**The effect of referral to an open-group behavioural weight management programme on the relative risk of normoglycaemia, non-diabetic hyperglycaemia and type 2 diabetes: secondary analysis of the WRAP trial**

Amy L Ahern PhD, Prof Simon J Griffin DM, Graham M Wheeler PhD, Stephen J. Sharp MSc, Prof Paul Aveyard PhD, Emma J Boyland PhD, Prof Jason CG Halford PhD, Prof Susan A Jebb PhD.

MRC Epidemiology Unit, University of Cambridge

University College London

Nuffield Department of Primary Care Health Sciences, University of Oxford

Department of Psychological Sciences, University of Liverpool

**Abstract**

**Aims**

We examined the impact of open-group behavioural weight management programmes on diabetes risk among i) those with BMI ≥28kg/m2 and ii) those with non-diabetic hyperglycaemia (NDH).

**Methods**

This was a secondary analysis of data from the WRAP trial, in which participants (N=1267; ≥18 years, BMI ≥28kg/m2) were randomised to: brief intervention (BI; self-help booklet), a weight management programme (WW, formerly Weight Watchers) for 12-weeks, or WW for 52 weeks. We used multinomial logistic regression to examine the effect of intervention group on the risk of hyperglycaemia and diabetes at 12 months in all participants with glycaemic status at both time points (N=480; 38%) and those with NDH at baseline (N=387; 31%). We used mixed effects models and linear fixed effects models to examine the effect of intervention group on body weight and HbA1c at 12 months in people with NDH.

**Results**

There was a 61% relative reduction in risk of NDH at 12 month follow up [12-weeks vs BI: Relative Risk Ratio, RRR=0.39 (95% CI 0.18, 0.87), p=0.021; 52-weeks vs BI: RRR=0.38 (95% CI 0.17, 0.86), p=0.020]. For intervention effects on risk of diabetes, confidence intervals were wide and overlapped 1 [12-weeks vs BI: RRR=0.49 (95% CI 0.12, 1.96), p=0.312; 52-weeks vs BI: RRR=0.40 (95% CI 0.10, 1.63), p=0.199]. Participants with hyperglycaemia at baseline in the weight management programme were more likely to have normoglycaemia at 12 month follow up [12-week programme vs BI: RRR=3.57 (CI 1.24, 10.29), p=0.019; 52-week programme vs BI: RRR=4.14 (CI 1.42, 12.12), p=0.009].

**Conclusions**

Open group behavioural weight management programmes can prevent the development of NDH in people with overweight and obesity and normalise glycaemia in people with NDH.

**Keywords**

Diabetes, Non-diabetic Hyperglycaemia, prevention, weight loss, obesity

**Introduction**

Large randomised controlled trials have demonstrated that intensive behavioural programmes can reduce or delay the incidence of type 2 diabetes (T2D) by 30-60% in people with non-diabetic hyperglycaemia (NDH) identified by screening using repeated oral glucose tolerance tests (OGTT).(1) However population screening using OGTT would represents a significant burden to patients, health service staff and resources.(2) More pragmatic screening tests, such as glycated haemoglobin (HbA1c), have been recommended(2,3), but would still be costly if conducted with sufficient frequency to identify the large numbers of patients developing hyperglycaemia each year. Excess weight is a strong predictor of T2D (4) and identifying individuals at risk of T2D on the basis of body mass index (BMI) may be a cheaper and simpler approach(5). Diabetes prevention programmes that only include people with a BMI ≥25 kg/m² show 50% greater reduction in risk of T2D than those that also enrol people with lower BMI.(6) However, to date, no studies of diabetes prevention programmes have used excess weight as the sole inclusion criterion.

Intensive behavioural programmes evaluated in the diabetes prevention trials can only be offered to a fraction of those with hyperglycaemia because they are costly and the necessary specialised workforce is scarce. A recent systematic review found that less intensive behavioural programmes in routine healthcare or community settings achieved a 26% reduction in T2D risk, and a lower average weight loss of 2.6kg (compared to 58% risk reduction and 6kg weight loss in the US Diabetes Prevention Programme).(7) However, this review only included programmes with the specified aim of reducing diabetes incidence and excluded most behavioural programmes that focus on weight loss, despite both types of programme encouraging very similar changes in diet and physical activity using similar behavioural strategies. Commercial open-group behavioural weight management programmes, such as WW® (formerly Weight Watchers) and Slimming World, are some of the most commonly commissioned weight management treatments in the UK, have evidence of effectiveness from randomised controlled trials (RCT) and are less costly than most diabetes prevention programmes.(8–11) However, there is little direct evidence of the impact of these generic weight loss programmes on the risk of developing hyperglycaemia or diabetes, or on the reversion of people with diabetes or NDH to NDH or normoglycaemia.

Two recent studies have evaluated the effectiveness of referral to WW combined with a specific diabetes prevention education session among people with NDH. In a US randomised controlled trial, this combined intervention achieved greater weight loss (5.5% vs. 0.2%, p<0.001) and greater reductions in HbA1c (-0.22% vs −0.14%; p = 0.032) at 12 months compared with a diabetes education counselling session and self-help materials developed by the US Diabetes Education Program .(12) In an uncontrolled study of a similar combined intervention in the UK NHS, a reduction in mean weight of 10kg and in HbA1c of 2.8mmol/mol was observed at 12 months using an intention to treat analysis.(13) However, no studies have examined the impact of the standard WW programme among people with NDH, or the effect of such programmes on risk of T2D in individuals recruited on the basis of BMI alone.

In the WRAP trial (Weight loss Referrals for Adults in Primary Care, ISRCTN 82857232) 1267 adults identified by their primary care physician as having a BMI≥28kg/m² were randomised to one of three weight loss interventions: brief intervention, 12-week referral to a commercial open-group weight management programme (WW), or 52-week referral to the same programme.(9) Participants referred to the programmes lost more weight than those in the brief intervention. The 52-week programme was associated with greater reductions in weight, HbA1c and fasting blood glucose than the 12-week programme and the brief intervention. Here we use data from the WRAP trial to examine the effect that referral to an open-group behavioural programme has on the likelihood of hyperglycaemia and T2D after 1 year among adults. We also quantified effects on glycaemia in the subsample of participants with hyperglycaemia at baseline.

**Methods**

Study Design

The full protocol (including measures and assays) and primary analyses from the WRAP trial have been published elsewhere (9,14). In brief, this was a multi-centre, non-blinded, parallel groups trial with uneven randomisation. Participants were adults aged ≥18 years, with a BMI≥28kg/m2, identified via a search of electronic primary care records and invited to participate by mail. We randomised 1267 eligible participants to one of three weight management interventions in a 2:5:5 ratio: brief intervention, 12 weeks of an open-group behavioural programme (WW), or 52 weeks of the same behavioural programme.

Participants attended measurement appointments at the research centre or their local GP practice at baseline and 12 months. The trial is registered at Current Controlled Trials ISRCTN82857232. Given the focus of this trial on the impact of programme duration on weight-loss, we did not originally declare the incidence of hyperglycaemia or diabetes as outcomes.

Interventions

Participants in the brief intervention group received a printed booklet of self-help weight-management strategies from the British Heart Foundation. Participants in the behavioural programmes were given vouchers to attend weekly WW meetings and use WW web-based tools for the duration of the intervention (12 weeks or 52 weeks). The WW intervention provides advice, support and encouragement to lose weight and then maintain any loss, and uses a range of evidence-based behaviour change techniques to support changes to a lower energy diet and increases in physically activity.

Outcomes

The primary outcome of the WRAP trial was body weight and this was measured at each time-point. Participants were also asked to report medication use in the previous 3 months. Other cardiovascular risk factors, including plasma glucose, HbA1c and lipid profile were measured via a fasting blood sample at baseline and 12 months, which was optional for participants. For participants who provided a blood sample, we categorised participants as having normoglycaemia, NDH, or type 2 diabetes at baseline and 12 months using American Diabetes Association criteria for HbA1c (39-47mmol/mol = NDH; ≥48 mmol/mol = diabetes) and fasting glucose (5.6-6.9 mmol/mol= NDH; ≥7mmol/mol = diabetes)and use of diabetes medication. (15)

Statistical Analysis

To examine whether intervention group was associated with the risk of diabetes or hyperglycaemia (relative to normoglycaemia) at 12 months (primary analysis), we used multinomial logistic regression and adjusted for baseline glycaemic category, baseline weight, age, research centre and sex. Effect sizes were reported as relative risk ratios (RRRs), e.g. the risk ratio of diabetes (relative to normoglycaemia) comparing 12 weeks vs brief intervention. We conducted two sensitivity analyses. The first sensitivity analysis excluded participants for whom use of metformin was the only criteria for diabetes categorisation, because metformin has indications other than diabetes. The second sensitivity analysis used WHO criteria to categorise glycaemic status (for HbA1c: 42-47mmol/mol = NDH, ≥48 mmol/mol = diabetes; for fasting glucose: 6.1-6.9 mmol/mol= NDH, ≥7mmol/mol = diabetes). (16)

To evaluate the effect of the three interventions among participants who had NDH at baseline, we examined the differences between groups in mean change from baseline to 12 months for weight, fasting glucose and HbA1c. We undertook a missing at random (MAR) analysis using a variance components model; we imputed 50 data sets using a multiple imputation with chained equations (MICE) approach, as the joint distribution of target variables did not appear to come from a multivariate Normal distribution. The imputation model regressed the target variable on centre and imputation was stratified by treatment group. We then calculated mean (SE) change in the target variable from the imputed data sets For analyses on weight change, we fit a multivariate mixed effects model using generalised least squares to each imputed data set with intervention group, time-point, intervention group-by-time-point interaction and centre as fixed effects. Random intercepts were permitted for each participant. Results were then combined across all imputed data sets using Rubin’s rules.(17) For analysis of fasting glucose and HbA1c levels, data were available for baseline and 12 months . We therefore used linear regression on the imputed data sets to estimate treatment effects, with target variable at 12 months as the outcome, with adjustment made for baseline value, centre and intervention group.

To examine whether intervention group was associated with glycaemic status category at 12 months in people with NDH at baseline, we used the same multinomial logistic regression method described above in the subsample of WRAP participants who were categorised as having non-diabetic hyperglycaemia at baseline.

Analyses were performed using Stata version 14.2.(18)

Role of the Funding Source

The funders had no role in the design of the study or the collection, analysis and interpretation of data.

**Results**

We ascertained glycaemic status at baseline for 879 participants, and at both baseline and 12 months for 480 participants.

The primary analysis included the 480 participants with glycaemic status at both time-points. Characteristics of these participants are shown in Table 1. This subset of participants had a slightly higher mean age (Difference in means =5.92, 95% CI 4.39, 7.44 years) and a larger proportion of men (38% vs 28%) than members of the trial population who were not eligible for inclusion in this analysis, but there was no evidence of a difference in baseline weight.

Participants referred to the 12-week and 52-week programmes were less likely than those in the brief intervention group to be categorised as having non-diabetic hyperglycaemia compared to normoglycaemia at 12 months [12-week programme vs brief intervention: RRR=0.39 (95% CI 0.18, 0.87), p=0.021; 52-week programme vs brief intervention: RRR=0.38 (95% CI 0.17, 0.86), p=0.020] (Figure 1a). Although the point estimates of the RRR suggested that participants in the 12-week and 52-week programmes are less likely to have diabetes at 12 months, the confidence intervals were wide and compatible with both a negative and positive association [12-week programme vs brief intervention: RRR=0.49 (95% CI 0.12, 1.96), p=0.312; 52-week programme vs brief intervention: RRR=0.40 (95% CI 0.10, 1.63), p=0.199] (Figure 1b). Table 2 shows frequency of changes from one diabetes status category to another, by intervention group.

A sensitivity analysis, which excluded participants who were taking metformin but whose HbA1c levels were within the normal range, showed similar results. Sensitivity analyses using WHO criteria for NDH showed no evidence of a difference between groups for risk of NDH [12-week programme vs brief intervention: RRR=0.63 (95% CI 0.25, 1.61), p=0.338; 52-week programme vs brief intervention: RRR=0.58 (95% CI 0.23, 1.50), p=0.262] and diabetes [12-week programme vs BI: RRR=0.79 (95% CI 0.20, 3.10), p=0.736; 52-week programme vs brief intervention: RRR=0.63 (CI 0.16, 2.51), p=0.510] at 12 months.

At baseline 387 participants (46%) had HbA1c levels within the non-diabetic hyperglycaemia (NDH) category (brief intervention, N=66; 12-week programme, N=173; 52-week programme, N=148). Baseline characteristics of these participants are shown in Table 1. Changes in weight, fasting glucose and HbA1c between baseline and 12 months are shown by intervention group in Table 3. Participants in the 12-week and 52-week programme groups lost more weight than the brief intervention group after 12 months [12-week programme vs brief intervention: -3.00 kg (95% CI -5.05, -0.94), p=0.0044; 52-week programme vs brief intervention: -4.27 kg (95% CI -6.43, -2.10), p=0.0001]. There was no evidence of a difference between the 52-week programme and the 12 week programme [-1.27 kg (95% CI -2.76, 0.22), p=0.0958]. There were mean reductions in HbA1c and fasting blood glucose at 12 months in all groups (Table 3), but no evidence of differences between the groups.

Using WHO criteria for HbA1c and fasting glucose to categorise glycaemic status, 156 participants had NDH at baseline. Sensitivity analysis using WHO criteria showed very similar results, but there was a larger difference in weight loss between the 12-week and 52-week programmes at 12 months.

Participants with NDH referred to the 12-week and 52-week programmes were more likely than those in the brief intervention group to have reverted to normoglycaemia at 12 months [12-week programme vs brief intervention: RRR=3.57 (CI 1.24, 10.29), p=0.019; 52-week programme vs brief intervention: RRR=4.14 (CI 1.42, 12.12), p=0.009] (Figure 2a). There was little evidence to suggest that those referred to these programmes were less likely to have diabetes at 12 months as confidence intervals were wide and overlapped 1 [12-week programme vs brief intervention: RRR=0.90 (CI 0.15, 5.33), p=0.905; 52-week programme vs brief intervention: RRR=0.25 (CI 0.02, 3.04), p=0.279] (Figure 2b).

Discussion

Summary

In this secondary analysis of data from the WRAP trial, we found that participants with overweight or obesity who were randomised to an open-group behavioural weight management programme were 61% less likely to have non-diabetic hyperglycaemia at 12 months follow up than participants allocated to a brief intervention. Few people were categorised as having diabetes at the 12 month follow up (7 people, 1%), which reduced our ability to detect differences between groups in T2D incidence, and there was no evidence of a difference between groups in diabetes status at this time-point. Among participants with NDH at baseline, participants in the behavioural weight management programmes were more likely to have normoglycaemia at 12 months than those who received brief self-help materials.

Strengths and limitations

This study is limited by the relatively small proportion of WRAP trial participants who provided blood samples at baseline and follow up and could be included in the analyses. However, no differences were identified between these participants and the whole WRAP sample. Blood samples were only collected at baseline and 12 months. In contrast to the original explanatory diabetes prevention trials few studies of pragmatic programmes have followed participants beyond one year. Nevertheless, this short follow up meant that only a small proportion of participants developed diabetes which reduced study power. The study is also limited by the use of a single measure of HbA1c, glucose and/or medication to classify NDH and diabetes. Given the focus of this trial on the impact of programme duration on weight-loss, we did not originally declare the incidence of hyperglycaemia or diabetes as outcomes. Strengths of the study include the randomised trial design and the recruitment of a community-based sample with minimal exclusion criteria that is broadly generalizable to the UK population. While men where underrepresented, there is a higher proportion (32%) of men in this trial than is typically found in trials of weight management interventions and there was no evidence that gender moderated the effect of the intervention.(9) Over half of participating practices were in areas with a high index of multiple deprivation. (19)

Comparison with other literature

Overweight and obesity is one of the strongest risk factors for type 2 diabetes (T2D)(4), and weight loss is the principal target of diabetes prevention programmes(7,20). However, the dominant paradigm for diabetes prevention is identification of individuals at high risk (defined as those with non-diabetic hyperglycaemia) via population screening, and referral to a specialist diabetes prevention programme. This study demonstrates that delivering a behavioural weight management programme to all people with overweight and obesity could be an effective approach to diabetes prevention, with a 60% reduction in risk of non-diabetic hyperglycaemia at 12 month follow up. The reduction in risk of diabetes was of a similar magnitude, but the width of the confidence intervals suggest this evidence is weak.

In a population based cohort of 30,000 middle-aged people, we have previously demonstrated that over a 10 year period, moderate weight loss (3-7%), could prevent 2 in 5 cases of type 2 diabetes.(5) Using BMI to identify high risk individuals is cheaper and more feasible than population level testing of blood glucose and could identify people earlier in the disease trajectory, thereby preventing progression to non-diabetic hyperglycaemia. This is important because glycaemia has an approximately linear association with cardiovascular events and mortality.(21,22) Consequently, Geoffrey Rose’s prevention paradox may apply(23), such that more heart attacks will be prevented by shifting the overall population distribution of body mass index and glycaemia than by targeting scarce resources at the minority at highest risk. If the focus of diabetes prevention shifted to those with excess weight, commonly commissioned weight management programmes could be readily incorporated into diabetes prevention policy. We have previously estimated that the 12-week programme, costing approximately £55, is a more cost-effective intervention than the 52-week programme costing approximately £190(9), but this is still lower than the estimated average cost per person of the UK NHS diabetes prevention programmes (£270).(8) The large open-groups, rolling curriculum format, and variety of times and locations of meetings mean that people can start at any time, choose a time and location that suits them, and key information is repeated if they miss sessions. This greater flexibility than the closed group sessions typical of diabetes prevention programmes may increase attendance and adherence. This study also demonstrated for the first time that a standalone open group behavioural weight management programme is a potentially effective option to reduce the risk of diabetes in people with non-diabetic hyperglycaemia. When we restricted the eligible population to participants with NDH at baseline, we showed that the behavioural weight management programme led to slightly greater weight loss than reported in a meta-analysis of pragmatic diabetes prevention programmes.(6) However, our results are similar to findings from a US trial comparing attendance at Weight Watchers meetings combined with a diabetes education session to a US National Diabetes Education Program individual counselling session and self-help materials.(12) Reductions in HbA1c were larger than the pooled mean in the meta-analysis of pragmatic interventions to prevent diabetes,(6) and similar to a US trial of a commercial programme adapted to prevent diabetes.(12) However, the confidence intervals around the estimate of this effect in our study were large and crossed zero, probably due to the relatively small sample/group size in the present study. Taken together with evidence from a similar combined intervention in a scheme running in the UK NHS which observed a mean reduction in weight of 10kg and in HbA1c of 2.8mmol/mol(13) among people with NDHin primary care, these findings suggest that this open-group behavioural weight management programme has comparable effectiveness to dedicated diabetes prevention programmes in people with NDH, and could be incorporated into diabetes prevention pathways. It is unclear whether the education/activation session incorporated in the US trial and UK NHS models adds value, but it is clear that the weight management programme itself is a crucial component.

Implications for practice

The weight losses and reductions in glycaemia are smaller than those offered by bariatric surgery or formula diet meal replacements(24,25), but are clinically meaningful and comparable to intensive, specialist led diabetes prevention programmes.(6,7,20) Offering these programmes to all people with overweight and obesity would support people early in the disease trajectory and reduce risk of non-diabetic hyperglycaemia as well as diabetes. The weight loss achieved through these programmes also has other physical and mental health benefits.(26) However, where limited resources necessitate a focus on people who already have NDH, these programmes still offer an effective approach. Commercial versions of these programmes already have the existing infrastructure to enable (inter)national rollout and there is evidence that they can be incorporated into existing models of weight management and diabetes prevention.

Conclusions

Among people known to have hyperglycaemia, a standalone open-group behavioural weight management programme leads to successful weight loss and reductions in glycaemia which appear comparable to specialist diabetes prevention programmes. Identifying individuals at risk of diabetes on the basis of BMI alone and offering them a widely available weight management programme might be a more pragmatic, scalable and efficient diabetes prevention strategy than screening for hyperglycaemia and referral to specialist programmes and might facilitate intervention earlier in the disease trajectory.

Acknowledgments

The WRAP trial is funded by the National Prevention Research Initiative through research grant MR/J000493/1. The funding partners relevant to this award are (in alphabetical order): Alzheimer’s Research Trust, Alzheimer’s Society, Biotechnology and Biological Sciences Research Council, British Heart Foundation, Cancer Research UK, Chief Scientist Office, Scottish Government Health Directorate, Department of Health, Diabetes UK, Economic and Social Research Council, Health and Social Care Research and Development Division of the Public Health Agency (HSC R&D Division), UK Medical Research Council (MRC), The Stroke Association, Wellcome Trust, Welsh Assembly Government, and World Cancer Research Fund. The cost of the Weight Watchers programme, blood sampling and analysis were funded by WW (formerly Weight Watchers International) as part of an MRC Industrial Collaboration Award. During the conduct of the WRAP trial ALA and SAJ were supported by the MRC (grant number U105960389). ALA and SJG are supported by the MRC (grant MC\_UU\_12015/4). SAJ and PA are NIHR Senior Investigators and supported by the Oxford NIHR Biomedical Research Centre and Oxford NIHR Applied Research Centre. No funders were involved in the design or conduct of the study or the analysis or interpretation of data. ALA had access to all data in the study and had the final responsibility to submit for publication.

We thank the practice staff and research assistants who conducted study visits and provided research support over the course of the trial; the Nutritional Bioanalysis Laboratories at MRC Human Nutrition Research who did glucose and lipid assays; National Institute for Health Research Cambridge Biomedical Research Centre Core Biochemistry Assay Laboratory who did the HbA1c assays; the Volunteer Services and Clinical Studies team and the Data Management team at MRC Human Nutrition Research for supporting data collection, entry and management.

Competing Interests Statement

ALA is Principal Investigator on an NIHR PGfAR-funded trial in which the intervention is delivered by WW at no cost. PA and SAJ are principal investigators on a trial funded through a grant to the University of Oxford from Cambridge Weight Plan. PA has done half a day’s consultancy for Weight Watchers and spoken at a symposium at the Royal College of General Practitioners conference that was funded by Novo Nordisk. Neither led to payments to him personally. JCGH has a trial funded by the American Beverage Association. All other authors declare no competing interests.

Authors Contributions

ALA, PA, JCGH, EJB & SAJ are Investigators on the WRAP trial and designed and conducted the trial. ALA & SJG conceived this study and ALA, SJG, GMW & SJS designed the analysis. ALA & GMW conducted the analysis. All authors were involved in data interpretation and critical revision of the manuscript and approved the final version.

**References**

1. Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ. 2007;334(7588):299.

2. World Health Organisation (WHO). Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Diabetes Res Clin Pract [Internet]. 2011;93(3):299–309. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0168822711001318

3. Nathan DM, Balkau B, Bonora E, Borch-Johnsen K, Buse JB, Colagiuri S, et al. International expert committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care. 2009;32(7):1327–34.

4. Abdullah A, Peeters A, de Courten M, Stoelwinder J. The magnitude of association between overweight and obesity and the risk of diabetes: A meta-analysis of prospective cohort studies. Diabetes Res Clin Pract. 2010;

5. Feldman AL, Griffin SJ, Ahern AL, Long GH, Weinehall L, Fhärm E, et al. Impact of weight maintenance and loss on diabetes risk and burden: a population-based study in 33,184 participants. BMC Public Health. 2017;17(1).

6. Nuzhat A, Spong R, Carter P, Davies M, Dunkley A, Gillies C, et al. A systematic review and meta- analysis assessing the effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes mellitus in routine practice About Public Health England [Internet]. England, Public Health. 2015. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment\_data/file/456147/PHE\_Evidence\_Review\_of\_diabetes\_prevention\_programmes-\_FINAL.pdf

7. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393–403.

8. Thomas C, Sadler S, Breeze P, Squires H, Gillett M, Brennan A. Assessing the potential return on investment of the proposed UK NHS diabetes prevention programme in different population subgroups: An economic evaluation. BMJ Open. 2017;

9. Ahern AL, Wheeler GM, Aveyard P, Boyland EJ, Halford JCG, Mander AP, et al. Extended and standard duration weight-loss programme referrals for adults in primary care (WRAP): a randomised controlled trial. Lancet. 2017;389(10085):2214–25.

10. Jebb SA, Ahern AL, Olson AD, Aston LM, Holzapfel C, Stoll J, et al. Primary care referral to a commercial provider for weight loss treatment versus standard care: a randomised controlled trial. Lancet [Internet]. 2011;378(9801):1485–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21906798

11. Aveyard P, Lewis A, Tearne S, Hood K, Christian-Brown A, Adab P, et al. Screening and brief intervention for obesity in primary care: a parallel, two-arm, randomised trial. Lancet [Internet]. 2016;6736(16):1–9. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0140673616318931

12. Marrero DG, Palmer KNB, Phillips EO, Miller-Kovach K, Foster GD, Saha CK. Comparison of commercial and self-initiated weight loss programs in people with prediabetes: A randomized control trial. Am J Public Health. 2016;

13. Piper C, Marossy A, Griffiths Z, Adegboye A. Evaluation of a type 2 diabetes prevention program using a commercial weight management provider for nondiabetic hyperglycemic patients referred by primary care in the UK. BMJ Open Diabetes Res Care. 2017;

14. Ahern AL, Aveyard PN, Halford JC, Mander A, Cresswell L, Cohn SR, et al. Weight loss referrals for adults in primary care (WRAP): protocol for a multi-centre randomised controlled trial comparing the clinical and cost-effectiveness of primary care referral to a commercial weight loss provider for 12 weeks, referral for 52 week. BMC Public Health [Internet]. 2014 Jan [cited 2015 Jan 20];14(1):620. Available from: http://www.biomedcentral.com/1471-2458/14/620

15. Of D, Mellitus D. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;

16. World Health Organisation (WHO), International Diabetes Federation (IDF). Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia. World Heal Organ. 2006;

17. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons; 2004.

18. StataCorp. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP. 2015. 2015.

19. Ahern AL, Aveyard P, Boyland EJ, Halford JCG, Jebb SA. Inequalities in the uptake of weight management interventions in a pragmatic trial: An observational study in primary care. Br J Gen Pract. 2016;66(645).

20. Lindstrom J, Louheranta a., Mannelin M, Rastas M, Salminen V, Eriksson J, et al. The Finnish Diabetes Prevention Study (DPS). Diabetes Care [Internet]. 2003;26(12):3230–6. Available from: http://care.diabetesjournals.org/content/26/12/3230.short

21. Chamnan P, Simmons RK, Forouhi NG, Luben RN, Khaw KT, Wareham NJ, et al. Incidence of type 2 diabetes using proposed HbA1c diagnostic criteria in the european prospective investigation of cancer-norfolk cohort: Implications for preventive strategies. Diabetes Care. 2011;

22. Simmons RK, Sharp S, Boekholdt SM, Sargeant LA, Khaw KT, Wareham NJ, et al. Evaluation of the Framingham risk score in the European prospective investigation of cancer-Norfolk cohort: Does adding glycated hemoglobin improve the prediction of coronary heart disease events? Arch Intern Med. 2008;

23. Rose G. Sick individuals and sick populations. Int J Epidemiol. 2001;30(3):427–32.

24. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): An open-label, cluster-randomised trial. The Lancet. 2017;

25. Astbury NM, Aveyard P, Nickless A, Hood K, Corfield K, Lowe R, et al. Doctor Referral of Overweight People to Low Energy total diet replacement Treatment (DROPLET): Pragmatic randomised controlled trial. BMJ. 2018;

26. Vidal J. Updated review on the benefits of weight loss. Int J Obes Relat Metab Disord. 2002;26 Suppl 4:S25–8.

**Table 1. Baseline characteristics of participants.**

|  |  |  |
| --- | --- | --- |
|  | **Participants with assessment of glycaemic status** **at baseline and 12 months** | **Participants with non-diabetic hyperglycaemia at baseline** |
|  | **Brief Intervention(N=70)** | **12-week programme(N=210)** | **52-week programme(N=200)** |  **Brief Intervention****(N=66)** | **12-week programme****(N=173)** | **52-week programme****(N=148)** |
|  | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
| Age (years) | 57.7 (13.2) | 56.8 (12.3) | 56.7 (12.6) | 54·6 (11·9) | 58·1 (12·0) | 56·7 (12·5) |
| Height (cm) | 167.6 (9.6) | 168.2 (8.6) | 166.5 (9.2) | 167 (9·9) | 167 (9·5) | 166 (9·2) |
| Weight (kg) | 95.3 (14.6) | 95.8 (16.6) | 95.2 (16.1) | 97·1 (14·7) | 94·7 (14·8) | 93·4 (16·5) |
| HbA1c (mmol/mol) | 42.5 (10.6) | 42.0 (11.1) | 42.0 (10.4) | 41·0 (2·4) | 40·6 (2·6) | 40·7 (3·1) |
| Glucose (mmol/l) | 5.8 (1.5) | 5.8 (1.9) | 5.9 (1.8) | 5·4 (0·5) | 5·4 (0·5) | 5·4 (0·5) |
| Glycaemic Status (n; %\*) |  |  |  |  |  |  |
|  Normal glycaemia | 19 (27%) | 68 (32%) | 73 (37%) | - | - | - |
|  Non-diabetic hyperglycaemia | 32 (46%) | 99 (47%) | 86 (43%) | 66 (100%) | 173 (100%) | 148 (100%) |
|  Diabetes | 19 (27%) | 43 (20%) | 41(21%) | - | - | - |

\*May not add to 100% because of rounding to nearest whole number

**Table 2: Frequency table of glycaemic status at baseline and 12 months by intervention group.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Glycaemic Status** | **Baseline** | **Normo** |  | **NDH** |  | **Diabetes** |
| **12 months** | **Normo** | **NDH** | **Diabetes** |  | **Normo** | **NDH** | **Diabetes** |  | **Normo** | **NDH** | **Diabetes** |
| **Treatment Group** | **Brief Intervention** | 16 (84%) | 3 (16%) | 0 (0%) |  | 5 (16%) | 25 (78%) | 2 (6%) |  | 2 (11%) | 2 (11%) | 15 (79%) |
| **12 week programme** | 63 (93%) | 5 (7%) | 0 (0%) |  | 39 (39%) | 56 (57%) | 4 (4%) |  | 2 (5%) | 7 (16%) | 34 (79%) |
| **52 week programme**  | 67 (92%) | 6 (8%) | 0 (0%) |  | 37 (43%) | 48 (56%) | 1 (1%) |  | 0 (0%) | 9 (22%) | 32 (78%) |

**Normo = Normoglycaemia; NDH = Non-diabetic hyperglycaemia**

**Table 3: Changes in weight from baseline (mean, SE) to 12 months by intervention group in participants with non-diabetic hyperglycaemia at baseline**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Intervention** |  | **52-week programme** **vs Brief Intervention** |  | **12-week programme** **vs Brief Intervention** |  | **52-week programme** **vs 12-week programme** |
|   | **N** | **Brief Intervention** | **12- week programme** | **52-week programme** |  | **Adjusted** **Difference** | **p-value** |  | **Adjusted** **Difference** | **p-value** |  | **Adjusted** **Difference** | **p-value** |
| **Weight (kg**) | 387 | -2.66 (0.95) | -5.66 (0.62) | -6.93 (0.67) |  | -4.27 (-6.43, -2.10) | 0.0001 |  | -3.00 (-5.05, -0.94) | 0.0044 |  | -1.27 (-2.76, 0.22) | 0.0958 |
| **Glucose (mmol/L)** | 203 | -0.19 (0.11) | -0.30 (0.05) | -0.32 (0.06) |  | -0.12 (-0.33, 0.10) | 0.286 |  | -0.13 (-0.34, 0.08) | 0.224 |  | 0.01 (-0.13, 0.16) | 0.853 |
| **HbA1c (mmol/mol)** | 387 | -1.06 (0.55) | -1.37 (0.28) | -1.94 (0.28) |  | -1.03 (-2.21, 0.16) | 0.0891 |  | -0.45 (-1.63, 0.72) | 0.445 |  | -0.57 (-1.34, 0.20) | 0.143 |
| **HbA1c (%)** | 387 | -0.10 (0.05) | -0.13 (0.03) | -0.18 (0.03) |  | -0.09 (-0.20, 0.01) | 0.0891 |  | -0.04 (-0.15, 0.07) | 0.445 |  | -0.05 (-0.12, 0.02) | 0.143 |

Missing at random analysis; uses 50 imputed data sets obtained from multiple imputation via chained equations (MICE). Treatment effects obtained from mixed effects models with residuals structured as a first-order auto-regressive process stratified by treatment group. Adjusted differences are shown between treatment groups. Analyses are adjusted for baseline observation and centre.



**Figure 1a: Relative risk ratios (RRR) for non-diabetic hyperglycaemia at 12 months. 12 week and 52 week behavioural programmes compared to brief intervention (BI), adjusted for baseline glycaemic status, baseline age, baseline weight, sex, and centre.**



**Figure 1b: Relative risk ratios (RRR) for diabetes at 12 months. 12 week and 52 week behavioural programmes compared to brief intervention (BI), adjusted for baseline glycaemic status, baseline age, baseline weight, sex, and centre.**



**Figure 2a: Relative risk ratios (RRR) for normoglycaemia at 12 months in participants with non-diabetic hyperglycaemia at baseline. 12 week and 52 week behavioural programmes compared to brief intervention (BI), adjusted for, baseline weight, age, sex and centre.**



**Figure 2b: Relative risk ratios (RRR) for diabetes at 12 months in participants with non-diabetic hyperglycaemia at baseline. 12 week and 52 week behavioural programmes compared to brief intervention (BI), adjusted for, baseline weight, age, sex and centre.**