaire assessing frequency of engagement in resistance activity and sedentary time [2,3] Dietary behaviours related to fat and fiber intake were assessed using a self-reported Diet Behaviour Questionnaire (DBQ) adapted from an existing dietary questionnaire.[4] The WBQ-12 questionnaire was used to measure general well-being, including negative well-being, energy and positive well-being [5] Health related quality of Life was measured using the validated EQ-5D questionnaire.[6,7] Diabetes quality of life was assessed using item 1 from the ADDQol questionnaire. [6,7] Measures of deprivation for each participant were derived from published indices of deprivation [8]

2) e Statistical analysis plan

The primary and secondary analyses and original statistical analysis plan have been described [9] . Secondary analyses included a per-protocol analysis and analysis of secondary outcome measures. We used multiple imputation to assess sensitivity of results to missing data. A secondary analysis adjusting for potential prognostic factors was agreed prior to the final analysis. Secondary continuous outcome measures were analysed using a general linear model in a similar fashion using the latest measurement at study exit as outcome. Time-until progression to T2DM was also analysed using a discrete time survival analysis model. Longitudinal analyses of the repeated continuous secondary endpoints were undertaken to assess for differences between arms over time, using a random effect approach. Magnitudes of effects were estimated for all two-way comparisons of intervention groups and no adjustment for multiple testing was undertaken. In order to assess dose-response relationships with between progression and adherence to the interventions, analyses were undertaken in each intervention group separately. Four sets of between-group comparisons were made, INT-DPM vs INT being the primary comparison, and INT vs CON, INT-DPM vs CON, and INT combined with INT-DPM vs CON being secondary comparisons. The first of these was not adjusted for duration of follow-up, and the second additionally adjusted for baseline age and BMI as these were known prognostic variables. Sensitivity analysis was adjusted for baseline age, BMI and IFG levels. Subgroup analyses were conducted separately for gender, age (<65 vs >=65), deprivation quartile, BMI quartile, and baseline diagnosis (IFG vs NDH) subgroups, by including subgroup-treatment group interaction terms in the respective models. Secondary outcomes were compared at 12 month and 24 month time points using an unadjusted analysis with a two-sample t-test, and an adjusted analysis with linear regression models adjusting for baseline values of the respective outcome variables. Secondary outcomes which were ordinal were compared using ordinal logistic regression models. A within-group comparison was made to assess dose-response relationships, within each intervention group, as follows. Firstly, an unadjusted analysis was conducted in each group by fitting a Cox-proportional hazard model for progression and a linear regression model for the other outcomes, with dose the only covariate in the model. Secondly, an adjusted analysis was conducted by selecting variables using forward selection. For INT group the 'dose of intervention' attained was defined as: LOW (less than 30% attendance at sessions), MODERATE (between 30% and 59% attendance), and HIGH (at least 60% attendance at sessions). For the INT – DPM group, these doses were defined as: LOW (less than 30% attendance at sessions regardless of calls connected OR less than 30% of calls connected regardless of attendance at sessions);

MODERATE (between 30% and 59% attendance at sessions and more than 30% of calls connected or between 30% and 59% of calls connected and more than 30% attendance at sessions); HIGH (at least 60% attendance at sessions AND at least 60% of calls connected). We also analysed and present data using a proportional hazards model as a secondary analysis. The assumptions underlying the original statistical analysis plan, sample size estimates, and initial power calculations have been described.[8] Original power estimates were based on assumed transition rates from IFG to T2DM in Northern European white populations, an estimated relative risk of 0.51 after diet and lifestyle intervention and an 8 % progression rate in CON and a 4% annual progression in the INT.[8] An original model 36 month intervention asymmetrically randomized controlled trial of 170 controls [CON] and 390 INT participants would give 80% power at 5% significance level to detect this difference in proportions progressing. We hypothesized that the intervention effect size would be further enhanced by additional support from the DPM and the DPM group would experience a T2DM incidence rate of 2% per annum. A group of 390 additional participants (INT –DPM) would provide 80% power at 5% significance level to detect this difference in proportions progressing between INT – DPM (2%) and INT (4%) arms. When entry to trial was extended to include participants with NDH – IFG , progression rate to a Type 2 diabetes diagnosis was assumed to be at an annualised transition rate of 7.5% in a CON arm.[8] A final accrued sample size of 972, with a maximum 46 month follow up in the proposed randomization ratio, gave 99.7% power to detect this difference between CON and INT, 84% power between CON and INT-DPM, and 78.6–80.2% power between the two intervention arms. The power finally attained by the numbers of participants at an average follow-up of 24.7 months, at 5% significance level, was 99.4 % (INT vs CON), 80.9 % (INT – DPM vs CON) and 69.1% (INT-DPM vs INT).

3) e Intervention.

Intervention fidelity was assessed using two main methods. Firstly, all sessions for all study arms were audio recorded (participants consented to this), the recordings were downloaded onto a secured internal hard drive accessible only by intervention staff. Secondly, DPFs were required to complete a checklist at the end of every session reporting on the levels of fidelity reached during that session. Checklists were individually tailored for the six Education sessions, control session and a further checklist was developed to be used for all 15 Maintenance sessions. Multiple items were assessed that matched the sections of the session plan documents and depending on session, the number of items included on the checklist to assess fidelity ranged from 10-21, on whether they delivered that specific component of the intervention 'fully', 'partially' or 'not at -all'. A comments box was available next to each assessment item. If the answer was 'partially' or 'not at all', the DPF was required to explain why this was the case. Completion rate for the checklists was recorded at 91.7%. During the recruitment period, there was no available structured diet and lifestyle programme for people with high risk glycemic categories, and there was no parallel recruitment into the English national prevention programme which started in the study area after the NDPS had finished.

4) eHealth Economic Analysis : methods

To estimate costs (from a UK National Health Service (NHS) perspective at 2016-17 prices), those who delivered the intervention recorded the resource use (time inputs) associated with the training, education and maintenance sessions, plus ongoing supervision/support. Additionally, all participants were asked to complete a self-report health service use questionnaire at 6, 12, 24 and 40 month time points.[9] Unit costs were assigned to each item of resource use.[10-13] Additional DPM costs included training, a telephone charge cost for each call and DPM supervision, as well as a single honorarium payment of £350 for each DPM. Effectiveness was estimated based on the clinical primary outcome (progression to Type 2 DM) and cost- per quality adjusted life year (QALY) analysis based on EQ-5D-3L.[14-16] Incremental costs per T2DM progression averted and incremental cost per QALY were estimated over a 24 month follow-up period, where costs and QALYs incurred after 12 months were discounted at 3.5% and multiple imputation was used to estimate missing data. [16-18] Bivariate regression analysis was undertaken and the incremental cost-effectiveness ratios (ICER : mean incremental cost/mean incremental effect) estimated. Please note on 1.31.17 conversion rate was £1GBP to $1.25 USD, and equivalent conversion rate on 1.30.20 was £1GBP to $1.30 USD. The full results of these analyses will be reported separately.

5) e Randomization.

Randomization procedure was conducted by a DPF during a 30 minute individual appointment, and randomization of participants conducted automatically using a dedicated function in the trial data management system. The randomization mechanism consisted of a pre-prepared random list of codes (for the Intervention and control groups) stored in the trial database. To reduce the risk of predicting the next allocation while maintaining a reasonable even spread of intervention and control patients, the list was constructed of blocks of 17 codes (3 CON, 7 INT, and 7 INT- DPM) to approximate the proportions of 170:390:390 respectively. Ethical approval was obtained from the National Research Ethics Service (NRES), Essex 1 Research Ethics Committee (10/H0301/55; 13.1.2011).

6) e Results and response by dose of intervention

Of 424 INT participants, 125 (29.7%), 77 (18.2%) and 221 (52.1%) respectively received low, medium and high doses of the intervention. Of 426 INT-DPM participants, 135 (31.7%), 107 (25.1%) and 184 (43.2%) respectively received low, medium and high doses of the intervention. Compared to the equivalent groups (within INT or INT-DPM) who attained a low dose exposure to the intervention, the high dose exposure groups at 12 months had highly significant adjusted reductions in mean HbA1c, weight, and fasting plasma glucose (Table 7). This significant effect was maintained for weight loss in the high dose group at 24 months for both groups (INT : - 3.44kg ; - 5.51,-1.37; p = 0.001; INT – DPM : - 3.65kg ; -5.99, -1.32; p = 0.002), compared to the low dose attained group, indicating that a significant and clinically meaningful effect on weight was maintained at 2 years (Table 7). There was no significant difference in primary outcome by dose attained however, with 11/126 (8.7%) low dose and 32/221(14.4%) high dose participants in the INT arm developing diabetes (adjusted odd ratios compared to low dose 1.72 [95%CI 0.54 , 5.46). The equivalent data for the INT – DPM arm were 21/135 (15.5%) and 28/184 (15.2%).

eTable 1 Percentage of individuals who progressed to Type 2 diabetes in each arm

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	CON	INT	INT – DPM
Progression	39/ 178 (21.9%)	55 / 424 (13.0%)	62 / 426 (14.6%)
Progression (excluding those with no follow-up data) *	39/ 171 (22.8%)	55/ 403 (13.7%)	62 / 414 (15.0%)

CON: control arm without trial intervention, INT : standard intervention group , INT – DPM : intervention group with additional diabetes prevention mentors . * No post baseline biochemical data.

eTable 2. Differences between trial arms at 12 months : adjusted mean differences (95% CI) in linear regression models

Analysis	INT-DPM vs INT	p	INT vs CON	p	INT- DPM vs CON	p	Combined INT v CON	p
HbA1c, %	0.01 (-0.47, 0.5)	0.95	-0.64 (-1.3, 0.02)	0.06	-0.6 (-1.25, 0.05)	0.07	-0.63 (-1.2, -0.04)	0.04
Fasting plasma glucose, mg/dl	-0.02 (-0.11, 0.07)	0.68	-0.02 (-0.13, 0.09)	0.71	-0.04 (-0.15, 0.08)	0.54	-0.03 (-0.13, 0.07)	0.6
Weight, kg	-0.39 (-1.06, 0.28)	0.26	-1.56 (-2.39, -0.74)	0.001	-1.96 (-2.85, -1.06)	0.001	-1.76 (-2.55, -0.97)	0.001
Body mass index, kg/m^2	-0.13 (-0.36, 0.1)	0.25	-0.52 (-0.81, -0.23)	0.001	-0.66 (-0.97, -0.35),	0.001	-0.59 (-0.86, -0.31)	0.001
Body fat , % [a]	-0.56 (-1.02, -0.11)	0.01	-0.31 (-0.88, 0.26)	0.29	-0.88 (-1.48, -0.27),	0.005	-0.58 (-1.13, -0.04)	0.034
Body fat mass,kg [a]	-0.84 (-1.57, -0.12)	0.02	-0.51 (-1.34, 0.32)	0.23	-1.45 (-2.39, -0.5),	0.003	-0.98 (-1.82, -0.14)	0.022
Waist circumference, cm	-0.25 (-1.14, 0.64)	0.58	-2.36 (-3.72, -1),	0.001	-2.59 (-4.02, -1.17),	0.001	-2.48 (-3.67, -1.29)	0.001
MET mins / week [b]	1.21 (-603.8, 606)	0.99	905.5 (209.7, 1601)	0.01	914.8 (159.9, 1669.6)	0.018	915.5 (235, 1596)	0.008
Physical activity category [b]	1.05 (0.69, 1.62)	0.81	2.19 (1.29, 3.71)	0.004	2.43 (1.4, 4.23),	0.002	2.27 (1.39, 3.7)	0.001
Resistance days/wk [b]	0.97 (0.63, 1.5)	0.90	2.34 (1.25, 4.38)	0.008	2.25 (1.22, 4.16),	0.009	2.29 (1.29, 4.06)	0.005
Minutes sitting/wk [b]	1.21 (-603 , 606)	0.99	905.5 (210, 1601)	0.01	914.8 (160, 1670)	0.018	915.55 (235, 1596)	0.008
Fat scale score [c]	0 (-0.06, 0.05)	0.94	0.02 (-0.05, 0.09)	0.52	0.02 (-0.05, 0.09)	0.56	0.02 (-0.04, 0.09)	0.51
Fiber scale score [c]	-0.02 (-0.09, 0.05),	0.53	0.04 (-0.04, 0.12)	0.34	0.01 (-0.07, 0.1)	0.75	0.03 (-0.05, 0.11)	0.52
WBQ - 12 [d]	-0.16 (-0.98, 0.67)	0.71	0.92 (-0.14, 1.98)	0.09	0.86 (-0.26, 1.97)	0.13	0.92 (-0.05, 1.89)	0.06
EQ – 5D [d]	0.01 (-0.02, 0.03)	0.70	-0.01 (-0.05, 0.02)	0.46	-0.01 (-0.04, 0.02)	0.586	-0.01 (-0.04, 0.02)	0.47
ADDQoL [d]	0.05 (-0.1, 0.19)	0.50	0.18 (0, 0.36)	0.06	0.22 (0.02, 0.42)	0.028	0.2 (0.03, 0.37)	0.021
HOMA – B (%) [e]	0.17 (-3.77, 4.12)	0.93	-0.69 (-5.36, 3.98)	0.77	-1.29 (-6.87, 4.29)	0.65	-0.95 (-5.63, 3.73)	0.69
HOMA – S (%) [e]	4.21 (-3.88, 12.3)	0.31	1.28 (-7.99, 10.54)	0.79	5.02 (-6.09, 16.12)	0.38	3.24 (-6.17, 12.66)	0.50

Data shown as change in mean and 95% CI. INT : Standard intervention arm ; INT – DPM : intervention arm with diabetes prevention mentors (DPM) ; Combined intervention : both intervention groups combined; CON : no trial intervention. Fat mass (kg and %) by Tanita body composition analyser.[9 a] Physical activity scales (energy expenditure during physical activity [metabolic equivalent of task (MET) minutes per week] , resistance - questionnaire assessment of frequency of resistance activity (days per week), and low physical activity category, and sedentary time from international physical activity questionnaire IPAQ.[2,3,9, b] Dietary fat and fiber scores based on self-reported Diet Behaviour Questionnaire (DBQ).[4, c d] Well - being score (WBQ-12) questionnaire [5,6 ,d] , health related quality of life score (EQ-5D) questionnaire [6,d] and ADDQoL first question.[7,d] Homeostasis model assessment (HOMA) of baseline insulin sensitivity (S) and beta cell function (B) as % of standard reference range. [1,9,e] To convert conventional units to SI unit, for plasma glucose (mg/dl) multiply by 0.0555 (mmol/l), and glycated hemoglobin (%) by 0.0915 IFCC units (mmol/mol) + 2.15. Please note reference number sequence relates to reference list in Supplementary Online material.

eTable 3. Differences between trial arms at 24 months - adjusted mean differences (95% CI) in linear regression models

Analysis	INT-DPM vs INT	p	INT vs CON	p	INT- DPM vs CON	p	Combined INT v CON	p
HbA1c, %	-0.03 (-0.69,0.62)	0.92	-0.72 (-1.66,0.22)	0.13	-0.77 (-1.69,0.14)	0.09	-0.74 (-1.57,0.1)	0.08
Fasting plasma glucose, mg/dl	0.04 (-0.07,0.16)	0.47	-0.12 (-0.27,0.03)	0.11	-0.07 (-0.24,0.1)	0.41	-0.09 (-0.24,0.05)	0.21
Weight, kg	-0.39 (-1.35,0.56)	0.42	-1.28 (-2.54,-0.02)	0.05	-1.66 (-2.93,-0.4)	0.01	-1.47 (-2.64,-0.3)	0.01
Body mass index, kg/m^2	-0.16 (-0.49,0.17)	0.35	-0.42 (-0.87,0.02)	0.06	-0.6 (-1.04,-0.16)	0.008	-0.5 (-0.91,-0.1)	0.01
Body fat , % [a]	-0.5 (-1.13,0.12)	0.11	-0.02 (-0.82,0.78)	0.96	-0.56 (-1.41,0.29)	0.20	-0.28 (-1.05,0.48)	0.47
Body fat , kg [a]	-0.68 (-1.53,0.17)	0.12	-0.3 (-1.44,0.84)	0.61	-1.01 (-2.1,0.07)	0.07	-0.65 (-1.68,0.39)	0.22
Waist circumference, cm	-1.52 (-3.05,0.01)	0.05	-0.79 (-3,1.42)	0.48	-2.31 (-3.75,-0.87)	0.002	-1.56 (-3.4,0.2)	0.09
MET mins / week [b]	179.8 (-670,1029)	0.68	911.6 (-196 , 2019)	0.11	1075.3 (-4.2, 2154)	0.05	985.8 (-36 , 2008)	0.06
Physical activity category [b]	1.22 (0.7,2.14)	0.48	2.05 (1.01,4.13)	0.05	2.52 (1.22,5.2)	0.01	2.24 (1.15,4.37)	0.02
Resistance days/wk [b]	1.1 (0.62,1.96)	0.74	4.37 (1.46,13.11)	0.008	5.11 (1.82,14.36)	0.002	4.77 (1.73,13.16)	0.003
Minutes sitting/wk [b]	-26.9 (- 85, 32)	0.37	-8.09 (-89.0 ,72.8)	0.84	-31.1 (-108.4,46.2)	0.43	-21.43 (-93.1 ,50.3)	0.56
Fat scale score [c]	-0.01 (-0.09,0.07)	0.78	0.11 (0.01,0.2)	0.03	0.1 (-0.01,0.2)	0.07	0.1 (0.01,0.19)	0.03
Fiber scale score [c]	-0.01 (-0.1,0.09)	0.9	0.12 (0,0.24)	0.04	0.1 (-0.02,0.22)	0.10	0.11 (0,0.22)	0.06
WBQ - 12 [d]	0.14 (-1.02,1.31)	0.81	0.91 (-0.56,2.38)	0.22	1.05 (-0.45,2.55)	0.17	0.98 (-0.36,2.33)	0.15
EQ – 5D [d]	-0.02 (-0.07,0.02)	0.26	-0.01 (-0.06,0.03)	0.57	-0.04 (-0.09,0.02)	0.22	-0.02 (-0.07,0.02)	0.32
ADDQoL [d]	-0.03 (-0.23,0.17)	0.74	0.06 (-0.18,0.3)	0.67	0.02 (-0.23,0.28)	0.85	0.04 (-0.19,0.27)	0.72
HOMA – B (%) [e]	-3.77 (-8.34,0.81)	0.11	1.02 (-5.31,7.35)	0.75	-2.88 (-9.56,3.8)	0.40	-0.87 (-6.72,4.97)	0.77
HOMA – S (%) [e]	1.04 (-10.8,12.4)	0.86	8.5 (-4.2, 21.1)	0.18	10.5 (-4.9,26)	0.18	9.36 (-4.06,22.8)	0.17

Data shown as change in mean and 95% CI. INT: Standard intervention arm ; INT – DPM : intervention arm with diabetes prevention mentors (DPM) ; Combined intervention : both intervention groups combined; CON : no trial intervention. Fat mass (kg and %) by Tanita body composition analyser. [9 a] Physical activity scales (energy expenditure during physical activity [metabolic equivalent of task (MET) minutes per week] , resistance - questionnaire assessment of frequency of resistance activity (days per week), and low physical activity category, and sedentary time from international physical activity questionnaire IPAQ. [2,3,9, b] Dietary fat and fiber scores based on self-reported Diet Behaviour Questionnaire (DBQ). [4, c d] Well - being score (WBQ-12) questionnaire [5,6 ,d] , health related quality of life score (EQ-5D) questionnaire [6,d] and ADDQoL first question.[7,d] Homeostasis model assessment (HOMA) of baseline insulin sensitivity (S) and beta cell function (B) as % of standard reference range. [1,9,e] To convert conventional units to SI unit, for plasma glucose (mg/dl) multiply by 0.0555 (mmol/l), and glycated hemoglobin (%) by 0.0915 IFCC units (mmol/mol) + 2.15. Please note reference number sequence relates to reference list in Supplementary Online material.

eTable 4. Descriptive data for outcomes at 12 months by trial arm

Analysis	CON	n	INT	n	INT- DPM	n
HbA1c, mean (SD), %	6.0 (0.4)	135	6.0 (0.4)	304	6.0 (0.4)	305
Fasting plasma glucose, mean (SD), (mg/dl)	108 (11)	135	108 (10)	303	108 (11)	304
Weight, mean (SD), kg	87.2 (16.5)	135	85.6 (16.3)	304	84.5 (16.20)	300
Body mass index, mean (SD), kg/m^2	30.0 (4.7)	128	29.4 (5.03)	304	29.1 (5.05)	300
Body fat, mean (SD), % [a]	30.61 (10.6)	128	28.70 (11.3)	297	28.07 (11.2)	292
Body fat, mean (SD), kg [a]	34.8 (8.41)	128	33.0 (8.9)	297	32.7 (9.0)	292
Waist circumference, mean SD, cm	103.2 (14.3)	135	101.2 (12.8)	304	100.9 (12.6)	301
MET mins / week, mean (SD) [b]	2974 (3065)	90	3679 (3011)	221	3869 (3295)	187
Low Physical activity category, n (%) [b]	25 (27.8)	90	36 (16.3)	221	27 (14.4)	187
Resistance (0 – 1 days / week), n (%) [b]	63 (73.3)	86	120 (57.1)	210	114 (57.6)	198
Minutes sitting/wk, mean (SD) [b]	424 (284)	99	390 (232)	226	374 (242)	205
Fat scale score, mean (SD) [c]	2.35 (0.35)	105	2.39 (0.38)	235	2.39 (0.40)	226
Fiber scale score, mean (SD) [c]	2.40 (0.37)	106	2.48 (0.40)	233	2.42 (0.43)	224
W - BQ12 mean (SD), [d]	25.7 (6.9)	97	26.8(6.2)	224	26.6 (5.5)	212
EQ – 5D, mean (SD), [d]	0.03 (0.15)	94	-0.00 (0.15)	196	0.01 (0.14)	195
ADDQoL. mean (SD), [d]	1.4 (0.9)	101	1.6 (0.9)	235	1.6 (0.96)	222
HOMA – B, mean (SD), % [e]	89.0 (39)	129	82.6 (33)	296	81.0 (33)	284
HOMA – S, mean (SD), % [e]	86.3 (57)	129	92.1 (56)	296	98.6(64)	284

Data shown as mean and 1SD. INT: Standard intervention arm ; INT – DPM : intervention arm with diabetes prevention mentors (DPM) ; Combined intervention : both intervention groups combined; CON : no trial intervention. Fat mass (kg and %) by Tanita body composition analyser. [9 a] Physical activity scales (energy expenditure during physical activity [metabolic equivalent of task (MET) minutes per week] , resistance - questionnaire assessment of frequency of resistance activity (days per week), and low physical activity category, and sedentary time from international physical activity questionnaire IPAQ. [2,3,8, b] Dietary fat and fiber scores based on self-reported Diet Behaviour Questionnaire (DBQ). [4, c d] Well - being score (WBQ-12) questionnaire [5,6 ,d] , health related quality of life score (EQ-5D) questionnaire [6,d] and ADDQoL first question.[7,d] Homeostasis model assessment (HOMA) of baseline insulin sensitivity (S) and beta cell function (B) as % of standard reference range. [1,9,e] To convert conventional units to SI unit, for plasma glucose (mg/dl) multiply by 0.0555 (mmol/l), and glycated hemoglobin (%) by 0.0915 IFCC units (mmol/mol) + 2.15. Please note reference number sequence relates to reference list in Supplementary Online material.

eTable 5. Descriptive data for outcomes at 24 months by trial arm

Analysis	CON	n	INT	n	INT- DPM	n
HbA1c, mean (SD), %	6.1 (0.4)	75	6.1 (0.3)	186	6.0 (0.3)	192
Fasting plasma glucose, mean (SD), (mg/dl)	110 (11)	75	108 (10)	186	110 (11)	190
Weight, mean (SD), kg	85.8 (16.0)	75	85.78 (16.9)	186	84.4 (17.2)	191
Body mass index, mean (SD), kg/m^2	29.8 (4.7)	75	29.5 (5.3)	186	29.8 (5.1)	190
Body fat, mean (SD), % [a]	33.7 (8.6)	71	33.5 (9.1)	176	32.0 (9.1)	185
Body fat, mean (SD), kg [a]	29.2 (10.0)	71	29.3 (12.3)	176	27.51 (11.3)	185
Waist circumference, mean SD, cm	102.9 (12)	75	102.8 (15)	185	100.6 (13.2)	190
MET mins / week, mean (SD) [b]	2746 (2957)	49	3677 (3411)	128	4290 (3658)	128
Low Physical activity category, n (%) [b]	15 (30.6)	49	20 (15.6)	128	15 (11.7)	128
Resistance (0 – 1 days / week), n (%) [b]	44 (86.3)	51	80 (62.0)	129	74 (55.6)	133
Minutes sitting/wk, mean (SD) [b]	425 (280)	55	405 (237)	134	362 (231)	140
Fat scale score, mean (SD) [c]	2.3 (0.4)	61	2.4 (0.4)	141	2.4 (0.4)	147
Fiber scale score, mean (SD) [c]	2.3 (0.4)	61	2.5 (0.4)	139	2.4 (0.5)	147
W - BQ12 mean (SD), [d]	26.4 (5.27)	58	26.9 (5.5)	137	26.8 (5.8)	143
EQ – 5D, mean (SD), [d]	0.02 (0.14)	56	0.00 (0.15)	117	-0.03 (0.21)	128
ADDQoL. mean (SD), [d]	1.53 (0.8)	60	1.61 (0.9)	142	1.52 (1.0)	152
HOMA – B, mean (SD), % [e]	86.7 (39)	71	78.6 (30)	178	74.3 (33)	180
HOMA – S, mean (SD), % [e]	83.6 (53)	71	96.3 (57)	178	103.5 (70)	180

Data shown as mean and 1SD. INT: Standard intervention arm ; INT – DPM : intervention arm with diabetes prevention mentors (DPM) ; Combined intervention : both intervention groups combined; CON : no trial intervention. Fat mass (kg and %) by Tanita body composition analyser.[9 a] Physical activity scales (energy expenditure during physical activity [metabolic equivalent of task (MET) minutes per week] , resistance - questionnaire assessment of frequency of resistance activity (days per week), and low physical activity category, and sedentary time from international physical activity questionnaire IPAQ.[2,3,9, b] Dietary fat and fiber scores based on self-reported Diet Behaviour Questionnaire (DBQ).[4, c d] Well - being score (WBQ-12) questionnaire[5,6 ,d] , health related quality of life score (EQ-5D) questionnaire[6,d] and ADDQoL first question.[7,d] Homeostasis model assessment (HOMA) of baseline insulin sensitivity (S) and beta cell function (B) as % of standard reference range.[1,9,e] To convert conventional units to SI unit, for plasma glucose (mg/dl) multiply by 0.0555 (mmol/l), and glycated hemoglobin (%) by 0.0915 IFCC units (mmol/mol) + 2.15. Please note reference number sequence relates to reference list in Supplementary Online material.

e Table 6 : Differences between trial arms at 12 months - <u>unadjusted</u> mean differences (95% CI) in linear regression models

Analysis	INT-DPM vs INT	p	INT vs CON	p	INT- DPM vs CON	p	Combined INT v CON	p
HbA1c, %	0.01 (-0.04, 0.0.06)	0.77	-0.03 (- 0.1,0.03)	0.32	- 0.03 (- 0.1, 0.04)	0.43	-0.03 (- 0.1,0.03)	0.32
Fasting plasma glucose, mg/dl	-0.7 (- 2.3, 0.05)	0.42	0.0 (- 2.2 , 1.9)	0.93	- 0.7 (- 2.5 , 1.4)	0.5	- 0.4 (- 2.4 , 1.4)	0.67
Weight, kg	-1.15 (-3.76,1.45)	0.38	-1.58 (-4.91,1.76)	0.35	-2.73 (-6.1, 0.59)	0.11	-2.15 (-5.2,0.9)	0.17
Body mass index, kg/m^2	-0.32 (- 1.13,0.48)	0.43	-0.61 (-1.61,0.39)	0.23	-0.93 (-1.93,0.08)	0.07	-0.77 (-1.7,0.16)	0.11
Body fat , % [a]	-0.29 (-1.74,1.16)	0.7	-1.84 (-3.66,-0.02)	0.05	- 2.13 (-3.96,-0.3)	0.02	-1.98 (-3.68,-0.29)	0.02
Body fat , kg [a]	-0.63 (-2.45,1.19)	0.5	-1.92 (-4.23,0.4)	0.1	-2.55 (-4.84,-0.25)	0.03	-2.23 (-4.36,-0.1)	0.04
Waist circumference, cm	-0.32 (-2.3 ,1.7)	0.76	-1.95 (-4.7 ,0.7)	0.16	-2.27 (-4.9 ,0.4)	0.1	-2.11 (-4.5 ,0.3)	0.09
MET mins / week [b]	190 (-423 ,804)	0.54	704 (-39 ,1449)	0.06	895 (81 ,1709)	0.03	792 (76 ,1507)	0.03
Physical activity category [b]	1.13 (0.78,1.63)	0.51	1.83 (1.15,2.9)	0.01	2.07 (1.29,3.33)	0.003	1.94 (1.26,2.98)	0.002
Resistance days/wk [b]	1.03 (0.7,1.51)	0.89	2.05 (1.19,3.54)	0.01	2.07 (1.2,3.58)	0.009	2.06 (1.23,3.43)	0.006
Minutes sitting/wk [b]	-15.4 (-59.8,28.9)	0.50	-34.5 (-93.2 ,24.3)	0.25	-49.9 (-111.3 ,11.6)	0.11	-41.8 (-95.4 ,11.8)	0.126
Fat scale score [c]	0 (-0.07,0.07)	0.99	0.04 (-0.05,0.12)	0.39	0.04 (-0.05,0.13)	0.41	0.04 (-0.04,0.12)	0.36
Fiber scale score [c]	-0.05 (-0.13,0.02)	0.17	0.07 (-0.02,0.16)	0.11	0.02 (-0.08,0.12)	0.68	0.05 (-0.04,0.13)	0.28
WBQ - 12 [d]	0.02 (-0.88,0.92)	0.96	0.75 (-0.35,1.84)	0.18	0.77 (-0.42,1.95)	0.2	0.76 (-0.27,1.79)	0.15
EQ – 5D [d]	0.01 (-0.02,0.04)	0.34	-0.03 (-0.07,0.01)	0.11	-0.02 (-0.05,0.02)	0.38	-0.02 (-0.06,0.01)	0.17
ADDQoL [d]	0.1 (-0.06,0.27)	0.22	0.17 (-0.04,0.37)	0.11	0.27 (0.04,0.5)	0.02	0.22 (0.02,0.41)	0.03
HOMA – B (%) [e]	-1.54 (-7.03,3.9)	0.58	-6.48 (-13.7,0.78)	0.08	-8.02 (-15.4 ,-0.63)	0.03	-7.23 (-13.8,-0.63)	0.03
HOMA – S (%) [e]	6.5 (-3.3,16.3)	0.19	5.75 (-6.0 ,17.5)	0.34	12.25 (-0.62, 25.1)	0.06	8.94 (-2.4 , 20.3)	0.12

Data shown as mean and 1SD. INT: Standard intervention arm ; INT – DPM : intervention arm with diabetes prevention mentors (DPM) ; Combined intervention : both intervention groups combined; CON : no trial intervention. Fat mass (kg and %) by Tanita body composition analyser. [9 a] Physical activity scales (energy expenditure during physical activity [metabolic equivalent of task (MET) minutes per week] , resistance - questionnaire assessment of frequency of resistance activity (days per week), and low physical activity category, and sedentary time from international physical activity questionnaire IPAQ. [2,3,9, b] Dietary fat and fiber scores based on self-reported Diet Behaviour Questionnaire (DBQ). [4, c d] Well - being score (WBQ-12) questionnaire [5,6 ,d] , health related quality of life score (EQ-5D) questionnaire [6,d] and ADDQoL first question.[7,d] Homeostasis model assessment (HOMA) of baseline insulin sensitivity (S) and beta cell function (B) as % of standard reference range. [1,9,e] To convert conventional units to SI unit, for plasma glucose (mg/dl) multiply by 0.0555 (mmol/l), and glycated hemoglobin (%) by 0.0915 IFCC units (mmol/mol) + 2.15. Please note reference number sequence relates to reference list in Supplementary Online material.

eTable 7 Differences between trial arms at 24 months - <u>unadjusted</u> mean differences (95% CI) in linear regression models

Analysis	INT-DPM vs INT	p	INT vs CON	p	INT- DPM vs CON	p	Combined INT v CON	p
HbA1c, %	0.02 (- 0.04, 0.1)	0.47	-0.06 (-0.17, 0.3)	0.19	- 0.04 (- 0.14,0.06)	0.41	- 0.05 (- 0.14, 0.34)	0.23
Fasting plasma glucose, mg/dl	0.4 (-0.1, 0.14)	0.7	- 1.4 (- 4.1, 7.3)	0.28	- 1.1 (- 4.1 , 2.0)	0.5	- 1.3 (- 4.0, 1.4)	0.35
Weight, kg	-1.39 (-4.85,2.07)	0.43	-0.06 (-4.55,4.42)	0.98	-1.46 (-5.99,3.07)	0.53	-0.77 (-4.97,3.43)	0.72
Body mass index, kg/m^2	-0.78 (-1.83,0.27)	0.15	-0.27 (-1.66,1.11)	0.7	-1.05 (-2.38,0.27)	0.12	-0.67 (-1.94,0.6)	0.3
Body fat , % [a]	-1.52 (-3.4,0.37)	0.11	-0.22 (-2.71,2.27)	0.86	-1.73 (-4.19,0.72)	0.17	-1.0 (-3.3,1.31)	0.4
Body fat , kg [a]	-1.8 (-4.25,0.64)	0.15	0.12 (-3.11,3.36)	0.94	-1.68 (-4.7,1.34)	0.27	-0.8 (-3.75,2.15)	0.59
Waist circumference, cm	-2.16 (- 5.0 ,0.66)	0.13	-0.13 (-3.9,3.6)	0.95	-2.3 (-5.8,1.2)	0.19	-1.23 (-4.6 ,2.2)	0.48
MET mins / week [b]	612 (-258,1483)	0.17	931 (-161 ,2022)	0.09	1543 (389 ,2697)	0.009	1237.23 (176.36,229	0.02
Physical activity category [b]	1.41 (0.88,2.25)	0.15	2.18 (1.16,4.07)	0.01	3.04 (1.61,5.75)	0.001	2.58 (1.44,4.62)	0.001
Resistance days/wk [b]	1.31 (0.81,2.12)	0.27	3.52 (1.47,8.43)	0.005	4.58 (1.92,10.89)	0.001	4.08 (1.77,9.4)	0.001
Minutes sitting/wk [b]	-41.96 (-97.4 ,13.6)	0.14	-21 (-99.9 ,57.9)	0.6	-63.0 (-140 ,14.1)	0.11	-42.4 (-112.8 ,28)	0.24
Fat scale score [c]	0 (-0.1,0.09)	0.92	0.08 (-0.03,0.2)	0.13	0.08 (-0.05,0.21)	0.21	0.08 (-0.03,0.19)	0.14
Fiber scale score [c]	-0.04 (-0.14,0.06)	0.45	0.15 (0.03,0.27)	0.02	0.11 (-0.02,0.25)	0.1	0.13 (0.01,0.25)	0.03
WBQ - 12 [d]	0.1 (-1.23,1.43)	0.88	0.88 (-0.83,2.6)	0.31	0.98 (-0.74,2.7)	0.26	0.94 (-0.62,2.49)	0.24
EQ – 5D [d]	-0.01 (-0.23,0.22)	0.95	0.04 (-0.22,0.3)	0.76	0.03 (-0.25,0.32)	0.82	0.04 (-0.22,0.29)	0.78
ADDQoL [d]	-0.03 (-0.08,0.02)	0.21	-0.02 (-0.06,0.03)	0.45	-0.05 (-0.11,0.01)	0.13	-0.03 (-0.08,0.02)	0.21
HOMA – B (%) [e]	-4.28 (-10.82,2.26)	0.2	-8.0 (-17.14,1.14)	0.09	-12.3 (-21.8,-2.76)	0.01	-10.2 (-18.5 ,-1.8)	0.02
HOMA – S (%) [e]	7.22 (-6.1 ,20.5)	0.29	12.7 (-2.9 ,28.2)	0.11	19.9 (1.7 , 38.0)	0.03	16.3 (0.3 ,32.2)	0.05

Data shown as mean and 1SD. INT: Standard intervention arm ; INT – DPM : intervention arm with diabetes prevention mentors (DPM) ; Combined intervention : both intervention groups combined; CON : no trial intervention. Fat mass (kg and %) by Tanita body composition analyser. [9 a] Physical activity scales (energy expenditure during physical activity [metabolic equivalent of task (MET) minutes per week] , resistance - questionnaire assessment of frequency of resistance activity (days per week), and low physical activity category, and sedentary time from international physical activity questionnaire IPAQ. [2,3,9, b] Dietary fat and fiber scores based on self-reported Diet Behaviour Questionnaire (DBQ). [4, c d] Well - being score (WBQ-12) questionnaire [5,6 ,d] , health related quality of life score (EQ-5D) questionnaire [6,d] and ADD QoL first question.[7,d] Homeostasis model assessment (HOMA) of baseline insulin sensitivity (S) and beta cell function (B) as % of standard reference range. [1,8,e] To convert conventional units to SI unit, for plasma glucose (mg/dl) multiply by 0.0555 (mmol/l), and glycated hemoglobin (%) by 0.0915 IFCC units (mmol/mol) + 2.15. Please note reference number sequence relates to reference list in Supplementary Online material.

e Table 8 Change in mean weight, fasting plasma glucose, and HbA1c at 12 and 24 months by participants achieving higher 'doses' of intervention (moderate, or high) compared to lowest dose participants, shown for both intervention arms (mean (95% CI)

12 months								
GROUP:	**INT**				**INT –DPM**			
	Moderate Dose	**p**	**High Dose**	**p**	**Moderate Dose**	**p**	**High Dose**	**p**
HbA1c, % *Unadjusted*	-0.1 (- 0.12, 0.02)	0.10	- 0.14 (- 0.22, -0.05)	0.002	-0.1 (- 0.17, 0.01)	0.07	-0.15 (- 0.22 , -0.1)	0.001
HbA1c, % *Adjusted*	- 0.11 (- 0.26, 0.02)	0.10	- 0.17 (- 0.28 ,-0.06)	0.004	- 0.02 (- 0.23, 0.01)	0.06	- 0.16 (- 0.01 , -0.05)	0.003
Weight (kg) *Unadjusted*	-1.32 (-2.75, 0.12)	0.07	-2.05 (-3.19,-0.91)	<0.001	-1.05 (-2.5,0.4)	0.16	-2.12 (-3.38,-0.85)	0.001
Weight (kg) *Adjusted*	-1.30 (-3.31, 0.7)	0.20	-2.20 (-3.82,-0.57)	0.008	-1.46 (-3.4,0.43)	0.13	-2.72 (-4.4,-1.04)	0.002
Fasting plasma glucose, mg/dl *Unadjusted*	0 (- 3.6 , 3.6)	0.99	- 1.1 (- 3.6 , 1.8)	0.49	- 1.8 (- 5.4, 0.11)	0.35	- 4.5 (-7.6, -1.3)	0.006
Fasting plasma glucose, mg/dl *Adjusted*	- 2.3 (- 6.8 , 2.2)	0.30	- 2.8 (- 6.9 ,0.9)	0.14	- 3.4 (- 7.6 , 0.9)	0.11	- 5.4 (- 9.0 ,- 1.6)	0.004
24 months								
HbA1c, % *Unadjusted*	-0.04 (- 0.17, 0.1)	0.55	- 0.21 (- 0.32, - 0.1)	<0.001	- 0.07 (- 0.18, 0.05)	0.27	- 0.001 (- 0.2, 0.1)	0.54
HbA1c, % *Adjusted*	0.01 (- 0.14, 0.2)	0.77	- 0.15 (- 0.3, -0.001)	0.05	-0.1 (- 0.19, 0.02)	0.10	-0.04 (-0.17, 0.1)	0.55
Weight (kg) ***Unadjusted***	-1.79 (-3.81, 0.22)	0.08	-3.29 (-4.97,-1.62)	0.001	-2.33 (-4.17,-0.49)	0.01	-2.78 (-5.1, -0.46)	0.02
Weight (kg) ***Adjusted***	-0.67 (-3.47, 2.13)	0.65	-3.65 (-5.99, -1.32)	0.002	-2.97 (-4.6,-1.34)	0.001	-3.44 (-5.5 , -1.37)	0.001
Fasting plasma glucose, mg/dl ***Unadjusted***	0.5 (- 4.1, 4.5)	0.82	0.7 (- 3.24 , 9)	0.72	- 0.7 (- 5.8, 4.3)	0.79	- 1.1 (-6.4, 4.4)	0.68
Fasting plasma glucose, mg/dl ***Adjusted***	0 (- 6.1,6.1)	0.99	- 0.18 (- 5.1, 5.0)	0.92	- 2.3 (- 6.4, 2.2)	0.30	- 0.7 (- 5.8, 4.4)	0.78

INT : Standard intervention group ; INT – DPM : intervention group with diabetes prevention mentors (DPM). To convert conventional units to SI unit, for plasma glucose (mg/dl) multiply by 0.0555 (mmol/l), and glycated hemoglobin (%) by 0.0915 IFCC units (mmol/mol) + 2.15 (if > 3.0%).

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