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Effect of physical activity and/or healthy eating on GDM risk: The DALI Lifestyle Study

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The DALI Lifestyle Study

Context: Lifestyle approaches for preventing gestational diabetes mellitus (GDM) have produced mixed results.
Objective: The aim of this study was to compare the effectiveness of three lifestyle interventions (Healthy eating (HE), Physical activity (PA) and both HE and PA (HE+PA)) with usual care (UC) in reducing GDM risk.
Design: Multicentre Randomised Controlled Trial 2012-2014: The Dali Lifestyle Study
Setting: Antenatal clinics across 11 centres in 9 European countries
Patients: Consecutive pregnant women <20 weeks gestation with a BMI≥29 kg/m^2 and without GDM by IADPSG criteria (n=436).Intervention: Women were randomized, stratified by site, to Control, HE, PA or HE+PA. Women received 5 face-to-face and up to 4 telephone coaching sessions, based on the principles of motivational interviewing. Gestational weight gain (GWG) <5kg was targeted. Coaches received standardized training and an intervention toolkit tailored to their culture/language.
Main outcome measures: GWG at 35-37 weeks, fasting glucose and insulin sensitivity (HOMA-IR) at 24-28 weeks.
Results: We randomized 108 women to HE&PA, 113 to HE, 110 to PA and 105 to UC. In the HE+PA group, but not HE or PA alone, women achieved substantially less GWG than controls by 35-37 weeks (-2.02 (95% CI -3.58; -0.46 kg). Despite this reduction there were no improvements in fasting or post-load glucose or,insulin concentrations or HOMA-IR. Birthweight, large and small for gestational age rates were similar.

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Conclusions: The combined HE+PA intervention was able to limit GWG but did not reduce fasting glycaemia. Lifestyle change alone is unlikely to prevent GDM among women with a BMI≥29 kg/m^2.

PRECIS: We studied pregnant women in a large European multi-centre RCT of physical activity and/or healthy eating and found no effect on GDM risk in spite of significant gestational weight gain limitation

INTRODUCTION

Gestational diabetes mellitus (GDM), high pre-pregnancy body mass index (BMI) and gestational weight gain (GWG) are independently associated with an increased risk of adverse perinatal outcomes, including macrosomia, operative delivery and shoulder dystocia (1). In GDM, such complications have a continuous relationship with maternal glucose concentrations during the oral glucose tolerance test (OGTT) (2). With the increasing prevalence of obesity in pregnancy and GDM (3), it has become increasingly important to develop evidence based clinical interventions that prevent the development of GDM and minimise excess GWG.

The development of type 2 diabetes through intensive lifestyle interventions can be reduced by 58% over 4 years in non-pregnant women who have previously had GDM (4). However, whether GDM can be prevented through antenatal lifestyle interventions, even with limitation in excess GWG, is disputed (5). RCTs have provided variable evidence that lifestyle interventions 'work' (6); likely because of different intervention protocols and study populations. Furthermore, at the moment, no studies are available that assessed, within the same population and with the same protocol, which intervention strategy is superior for the prevention of GDM.

The Vitamin D And Lifestyle Intervention for GDM prevention (DALI) (7,8) has harmonized some of these sources of variation. It is a European multicentre RCT testing different approaches for the reduction in GDM risk. The study is unique with 2 limbs: 1) the DALI Lifestyle Study which compares Healthy Eating (HE), Physical Activity (PA) and combined Healthy Eating and Physcial Activity (HE&PA) interventions with a control group and 2) the DALI Vitamin D study comparing Vitamin D supplementation with and without an HE&PA intervention. We now report on the DALI Lifestyle Study which tested which of the lifestyle interventions was most efficacious in reducing GWG, fasting glucose and improving insulin sensitivity measured with the homeostasis model assessment (HOMA-IR) (9).

METHODS

Design and Participants

The DALI Lifestyle Study was a multicenter RCT with a factorial study design conducted in nine European countries (United Kingdom, Ireland, Netherlands, Austria, Poland, Italy (Padua, Pisa), Spain, Denmark (Odense, Copenhagen) and Belgium) in 2012-2015 (7,8). Local ethics committee approval was obtained. Pregnant women with a pre-pregnancy body mass index (BMI) of ≥29 kg/m^2, ≤19+6days of gestation, having a singleton pregnancy, and aged ≥18 years were invited to participate. The BMI cut off was based upon data from across the DALI sites to allow recruitment of sufficient women into the trial from countries with lesser rates of maternal obesity (10). Exclusions included: diagnosed with GDM by OGTT using IADPSG/WHO 2013 criteria (fasting venous plasma glucose ≥ 5.1 mmol/l and/or 1 hour glucose ≥10 mmol/l and/or 2 hour glucose ≥ 8.5 mmol/l) (11,12), pre-existing diabetes, chronic medical conditions (local investigator defined eg valvular heart disease) or a psychiatric disorder, unable to walk ≥100 meters safely, requiring complex diets, not fluent in the major language of the country of recruitment or unable to have a conversation with the lifestyle coach in another language for which intervention materials were available.

Procedures

The main trial followed a pilot study (8), a protocol review and a standardization start-up site visit and included 6-monthly staff standardization workshops. The review resulted in no major

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protocol changes besides separating the Lifestyle and Vitamin D limbs, because of low randomization rates (due to a high prevalence of GDM at baseline and lower than projected recruitment rates).

After signed consent, assessments, including a 75 g OGTT (samples taken at 0, 60, 120 minutes), questionnaire and weight were made before 20 weeks (baseline), between 24-28 weeks (visit 2), between 35-37 weeks (visit 3), and 48 hours post birth as previously described (7,8).

Local laboratories rapidly provided OGTT results to assess study eligibility and to support referral for clinical care where needed. Blood samples were handled in a standardized manner and stored at -20º or -80º C until further analysis in the central trial laboratory in Graz, Austria. Where GDM developed after baseline, women were managed according to local practice. Supplementary Figure 1 provides a diagrammatic overview of assessments and intervention.

Randomization and blinding

Randomization to either HE&PA, HE, PA or UC (Figure 1) was performed using a computerized electronic random number generator, pre-stratified for site. The trial coordinator (DS) prepared and distributed sealed opaque envelopes, containing group allocations to each site. The allocation outcome was communicated to participants by the coach. Staff involved with measurements, but not participants, were kept blinded to the intervention. Statistical analyses were performed blinded for allocation.

Lifestyle interventions

After randomisation, women were assigned a lifestyle coach and the individual sessions were scheduled for each participant (7,8). The coaching involved discussion of 7 HE and/or 5 PA 'messages' based upon previous work (13) (Supplementary Table 1). The HE intervention promoted a food based, lower simple and complex carbohydrate, lower fat, higher fibre, higher protein diet including a focus on portion size and therefore a more limited intake of total calories. The PA intervention promoted both aerobic and resistance physical activity. All interventions recommended limitation in GWG to 5kg. Messages were supported by a 'toolkit' for each participant including participant handbook, educational materials (e.g. adapted F.I.T.T. model (frequency, intensity, time, type)) based on American College of Obstetricians and Gynaecologists guidelines (14), pedometers (Yamax Digiwalker SW-200, Tokyo, Japan),and flexible elastic dynabands (Thera-Band, Akron, USA). The message delivery was built upon principles of patient empowerment and cognitive behavioural techniques inspired by Motivational Interviewing (15). The number of contacts and time taken were expected to be the same, independent of the allocated intervention and included 5 face-to-face sessions of approximately 30-45 minutes duration, and up to 4 telephone calls of up to 20 minutes or contacts per Email. Face-to-face sessions took place largely in the hospital / midwife practice, depending on local arrangements. At least 4 face-to-face coaching sessions were expected to take place before the second measurement session (24-28 weeks) and the intervention was completed by 35 weeks of gestation.

Standardization of the lifestyle intervention was achieved through a coach training programme concluding with an observed session with an actor, provision of a desk-file including all materials and methods, and use of a personal digital assistant (PDA: HTC HD7 Windows phone), with bespoke software to provide a framework for the session. A 'paper' PDA including all fields was available for when there were any problems with the PDA. Standardisation sessions continued approximately every 6 months through the trial.

A key component was for women to strive to achieve a maximum GWG of 5 kg, as the lower limit of the recommended weight gain by the Institute of Medicine (IOM) for those with a BMI ≥30 kg/m^2 (16), and the observation of better outcomes among Danish obese women with this degree of GWG (17). The same weight target was used among the women with a BMI 29.0-29.9 kg/m^2, to avoid complicating the intervention protocol. If GWG was already beyond this before the start of, or during, the intervention, the advice was to maintain this weight

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throughout the remaining pregnancy. The coaches had scales available to assist women with their weight management, where scales were not available in the home.

Assessments

Information on demographics, pre-pregnancy weight, maternal/paternal smoking, alcohol consumption, past/current medical and obstetric history and medication use was gathered by questionnaire. Women attended the three assessments fasting and undertook a standardised, sitting, 75 g OGTT, with blood samples taken at 0, 60 and 120 minutes after glucose ingestion. Women completed the questionnaire and anthropometric measurements between blood tests. Local laboratories were used to rapidly obtain results to the OGTT to assess eligibility for the study and to support referral for clinical care where needed. Blood samples were centrifuged and separated serum and plasma aliquots (1000 µl or 250 µl) placed in microrack tubes and stored at -20º or -80º C until further analysis in the central trial laboratory in Graz, Austria, certified according to ISO 9001 standards.

Glucose was measured using the hexokinase method (DiaSys Diagnostic Systems, Holzheim, Germany) with a lower limit of sensitivity of 0.1 mmol/l. Central values are used for trial reporting.

Insulin was quantified by a sandwich-immunoassay (ADVIA Centaur, Siemens Healthcare Diagnostics Inc., Vienna) with an analytical sensitivity of 0.5 mU/l, intra-assay CVs of 3.3-4.6% and inter-assay CVs of 2.6-5.9%. All assays were carried out following the instructions of the manufacturer. HOMA-IR was calculated as (glucose*insulin)/22.5 (9).

Height was measured at baseline with a stadiometer (SECA 206, SECA, Birmingham, UK; Leicester Height Measure) and the average value of two measurements was used. Women were weighed on calibrated electronic scales (SECA 888; SECA 877) wearing no shoes and light clothes, to the nearest 0.1 kg; the average value of two measurements was used. Weight gain was defined as the change in objectively measured weight, and was calculated weight for three periods: baseline to 24-28 weeks, baseline to 35-37 weeks and 24-28 to 35-37 weeks.

Data from the medical records were obtained regarding co-morbidities, obstetric and perinatal outcomes and birth weight.

Effectiveness of the lifestyle interventions

Effectiveness of the physical activity intervention was assessed using the Pregnancy Physical Activity Questionnaire (PPAQ) (18) at the three time points. The original PPAQ consisted of 32 activities including household/caregiving, occupational, sports/exercise and inactivity measured during the current trimester. Open-ended questions allowed the respondent to add activities not already listed. In DALI, two questions for cycling to work (4.0 MET (metabolic equivalent of task)) and cycling for fun or exercise (8.0 MET) had been added, due to the frequent performance of these activities in some European countries. Participants were asked to select the category that best approximated the amount of time spent in one of these activities. The duration of time spent in each activity was multiplied by its intensity such that an average weekly energy expenditure (MET hours/week) was calculated for each activity. For the open-ended reported activities, a compendium of physical activities was used to obtain MET values for intensity (19). Activities were categorized by intensity (sedentary, light, moderate, vigorous), type and total activity (sum of all activity with an intensity above 1.5 MET). Self-reported moderate and vigorous activity were summed and presented as MET hours/week of MVPA.

Nutrition was assessed using a bespoke short food frequency questionnaire covering key foods linked to the intervention messages and based upon prior work (20). The number of portions/week for each key food component was calculated as the product of the frequency consumed/week and the number of portions each episode.

Outcomes

GWG at 35-37 weeks, and fasting glucose and HOMA-IR at 24-28 weeks were primary outcomes. GWG was defined as the change in objectively measured weight from baseline, as

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some women were unable to recall pre-pregnancy weight accurately. HOMA-IR was calculated (9).

Secondary outcomes included physical activity, nutrition, glucose concentrations 1 and 2 hours after glucose ingestion, fasting insulin concentrations, and insulin at 1 and 2 hours after glucose ingestion, GDM, birth weight, gestational age, and small- (SGA) or large-for-gestational age (LGA) babies.

Data from medical records provided co-morbidity, obstetric, birthweight and perinatal outcome and resource data.

Statistics

Sample size calculations have been reported previously (7), but were repeated based on means and standard deviations found in the pilot study (8). Based on the pilot data, the numbers needed in each intervention arm were: 41 women to detect a GWG difference of 4 kg (mean of 10 kg, standard deviation (SD) 5.8 kg); 19 women to measure a fasting glucose difference of 0.3 mmol/l (mean of 4.8 mmol/l, SD 0.3 mmol/l) and 220 women to find a difference 0.44 for the HOMA-IR (mean of 3.0, SD 1.8).

Insulin and HOMA-IR were log transformed because of skewness. For the 35-37 weeks assessment, fasting glucose and HOMA-IR were carried forward from 24-28 weeks if GDM was diagnosed, and women were excluded from the GWG analyses, since treatments (e.g. diet and/or insulin treatment) could influence weight gain. For sensitivity analyses of the intervention effects, missing data were multiply imputed, stratified by treatment group (21). Using Predictive Mean Matching, 20 complete data sets were created (i.e. loss of efficiency <0.05) (21). Data sets were analyzed separately and pooled estimates were calculated using Rubin's rules (22).

Data were analyzed according to intention-to-treat, and according to an *a priori* statistical analysis plan. Differences between subjects dropping out of the study and those who stayed in the study were assessed using T-test (normally distributed continuous variables), Mann-Whitney U test (skewed continuous variables) or Chi square test (categorical variables). To assess differences in outcomes at 24-28 and 35-37 weeks of gestation between intervention groups, multilevel analyses were performed, using two levels (site and individual). Analyses with glucose and insulin as outcome were adjusted for baseline values. Models with weight gain variables were adjusted for maternal BMI at baseline. Birth weight was adjusted for gestational age at birth. Two sided $p<0.05$ was taken as significant. Comparisons between the intervention groups demonstrated interactions with regards to GWG, and hence the factorial analysis (7) is not reported.

Analyses were performed in SPSS22, except multilevel analyses that were performed using MLwiN2.22.

RESULTS

Figure 1 shows the CONSORT diagram. Numbers randomised, and baseline characteristics in each group were comparable (Table 1). Gestational age on entry ranged from 8 to 19^{+6} weeks. Women who dropped out before the final OGTT (n=73 (17%)) had higher rates of chronic hypertension and past GDM (Supplementary Table 2).

Table 2 shows GWG, glucose, insulin and HOMA-IR at 24-28 and 35-37 weeks of gestation. Compared with UC, the HE&PA intervention was associated with significantly lower GWG, but similar fasting glucose and HOMA-IR, at both 24-28 and 35-37 weeks (Table 3). Neither HE nor PA alone achieved significant improvements in GWG, fasting glucose or HOMA-IR compared with UC (Table 3). Fasting glucose was higher in the HE compared to US at both time points. Results of the sensitivity analysis with imputed data were fully in line with these findings (data not shown).

The HE and HE&PA interventions were associated with significant improvements in healthy eating, while the PA intervention was associated with significantly greater MVPA at

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24-28 weeks (Table 4). Sedentary behavior was lower with the HE&PA intervention at 24-28 and 35-37 weeks and with HE at 24-28 weeks.

There were no significant differences between groups in the development of GDM, small- (SGA) or large-for-gestational-age (LGA) babies, besides a small but significantly lower gestational age at birth in the HE group compared to UC (Tables 2 and 3).

DISCUSSION

The DALI lifestyle trial was a pan-European study designed to find the most effective lifestyle intervention for preventing GDM in preparation for a larger RCT. The primary outcomes chosen to define 'effective' were GWG, fasting glucose and HOMA-IR. The effects of advice on healthy eating, physical activity and the combination of the two on these 3 outcomes were evaluated, allowing separation of the effects of the two intervention modalities. Women with glucose levels above the IADPSG/WHO criteria at baseline were excluded, making it a true trial for the prevention of incident GDM. Outcomes were evaluated at two time points in pregnancy: 24-28 weeks, the usual gestation at which testing for GDM occurs, and at 35-37 weeks, the latest gestation we felt that an OGTT could be reliably undertaken to assess sustainability of the intervention effect. Being across multiple countries, with recruitment largely through non-specialized antenatal clinics, DALI is representative of the wider pregnant, obese, European population, without evidence of elevated glucose concentrations between 9 - 20 weeks gestation. The intensive interventions, based on motivational interviewing, resulted in significant lifestyle improvements at both time periods of their assessment. Yet neither PA nor HE alone had any significant beneficial effect on GWG or metabolic outcomes (indeed HE was associated with an increased fasting glucose in this main trial, the converse to that found in our pilot). An improvement in both lifestyles, as in the combined intervention group, resulted in significant GWG limitation, but still with no impact on fasting glucose or insulin resistance. In spite of the significant changes in GWG, post-load glucose and insulin concentrations remained unchanged and this occurred with and without the PA intervention.

Of the large number of early lifestyle RCTs, only two, (one HE and one HE&PA intervention) showed a substantial (60-77%) reduction in the proportion of women developing GDM (23,24). Both RCTs were also associated with significant GWG reductions (3.4 kg (in obese participants) and 6.8 kg respectively) that were greater than the average GWG reduction of 1.4 kg that has been achieved in lifestyle RCTs (25). The recent RADIEL study showed a 39% adjusted reduction in GDM, although with a modest reduction in GWG of 0.5 kg (26); a finding potentially explained by the inclusion of about 30% women with prior GDM. However, the two largest recent RCTs of HE&PA interventions were negative: the UPBEAT (27) and LIMIT (28) studies showed a reduction in GWG of only 0.55 kg and 0.05 kg, respectively, which did not result in a reduction in GDM at 24-28 weeks. Furthermore, no previous trial, with the exception of RADIEL (26), excluded women with 'abnormal' glucose tolerance at baseline, and are therefore not genuine GDM prevention trials.

Although not one of our primary outcomes, birthweight was not significantly lower with the interventions, nor were their reductions in LGA or increases in SGA babies. A post hoc analysis did show reductions in babies with a birthweight ≥4.5kg in the LIMIT study(28) , but, DALI Lifestyle, along with other studies (25) did not find a similar effect on LGA rates. We were concerned about SGA rates with our limitation in GWG, but again no significant difference was found.

Previously, there were doubts over whether the negative findings in prior studies were due to interventions that had not achieved sufficient GWG difference (5), either because of the nature of the intervention involved, or due to controls gaining less weight than expected following successful adoption of their own lifestyle changes (6). However, the relatively high GWG reduction as in DALI Lifestyle, did not impact on metabolic parameters. Future studies might need even more intensive interventions, with greater support for women, leading to greater lifestyle changes. Perhaps even more imaginative tools, such as tele-health approaches,

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might be included (5). It is important to note that the need for intensive support during lifestyle interventions was clearly shown in the DPP (4). However, for practical purposes of knowledge transfer, the DALI study has demonstrated that a substantial reduction in GWG through lifestyle changes alone does not impact on glycemia in obese mothers. Whilst further escalation of the rigour of lifestyle intervention may start to impact on HOMA, the cost:benefit value will need to be assessed if the impact on GDM is limited, although the future health trajectory of both mother and child will also require analysis.

A further question is whether lifestyle change starting from, or before conception could be more effective than those commencing at the beginning of the second trimester. However, testing such an intervention before or in early pregnancy may prove challenging. The former could be investigated among women with prior GDM who are planning further pregnancies (although lifestyle interventions should be in place in any case). Women in early pregnancy are often not 'booked in' for antenatal care, and there are multiple practical reasons why commencing a trial so early in pregnancy may be problematic.

This study had several strengths, including its European multicenter randomized controlled trial design, its robust approach to intervention fidelity and inclusion of a health economic analysis. No increase in SGA rate was seen, consistent with the findings among obese women with GWG 0-5kg in Denmark (17). There has been a concern that inadequate weight gain could lead to the fetal 'thrifty phenotype' predisposing to long term metabolic risk (29,30).

Several limitations are noteworthy. DALI lifestyle was funded as an exploratory trial and was not large enough to evaluate differences in e.g. GDM. We wanted to overcome this using a 2x2 factorial design, assuming we would be able to compare 2 groups at a time, providing more power. However, given the greater interaction between the interventions than anticipated, we did not combine the intervention groups. Initial power calculations were based on both between groups and between factors, so this decision remained within the original study design. Based on pilot data, the power for HOMA was too low in this study. However, given the small differences between intervention groups these would not have been considered clinically relevant, even when statistically significant. We have not adjusted the significance level for multiple comparisons as the comparisons followed our *a priori* statistical analysis plan, and the differences in GWG are in line with (or better than) other RCTs, which speaks against the role of chance. There were some drop outs and missing data, but the missing data did not influence the results of the effect analysis much, since when using imputed data, the GWG difference was -2.3 kg (95%CI -3.7 to -0.9 kg). Fasting glucose was inexplicably, marginally, increased in the HE group. Others have suggested that diets higher in complex carbohydrate and low in fat might improve insulin sensitivity (31), and the DALI HE recommendation included lowering both carbohydrate and fat intake. Further work is required to understand a possible metabolic basis of these findings. However, as the pilot found a marginally lower fasting glucose with HE, we suggest both are likely due to chance.

Excluding women with glucose levels above the IADPSG/WHO 2013 criteria at baseline, was both a strength and a weakness. Conversion rates were still very high (19% by 24-28 weeks and 37% by 35-37 weeks), even after excluding approximately 20% of women with 'hyperglycaemia' in early pregnancy. As the criteria for GDM diagnosis early in pregnancy may need to be higher (32), it could be argued that some women who would have benefited from the DALI intervention were excluded. However, it has made DALI one of the few true trials for the prevention of incident GDM, rather than intervening among a group where a proportion at least had pre-existing GDM. GDM is clearly a heterogeneous condition with, for example, a significant proportion of women with 'early GDM', being more insulin resistant (33), and different anthropometry and glucose tolerance test profiles between women with GDM from different ethnic groups (34). Whether the impact of lifestyle approaches would be more effective in subgroups (as perhaps happened in the RADIEL study with its higher proportion of women with past GDM), warrants further study.

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We conclude that, although the DALI HE&PA intervention is an effective intervention as compared to UC for pregnant women with a BMI ≥29 kg/m^2 for limiting GWG, it is unlikely to prevent GDM. Further lifestyle interventions should probably concentrate on the first trimester, the pre-pregnancy period and special sub-groups.

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Authors' contributions
All authors contributed to the conception and/or design of the trial, read and corrected draft versions of the manuscript and approved the final manuscript. DS wrote the first draft of the paper, MNMvP undertook the statistical analyses, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. DS is Guarantor.

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Figure 1. CONSORT diagram of recruitment, randomization and drop out of the DALI lifestyle trial

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Table 1. Baseline characteristics of all women included per intervention group

Variable	UC N=105	HE & PA N=108	HE N=113	PA N=110	Total N=436
Age, year, mean ± SD	31.8 ± 5.6	31.9 ± 5.3	32.5 ± 5.5	31.7 ± 5.1	32.0 ± 5.4
Multiparous, N (%)	50 (48%)	56 (52%)	64 (57%)	51 (46%)	221 (51%)
European descent, N (%)	94 (90%)	95 (88%)	95 (84%)	94 (86%)	378 (87%)
Lives with partner, N (%)	100 (95%)	99 (92%)	108 (96%)	103 (94%)	410 (94%)
Higher education, N (%)	55 (52%)	59 (55%)	65 (58%)	60 (55%)	239 (55%)
Maternal smoking, N (%)	18 (17%)	11 (10%)	20 (18%)	18 (17%)	67 (15%)
Paternal smoking, N (%)	33 (32%)	29 (27%)	42 (38%)	39 (36%)	143 (33%)
History of GDM, N (%)	3 (5%)	4 (6%)	6 (7%)	4 (6%)	17 (6%)
1st degree FH DM, N (%)	28 (27%)	18 (17%)	28 (25%)	27 (25%)	101 (23%)
Chronic hypertension, N (%)	9 (9%)	12 (11%)	17 (15%)	17 (16%)	55 (13%)
Gestation on entry, weeks, mean ± SD	15.2 ± 2.4	15.2 ± 2.2	15.3 ± 2.5	15.5 ± 2.3	15.3 ± 2.3
Pre-pregnancy weight, kg, mean ± SD	92.0 ± 11.5	93.3 ± 13.7	92.5 ± 13.6	92.7 ± 13.4	92.6 ± 13.1
Weight at entry, kg, mean ± SD	94.2 ± 12.6	95.2 ± 13.8	94.9 ± 13.2	94.6 ± 12.8	94.7 ± 13.1
Height, cm, mean ± SD	165.9 ± 6.7	166.0 ± 6.6	165.2 ± 6.6	165.6 ± 7.2	165.7 ± 6.8
BMI pre-pregnancy, kg/m^2, mean ± SD	33.4 ± 3.5	33.8 ± 3.9	33.9 ± 4.4	33.7 ± 4.0	33.7 ± 4.0
BMI at entry, kg/m^2, mean ± SD	34.2 ± 3.9	34.5 ± 4.0	34.7 ± 4.2	34.4 ± 3.8	34.5 ± 4.0
Fasting glucose, mmol/l, mean ± SD	4.69 ± 0.35	4.62 ± 0.34	4.61 ± 0.38	4.55 ± 0.39	4.6 ± 0.4
1 h glucose, mmol/l, mean ± SD	7.0 ± 1.3	6.8 ± 1.2	6.7 ± 1.5	6.6 ± 1.4	6.8 ± 1.4
2 h glucose, mmol/l, mean ± SD	5.9 ± 1.1	5.9 ± 1.1	5.9 ± 1.1	5.7 ± 1.1	5.8 ± 1.1
Fasting insulin, mU/l, median (range*)	12.9 (9.6, 17.7)	12.8 (10.3, 17.2)	13.0 (9.0, 17.8)	11.7 (10.1, 15.3)	12.7 (9.9, 17.1)
1 h insulin, mU/l, median (range*)	89.9 (56.7, 157.8)	85.6 (60.6, 158.8)	87.3 (47.6, 149.7)	85.7 (53.1, 143.7)	87.8 (55.3, 153.3)
2 h insulin, mU/l, median (range*)	59.4 (39.9, 91.0)	60.4 (46.8, 100.0)	53.5 (39.9, 88.0)	55.8 (40.0, 77.8)	57.0 (41.3, 90.0)
HOMA-IR, median (range*)	2.8 (2.0, 3.7)	2.6 (2.1, 3.5)	2.7 (1.8, 3.8)	2.4 (2.0, 3.1)	2.6 (2.0, 3.5)

*Range from 25th to 75th percentile.

Abbreviations: UC=usual care; HE=Healthy Eating; PA=Physical Activity; HE&PA= Healthy Eating & Physical Activity; GDM=gestational diabetes; FH DM=Family History of diabetes; SD=standard deviation; BMI=body mass index; HOMA-IR= Homeostatic model assessment-insulin resistance.

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Table 2. Primary and secondary outcomes in the four intervention groups and intervention effects at 24-28 and 35-37 weeks and at birth

24-28 weeks	N	UC	N	HE & PA	N	HE	N	PA
Weight gain T1-T2, kg, mean ± SD†	100	4.3 ± 2.6	97	3.1 ± 2.4	102	3.5 ± 2.9	102	4.3 ± 3.0
Fasting glucose, mmol/l, mean ± SD	97	4.61 ± 0.41	89	4.63 ± 0.39	104	4.72 ± 0.45	98	4.58 ± 0.41
HOMA-IR, median (range*)	94	2.9 (2.2, 4.2)	87	2.9 (2.4, 3.6)	103	3.0 (2.2, 4.1)	97	2.9 (2.2, 4.2)
Secondary variables								
1 h glucose, mmol/l, mean ± SD	99	7.8 ± 1.5	91	7.9 ± 1.6	104	7.8 ± 1.8	96	7.6 ± 1.8
2 h glucose, mmol/l, mean ± SD	100	6.3 ± 1.2	90	6.3 ± 1.2	101	6.3 ± 1.2	95	6.2 ± 1.3
Fasting insulin mU/l, median (range*)	95	14.1 (11.3, 20.8)	88	14.2 (11.6, 17.6)	103	14.6 (10.6, 19.4)	98	14.8 (11.5, 20.1)
1 h insulin, mU/l, median (range*)	97	128.8 (76.6, 187.8)	90	143.4 (76.7, 182.2)	102	132.1 (71.8, 182.1)	94	112.3 (67.2, 186.8)
2 h insulin, mU/l, median (range*)	96	78.5 (54.4, 135.6)	89	82.3 (52.2, 131.0)	101	69.0 (50.9, 136.7)	93	70.6 (49.3, 121.1)
GDM, N (%)	100	19/100 (19%)	92	18/92 (20%)	106	26/106 (25%)	99	21/99 (21%)
35-37 weeks								
Weight gain T1-T3, kg, mean ± SD	79	8.8 ± 4.7	75	6.5 ± 3.8	74	8.0 ± 4.7	76	8.5 ± 5.0
Fasting glucose, mmol/l, mean ± SD ‡	94	4.60 ± 0.50	89	4.56 ± 0.51	91	4.73 ± 0.48	87	4.51 ± 0.41
HOMA-IR, median (range*) ‡	93	3.3 (2.2, 5.4)	85	3.1 (2.4, 4.1)	90	3.5 (2.7, 4.6)	87	3.3 (2.2, 4.3)
Secondary variables								
Weight gain T2-T3,kg, mean ± SD	79	4.4 ± 2.8	75	3.4 ± 2.2	71	4.5 ± 2.7	76	4.2 ± 2.9
Weight gain <5kg, N(%)	79	16/79 (20%)	75	27/75 (36%)	74	19/74 (26%)	76	18/76 (24%)
Weight gain not exceeding IOM, N(%)	79	19/79 (24%)	75	30/75 (40%)	74	21/74 (28%)	76	21/76 (28%)
1 h glucose, mmol/l, mean ± SD	90	8.2 ± 1.4	87	8.0 ± 1.3	88	8.2 ± 1.5	87	8.0 ± 1.5
2 h glucose, mmol/l, mean ± SD	90	6.5 ± 1.2	86	6.4 ± 1.1	89	6.9 ± 1.2	87	6.4 ± 1.1
Fasting insulin, mU/l, median (range*) ‡	93	16.5 (11.2, 24.3)	86	15.5 (12.4, 20.6)	90	16.8 (13.0, 22.0)	89	16.3 (12.1, 22.2)
1 h insulin, mU/l, median (range*)	90	187.8 (112.7, 225.2)	86	173.9 (117.8, 217.6)	88	181.5 (107.9, 232.2)	87	152.4 (95.5, 211.2)
2 h insulin, mU/l, median (range*)	89	118.7 (59.4, 174.3)	86	110.4 (68.5, 176.1)	89	134.5 (66.0, 194.1)	85	110.7 (61.6, 164.9)
GDM, N (%)	94	35/94 (37%)	84	27/84 (32%)	91	40/91 (44%)	89	30/89 (34%)
Birth outcomes (secondary variables)								
Gestational age at birth, weeks, mean ± SD	93	39.8 ± 1.6	93	39.8 ± 1.4	103	39.4 ± 2.1	98	39.5 ± 1.6
Birth weight g,mean ±SD	94	3571 ± 517	91	3472 ± 498	103	3448 ± 643	96	3456 ± 502
SGA < 10th percentile, N(%)	90	5/90 (6%)	86	7/86 (8%)	101	10/101 (10%)	87	5/87 (6%)
LGA > 90th percentile, N(%)	90	16/90 (18%)	86	8/86 (9%)	101	15/101 (15%)	88	12/88 (14%)

Abbreviations: Adj=adjusted for baseline; UC=usual care; HE=Healthy Eating; PA=Physical Activity; HE & PA= Healthy Eating & Physical Activity; GDM=gestational diabetes; SD=standard deviation; HOMA-IR= Homeostatic model assessment-insulin resistance; IOM=Institute of Medicine recommended maximum gestational weight gain; SGA=small for gestational age; LGA= large for gestational age

T1-T2=difference between 24-28 weeks and baseline; T1-T3= difference between 35-37 weeks and baseline; T2-T3= difference between 35-37 weeks and 24-28 weeks;

*Range from 25th to 75th percentile

‡ Value of 24-28 weeks was carried forward when, based on local OGTT, women had developed GDM

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Table 3. Adjusted differences or OR of primary and secondary outcomes; comparisons of intervention groups with usual care group.

24-28 weeks	Adj difference or OR (95% CI) HE & PA vs UC	Adj difference or OR (95% CI) HE vs UC	Adj difference or OR (95% CI) PA vs UC
Weight gain T1-T2, kg	**-1.19 (-1.90; -0.49)**	-0.64 (-1.33; 0.06)	0.12 (-0.58; 0.82)
Fasting glucose, mmol/l	0.03 (-0.07; 0.12)	**0.15 (0.05; 0.24)**	0.03 (-0.07; 0.12)
HOMA-IR ¶	0.002 (-0.11; 0.11)	0.04 (-0.07; 0.14)	0.07 (-0.04; 0.17)
Secondary Variables			
1 h glucose, mmol/l	0.24 (-0.17; 0.65)	0.08 (-0.33; 0.48)	0.08 (-0.33; 0.48)
2 h glucose, mmol/l	0.06 (-0.26; 0.37)	-0.01 (-0.32; 0.30)	-0.03 (-0.33; 0.28)
Fasting insulin mU/l ¶	0.00 (-0.10; 0.10)	0.01 (-0.09; 0.11)	0.07 (-0.03; 0.17)
1 h insulin, mU/l ¶	0.05 (-0.11; 0.20)	0.06 (-0.09; 0.21)	-0.01 (-0.16; 0.15)
2 h insulin, mU/l ¶	-0.06 (-0.23; 0.11)	0.00 (-0.17; 0.17)	0.001 (-0.17; 0.17)
GDM, %	OR 1.10 (0.48; 2.49)	OR 1.48 (0.69; 3.15)	OR 1.21 (0.55; 2.67)
35-37 weeks			
Weight gain T1-T3, kg †§	**-2.02 (-3.58; -0.46)**	-0.28 (-1.67; 1.12)	0.01 (-1.38; 1.39)
Fasting glucose, mmol/l ‡	-0.03 (-0.15; 0.09)	**0.16 (0.03; 0.28)**	-0.03 (-0.16; 0.09)
HOMA-IR ‡¶	-0.03 (-0.17; 0.12)	0.11 (-0.03; 0.25)	0.06 (-0.08; 0.20)
Secondary Variables			
Weight gain T2-T3,kg †§	**-0.81 (-1.76; -0.14)**	0.27 (-0.56; 1.10)	-0.11 (-0.92; 0.70)
Weight gain <5kg, % †§	**OR 2.26 (1.02; 4.98)**	OR 1.14 (0.50; 2.64)	OR 1.10 (0.47; 2.54)
Weight gain not exceeding IOM, % †§	**OR 2.13 (1.05; 4.33)**	OR 1.10 (0.52; 2.32)	OR 1.13 (0.54; 2.37)
1 h glucose, mmol/l ‡	-0.04 (-0.46; 0.38)	0.10 (-0.33; 0.53)	0.16 (-0.26; 0.58)
2 h glucose, mmol/l ‡	-0.17 (-0.51; 0.17)	0.21 (-0.14; 0.55)	0.02 (-0.32; 0.36)
Fasting insulin, mU/l ‡¶	-0.003 (-0.13; 0.13)	0.07 (-0.06; 0.20)	0.08 (-0.05; 0.21)
1 h insulin, mU/l ‡¶	-0.01 (-0.18; 0.16)	0.03 (-0.14; 0.20)	-0.07 (-0.24; 0.10)
2 h insulin, mU/l ‡¶	-0.06 (-0.25; 0.13)	0.12 (-0.07; 0.31)	-0.01 (-0.20; 0.18)
GDM, %	OR 0.80 (0.43; 1.49)	OR 1.33 (0.73; 2.40)	OR 0.86 (0.47; 1.58)
Birth outcomes (secondary Variables)			
Gestational age at birth, weeks	0.02 (-0.62; 0.66)	**-0.66 (-1.27; -0.04)**	-0.36 (-0.99; 0.27)
Birth weight, g ††	-105 (-243; 32)	-65 (-199; 69)	-65 (-202; 72)
SGA < 10th percentile, %	1.51 (0.46; 4.94)	1.87 (0.61; 5.69)	1.04 (0.29; 3.71)
LGA > 90th percentile, %	0.47 (0.19; 1.18)	0.81 (0.37; 1.76)	0.73 (0.32; 1.66)

All regression analyses were adjusted for baseline values of the outcome variable, except GDM.
Significant differences ($p<0.05$) are indicated in bold.
† Adjusted for BMI at baseline and number of weeks between measurements
‡ Value of 24-28 weeks was carried forward when, based on local OGTT, women had developed GDM
§ excluding women who developed GDM at 24-28 weeks according to local OGTT (n=60)
¶ Variable was log transformed for the regression analyses. Adjusted differences between usual care and intervention group need to be interpreted as % difference in the outcome variable.
†† adjusted for gestational age

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Table 4. Physical activity and healthy eating in the four intervention groups at 24-28 and 35-37 weeks and adjusted differences compared with usual care

	UC	HE&PA	HE	PA	Adj difference (95% CI) HE&PA vs UC	Adj difference (95% CI) HE vs UC	Adj difference (95% CI) PA vs UC
24-28 weeks							
Total PA, METhr/week, median (range)*†	130 (100; 189)	133 (98; 202)	141 (103; 198)	165 (117; 199)	0.00 (-0.12; 0.12)	0.02 (-0.10; 0.14)	0.08 (-0.04; 0.20)
MVPA, METhr/week, median (range)*†	30 (15; 63)	44 (21; 77)	36 (17; 80)	51 (27; 89)	0.24 (-0.01; 0.50)	0.09 (0.16; 0.33)	**0.36 (0.13; 0.60)**
Sedentary time, MET hour/week, mean ± SD	13 ± 10	11 ± 9	12 ± 8	12 ± 7	**-3.0 (-4.47; -0.45)**	**-2.18 (-4.14; -0.21)**	-1.96 (-3.93; 0.02)
Sugared drinks, mean ± SD	5.3 ± 5.2	5.2 ± 7.7	3.2 ± 4.5	6.9 ± 7.3	-0.9 (-2.7; 0.9)	**-2.0 (-3.8; -0.2)**	0.6 (-1.2; 2.4)
Vegetables, mean ± SD	12.0 ± 9.4	13.8 ± 8.1	15.5 ± 10.1	13.2 ± 9.1	**2.6 (0.1; 5.0)**	**4.5 (2.0; 7.0)**	0.2 (-2.2; 2.7)
Fibre, mean ± SD	34.1 ± 17.9	35.1 ± 17.6	35.6 ± 17.0	33.9 ± 18.0	-0.0 (-4.9; 4.8)	2.8 (-2.1; 7.7)	-1.6 (-6.4; 3.1)
Portion size, mean ± SD	16.4 ± 12.4	15.7 ± 12.3	13.4 ± 9.9	19.1 ± 12.2	**-4.0 (-7.4; -0.6)**	**-5.3 (-8.6; -1.9)**	-0.9 (-4.3; 2.4)
Protein, mean ± SD	8.7 ± 6.2	9.8 ± 6.5	9.6 ± 5.9	9.1 ± 5.2	1.4 (-0.2; 3.1)	1.0 (-0.7; 2.7)	0.2 (-1.4; 1.8)
Fat, mean ± SD	6.1 ± 5.8	5.6 ± 4.8	5.0 ± 6.4	6.5 ± 5.8	-1.1 (-2.9; 0.6)	-1.7 (-3.5; 0.02)	-0.2 (-1.9; 1.6)
Carbohydrates, mean ± SD	36.6 ± 18.8	33.7 ± 16.3	31.6 ± 15.0	36.3 ± 19.0	-4.8 (-9.0; 0.5)	**-4.8 (-9.6; -0.1)**	-2.8 (-7.5; 1.9)
35-37 weeks							
Total PA, MET hour/week, median (range)*	105 (76; 141)	111 (88; 163)	116(93; 169)	119 (86; 180)	0.09 (-0.06; 0.23)	0.10 (-0.04; 0.24)	0.09 (-0.06; 0.23)
MVPA, MET hour/week, median (range)*	22 (11; 42)	29 (8; 55)	21 (10; 59)	35 (16; 60)	0.16 (-0.14; 0.47)	0.11 (-0.20; 0.41)	0.31 (-0.002; 0.61)
Sedentary time, MET hour/week, mean ± SD	14 ± 10	11 ± 8	13 ± 10	14 ± 8	**-2.98 (-5.29; -0.67)**	-0.76 (-3.05; 1.54)	-0.50 (-2.79; 1.80)
Sugared drinks, portions /week, mean ± SD	5.0 ± 5.7	3.6 ± 4.8	3.3 ± 5.3	6.1 ± 6.8	**-2.0 (-3.7; -0.4)**	-1.6 (-3.2; 0.1)	0.4 (-1.3; 2.1)
Vegetables, portions /week, mean ± SD	13.1 ± 9.6	12.3 ± 8.0	15.6 ± 11.2	12.8 ± 11.1	0.3 (-2.4; 3.0)	**3.5 (0.8; 6.3)**	-1.1 (-3.7; 1.6)
Fibre, portions/week, mean ± SD	35.0 ± 17.9	31.8 ± 17.5	33.3 ± 18.0	31.6 ± 19.3	-4.0 (-9.2; 1.2)	0.0 (-5.2; 5.3)	-4.2 (-9.3; 1.0)
Portion size, mean ± SD	17.3 ± 11.4	15.9 ± 10.1	13.9 ± 10.8	19.5 ± 13.6	-2.9 (-6.6; 0.8)	**-4.5 (-8.2; -0.9)**	0.2 (-3.4; 3.8)
Protein, portions/week, mean ± SD	8.8 ± 7.1	8.7 ± 5.7	9.8 ± 8.6	8.8 ± 4.3	0.2 (-1.7; 2.1)	0.8 (-1.1; 2.7)	-0.4 (-2.3; 1.5)
Fat, portions/week, mean ± SD	6.6 ± 8.5	5.7 ± 5.7	4.7 ± 4.1	6.4 ± 4.3	-1.6 (-3.4; 0.2)	**-2.5 (-4.3; -0.7)**	-0.8 (-2.6; 0.9)
Carbohydrates, portions /week, mean ± SD	35.6 ± 18.3	31.9 ± 18.7	28.2 ± 14.2	35.0 ± 18.5	**-5.2 (-10.2; -0.3)**	**-7.0 (-11.9; -2.0)**	-3.0 (-7.9; 1.8)

Abbreviations: UC: usual care; HE=Healthy Eating; PA=Physical Activity; HE&PA= Healthy Eating & Physical Activity; SD=standard deviation; MET= metabolic equivalent of task; moderate-to-vigorous physical activity
All regression analyses assessing differences between intervention and control group were adjusted for baseline values of the outcome variable.
Significant differences ($p<0.05$) are indicated in bold. Range from 25th to 75th percentile.
† Variable was log transformed for the regression analyses. Adjusted differences between control and intervention group need to be interpreted as % difference in the outcome variable

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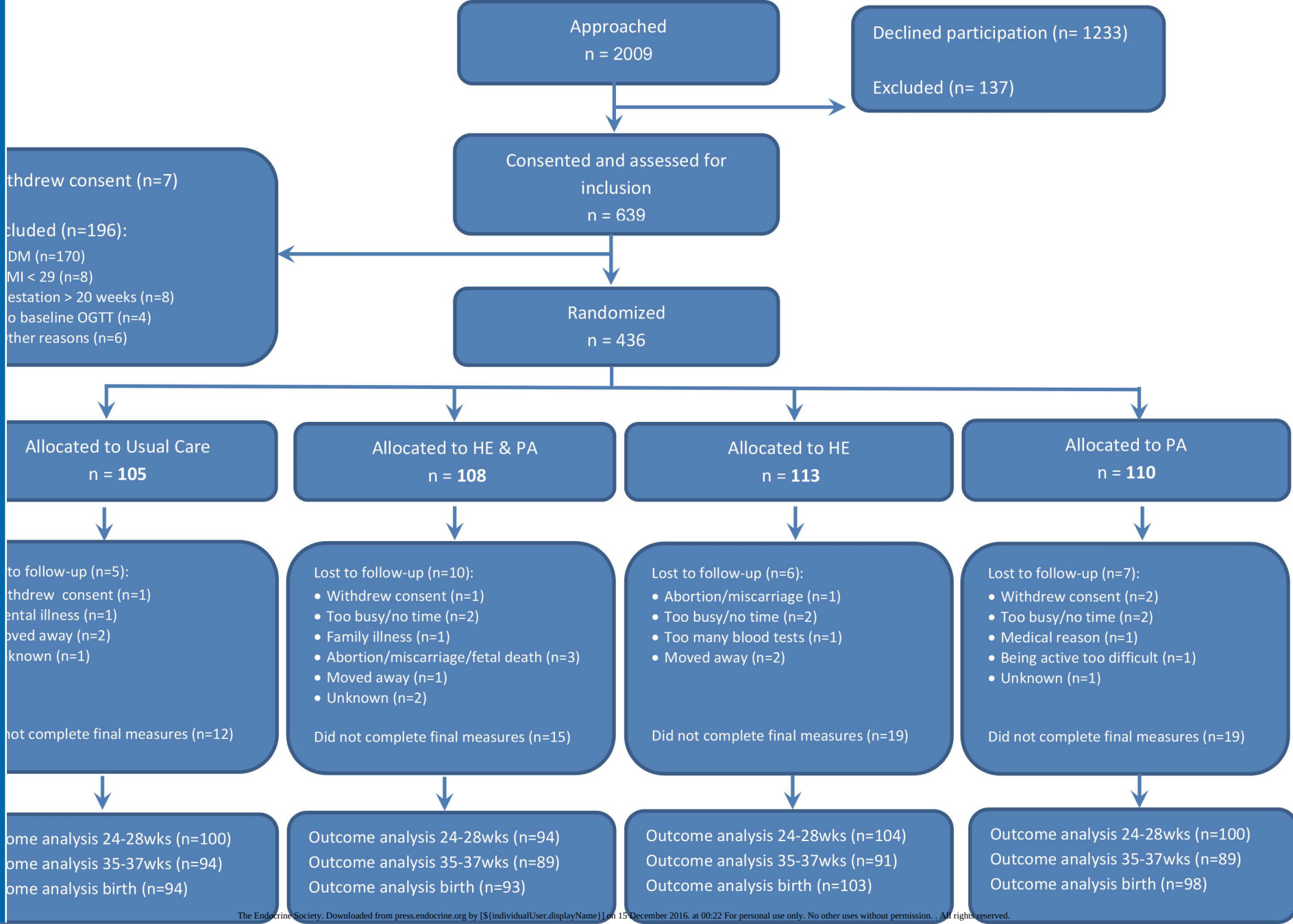

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