Lifestyle Counselling Intervention to prevent Gestational Diabetes Mellitus

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CHAPTER 4:

Results from a European multicentre, randomised trial of physical activity and/or healthy eating to reduce the risk of gestational diabetes mellitus (GDM): The DALI Lifestyle Pilot

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Objective: Ways to prevent gestational diabetes mellitus (GDM) remain unproven. We compared the impact of three lifestyle interventions (healthy eating (HE), physical activity (PA) and both HE and PA (HE+PA)) on GDM risk in a pilot multicentre randomised trial.

Research design and methods: Pregnant women at risk for GDM (BMI≥29 (kg/m^2)) from nine European countries were invited to undertake a 75-g oral glucose tolerance test before 20 weeks' gestation. Those without GDM were randomised to HE, PA or HE+PA. Women received five face-to-face and four optional telephone counselling sessions, based on the principles of motivational interviewing. A gestational weight gain (GWG) <5 kg was targeted. Coaches received standardized training and an intervention toolkit. Primary outcome measures were GWG, fasting glucose and insulin sensitivity (HOMA) at 35-37 weeks.

Results: Among the 150 trial participants, 32% developed GDM by 35-37 weeks and 20% achieved GWG <5 kg. HE women had less GWG (-1.6 kg (95% CI -3.0 to -0.2); P=0.02) and lower fasting glucose (-0.3 mmol/L (95% CI -0.4 to -0.1); P=0.01) than those in the PA group at 35-37 weeks. HOMA was comparable. No significant differences between HE+PA and the other groups were observed.

Conclusion*:* An antenatal HE intervention is associated with less GWG and lower fasting glucose compared with PA alone. These findings require a larger trial for confirmation, but support the use of early HE interventions in obese pregnant women.

INTRODUCTION

Gestational diabetes mellitus (GDM) is associated with increased risk of adverse perinatal outcomes, with a continuous relationship between glycaemia on oral glucose tolerance test (OGTT) and pregnancy outcome [210]. Obesity in pregnancy and excess gestational weight gain (GWG) are associated with similar adverse pregnancy outcomes, which are additional to any harm from antenatal hyperglycaemia [298].

Although obesity in pregnancy, excess GWG and GDM are associated with adverse outcomes, the evidence that interventions to reduce these harms are beneficial is mixed [249]. In a meta-analysis, combined lifestyle intervention (physical activity (PA) with healthy eating (HE)) was associated with reduced GWG (overall and in some studies), but not with improvement in perinatal outcomes (macrosomia or caesarean delivery) or significant reduction in GDM rates [249]. More recent large randomised controlled trials (RCTs) have shown no reduction in the incidence of GDM with lifestyle intervention, with limited differences in GWG between intervention and control women [189,271,335], but potential reductions in birth weight [189]. Although prevention of excessive GWG and macrosomia are key goals in such interventions, there has been concern that too little maternal weight gain could be associated with an increased incidence of small for gestational age babies and reduced offspring fat-free mass [48]. With these cautions, it is clear that further trials are needed to investigate efficacious approaches that will reduce GWG and progression to GDM, particularly in obese women.

We now report on the findings from the lifestyle pilot for DALI (Vitamin D And Lifestyle Intervention for GDM prevention) [160], undertaken to test the procedures, methodology and lifestyle interventions for the forthcoming full RCT within a European multicentre RCT of three different lifestyle approaches for the prevention of GDM. The pilot reports on risk of GDM rather than GDM itself and does not include the vitamin D intervention.

RESEARCH DESIGN AND METHODS

Overall study design

The pilot study for DALI is a multi-centre, RCT of three different lifestyle approaches that could prevent GDM. The pilot was undertaken across 10 European centres in nine countries, each with its own nutrition and physical activity cultural norms. This diversity in background populations was included to ensure that the intervention was applicable in different settings and populations. The study was approved by the relevant ethics committees. The pilot was registered as an RCT (ISRCTN70595832). The primary outcomes were maternal weight gain (defined as the weight change from baseline measurement to the last measurement at 35-37 weeks of gestation), fasting glucose, and insulin sensitivity as derived from the homeostasis model assessment (HOMA) at 35-37 weeks [201]. The pilot study was devised to recruit four women for each of the three interventions in each centre (total n=120).

Participants

Pregnant women aged ≥ 18 years, before 20 weeks of gestation with a pre-pregnancy body mass index (BMI) ≥ 29 kg/m^2 (based on feasibility following a review of European obesity prevalence) were eligible for inclusion. Women were excluded from the study if they were diagnosed with GDM by OGTT before randomisation, using World Health Organization (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) [348]. Other exclusion criteria were pre-existing diabetes, inability to walk ≥100 meters safely, multiple pregnancy, requiring a complex diet, a significant chronic medical condition or psychiatric disease, and inability to speak the major language of the country of recruitment fluently or to converse with the lifestyle coach in another language for which translated materials existed.

Recruitment

The ten centres were Cambridge (coordinating centre), Galway, Amsterdam, Leuven, Poznan, Pisa/Padova (as one centre), Barcelona, Vienna, Odense and Copenhagen. A common information sheet, in the local language, was given to eligible participants for consideration and the trial explained by the research midwife/nurse. Written consent was obtained for participation. The pilot study started in January 2012 and the last participant gave birth in August 2013.

Procedures

After signed consent, assessments were made by the research midwife/nurse before 20 weeks (screening/baseline), 24-28 weeks, and 35-37 weeks of gestation and after delivery. The lifestyle intervention was delivered by a lifestyle coach. Where GDM developed after baseline, women were managed according to local practice. Figure 4.1 in Chapter 3 (page 44) provides a diagrammatic overview of assessments and intervention.

Randomisation

Eligible women were randomly allocated to one of the three interventions: HE, PA, or both (HE+PA) following an allocation schedule prestratified for intervention centre, using a computerized random number generator. Sealed, opaque envelopes (containing the intervention arm to which each participant was allocated with a randomisation number) were sent to each site by the DALI trial coordinator (D.S.). After assurance of eligibility, the personal details of the participant were provided to the lifestyle coach who opened the next randomisation envelope. Those involved with measurements were kept blinded to the intervention through non-involvement and explicit training. Separation between coach and measurements team was assessed during site monitoring visits.

Lifestyle interventions

After randomisation, five face-to-face and four optional telephone counselling sessions were scheduled for each participant as shown previously in Figure 3.1. As previously described [160], counselling involved discussion of seven HE and/or five PA 'messages' based upon previous work [301] as shown in Table 3.1. Messages were supported by a 'toolkit' for the 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 (ACOG) guidelines [15], pedometers (Yamax Digiwalker SW-200, Tokyo, Japan) and flexible elastic dynabands (Thera-Band, Akron, USA). The message delivery was built upon behavioural theory principles, including patient empowerment and cognitive behavioural techniques inspired by motivational interviewing (MI) [215]. At least four face-to-face counselling sessions were expected to take place before the second measurement session and the intervention was completed by 35 weeks of gestation. Standardisation of the intervention was achieved through a training programme concluding with an observed session with an actor, provision of a desk-file with 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.

A key component for women was to strive to achieve a maximum GWG of 5 kg, as this is the lower limit of the weight gain recommended by the Institute of Medicine (IOM) for those with a BMI ≥30 [155] and following the observation of better outcomes among Danish obese women with this degree of weight gain [161]. If GWG was already beyond this before the start of the intervention or GWG exceeded 5 kg, women were supported to minimise their GWG thereafter. The coaches had scales available to assist women with their weight management, when scales were not available in the home.

Table 4.1: Lifestyle messages

Healthy Eating (HE) intervention

1) "Replace sugary drinks": Reduce intake of sugary drinks (e.g. replace with water).
2) "Eat more non-starchy vegetables": Eat more non-starchy vegetables.
3) "Increase fibre consumption": Choose high-fibre, over low fibre products (≥ 5g fibre/100g).
4) "Watch portion size": Be conscious about the amount of food eaten each meal.
5) "Eat protein": Increase intake of proteins (e.g. meat, fish, beans).
6) "Reduce fat intake": Reduce fat intake (e.g. snack, fast food, fried foods).
7) "Eat less carbohydrates": Reduce intake of carbohydrates (e.g. potatoes, pasta, rice, snacks, candy).

Table 4.1. continued

Physical activity (PA) intervention

1) “Be active every day”: Incorporate light and moderate PA as much as possible into daily life (e.g. by parking further away from destination or undertake special activities for pregnant women).
2) “Sit less”: Reduce sedentary time.
3) “Build your strength”: Incorporate upper and/or lower limb resistance exercise as PA.
4) “Take more steps”: increase the number of steps taken per day.
5) “Be more active at weekends”: Be more active during the weekends.

Assessments

At the three OGTT sessions (Figure 3.1), following a 10-hour fast, women completed questionnaires (including e.g. demographics, pre-pregnancy weight, lifestyle, past/current medical and obstetric history and medication use) and anthropometric measurements between blood tests. Local laboratories were used to rapidly obtain results of the OGTT to assess eligibility for the study. Blood samples were centrifuged and separated serum and plasma aliquots (1000 or 250 µl) were placed in microrack tubes and stored at -20ºC 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. Insulin was quantified by a sandwich-immunoassay (ADVIA Centaur, Siemens Healthcare Diagnostics Inc., Vienna, Austria) with an analytical sensitivity of 0.5 mU/L, intra-assay coefficients of variation (CVs) of 3.3-4.6% and interassay CVs of 2.6-5.9%. Leptin was measured using a sandwich ELISA (DRG Instruments, Marburg, Germany). The assay had an analytical sensitivity of 1.0 ng/mL, intra-assay CVs of 6.0-7.0% and interassay CVs of 8.7-11.6%. All assays were performed according the instructions of the manufacturer. HOMA was calculated as [glucose*insulin]/22.5 [201].

Height was measured at baseline with a stadiometer (SECA 206, SECA, Birmingham, U.K.; Leicester Height Measure) and the average value of two measurements was used. Women were weighed on calibrated electronic scales (SECA 888 and 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 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 comorbidities, obstetric and perinatal outcomes and birth weight.

Outcomes

As primary outcomes, GWG, fasting glucose and insulin sensitivity (HOMA) at 35-37 weeks were used as they will be in the main trial. Secondary outcomes were the number of women who developed GDM, birth weight, insulin concentration, and leptin concentration.

Statistics

Trial data were entered into a bespoke web-based electronic database using the Microsoft NET development environment. For the assessment at 35-37 weeks, fasting glucose and insulin, and insulin sensitivity were carried forward from 24-28 weeks if GDM was diagnosed. Women diagnosed with GDM at 24 weeks (n=24) were excluded from the 35-37 week GWG analyses. Insulin and HOMA data were log transformed because of skewness. As a pilot, no power calculations were performed to decide on sample size and it was arbitrarily agreed that four women would be recruited per intervention per site to test local procedures while minimizing pilot size.

Data were analysed according to the intention-to-treat principle. Analyses were performed blind to the intervention group allocation. Analyses for the RCT were performed according to an *a priori* statistical analysis plan and hence no adjustment was made to significance levels for multiple comparisons. Differences between total study sample and number of subjects dropping out of the study were assessed using Student *t*-test (normally distributed continuous variables), Mann-Whitney U test (skewed continuous variables) or X^2 test (categorical variables). To assess differences between intervention groups, multilevel analyses were performed, with two levels (coach and individual). This takes into account possible clustering effects, since the success of treatment can be dependent on the skills of the provider as well as specific characteristics of a treatment centre. Analyses were adjusted for baseline values of the outcome or for BMI at baseline and numbers of weeks between measurements for the analyses with GWG outcomes. In the regression analyses, all three intervention groups were entered simultaneously to calculate differences between groups. In the multilevel models, log-transformed data for insulin and HOMA were used. For dichotomous variables, logistic regression models were used to assess differences between intervention groups. A bilateral $P<0.05$ was taken as significant.

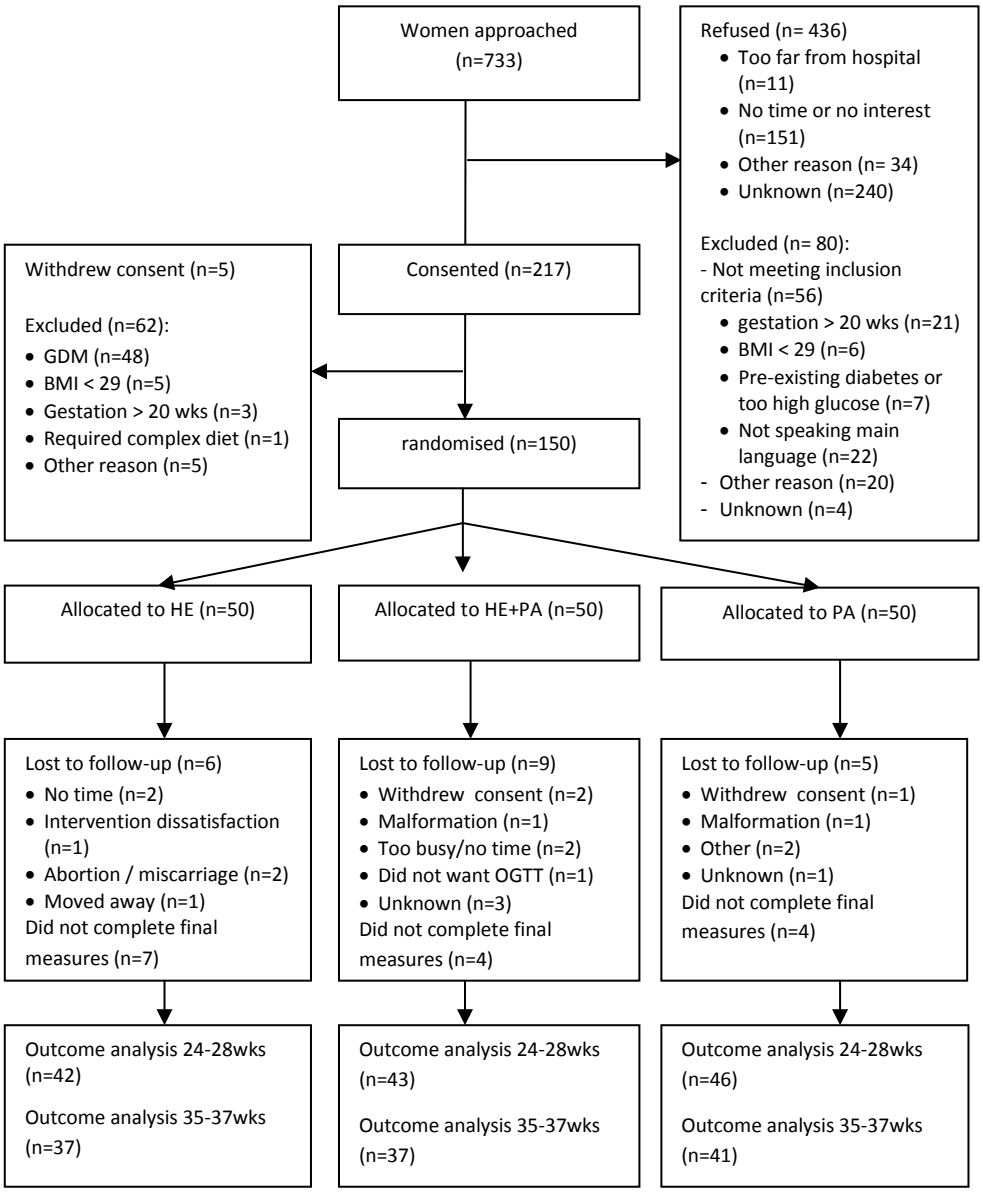

Figure 4.1: Consolidated standards of reporting trials (CONSORT) diagram of recruitment, randomisation, and dropout

RESULTS

Figure 4.1 shows the flow of the participants throughout the study. A large proportion (22%) had GDM on the initial OGTT and hence were not included in the RCT. The numbers in each group and their baseline characteristics were similar (Table 4.2). Women dropping out (n=35; 23%) before the final OGTT had higher post-OGTT load glucose and insulin concentrations and BMI at baseline (Table 4.2). Numbers per site ranged from 3 in Odense to 26 in Belgium. Seven of the 150 women showed a weight gain of 5 kg or more between self-reported pre-pregnancy weight and baseline measurements, but many women were either unaware of, or likely approximated, their pre-pregnancy weight.

On average women gained 8.6 kg (SD 4.6) from baseline to 35-37 weeks of gestation, and only 20% of women achieved the <5 kg GWG target from baseline across the three intervention groups. HE alone was associated with less weight gain by 24-28 weeks and 35-37 weeks than PA (-2.6 kg [95%CI -4.9; -0.2] and -1.6 kg [95%CI -3.0;-0.2]) respectively (Table 4.3). No differences were observed between HE+PA and the other two groups.

There were no significant differences in glucose, insulin or leptin measurements across groups at baseline or by 24-28 weeks' gestation (Table 4.3). However, by 35-37 weeks' gestation, HE had significantly lower fasting glucose and 2-hour insulin concentrations with non-significantly lower GDM incidence than PA. No significant differences between HE+PA and the other two groups were observed. There were no significant differences in HOMA or leptin (Table 4.3). At 24-28 weeks, 24 of 130 women (19%) had developed GDM and by 35-37 weeks this increased to 36 of 112 women (32%), of whom three women received insulin treatment.

Table 4.2: Baseline characteristics of all women included in the DALI lifestyle pilot per intervention group, and those who dropped out at 35-37 weeks' gestation

Variable	HE, *n* = 50	HE+PA, *n* = 50	PA, *n* = 50	Total, *n* = 150	Drop out 35-37 week *n* = 35 (23.3%)	P drop out vs continuing
Age (years)	31.1±6.0	30.5±5.0	33.1±5.2	31.6±5.5	32.3±5.8	0.37
Multiparous (%)	41.7%	46.0%	46.0%	44.6%	48.6%	0.70
European descent (%)	84.0%	88.0%	90.0%	87.3%	88.6%	1.00
Lives with partner (%)	90.0%	98.0%	87.8%	91.9%	**80.0%**	**0.007**
Higher education (%)	44.0%	64.0%	52.0%	53.3%	**37.1%**	**0.03**
Maternal smoking (%)	12.0%	22.0%	14.0%	16.0%	22.9%	0.29
Paternal smoking (%)	32.0%	38.0%	38.0%	36.0%	34.3%	0.84
History of GDM (%)	3.2%	3.4%	10.3%	5.6%	9.1%	0.59
First-degree family history diabetes (%)	28.0%	26.0%	24.0%	26.0%	28.6%	0.83
Chronic hypertension (%)	14.3%	10.0%	14.0%	12.8%	14.3%	0.78
Gestation on entry (weeks)	14.2±1.7	14.2±2.0	14.7±2.3	14.4±2.0	13.9±2.2	0.15
Pre-pregnancy weight (kg)	95.3±17.1	93.2±15.2	94.1±14.6	94.2±15.6	94.5±17.0	0.89
Weight at entry (kg)	96.4±17.0	93.9±14.8	96.6±14.9	95.7±15.5	96.0±16.9	0.87
Height (cm)	166.5±6.4	165.8±6.8	167.2±7.5	166.5±6.9	**163.0±6.2**	**<0.001**
BMI pre-pregnancy (kg/m^2)	34.3±5.6	33.9±4.6	33.6±4.4	33.9±4.9	**35.5±5.3**	**0.03**
BMI at entry (kg/m^2)	34.8±5.9	34.1±4.7	34.5±4.5	34.5±5.0	**36.0±5.2**	**0.04**
Fasting glucose (mmol/L)	4.4 ±0.4	4.6±0.6	4.5 ±0.4	4.5±0.5	4.6±0.3	0.11
1 hour glucose (mmol/L)	6.3 ± 1.7	6.5 ± 1.3	6.5 ± 1.5	6.4±1.5	**7.1±1.2**	**0.01**
2 hour glucose (mmol/L)	5.5 ±1.2	5.7 ± 1.3	5.5 ± 1.1	5.6±1.2	**6.2±1.3**	**0.001**
Fasting insulin (mU/L)	14.1 (10.5, 18.2)	12.2 (8.1, 17.9)	14.0 (10.3, 16.6)	13.5 (9.2, 17.8)	12.7 (8.9, 21.6)	0.76
1 hour insulin (mU/L)	85.9 (57.8, 156.3)	100.0 (73.3, 154.3)	66.6 (55.7, 120.0)	82.6 (61.5, 150.4)	**108.9 (80.9, 174.6)**	**0.003**
2 hour insulin (mU/L)	60.3 (36.0, 121.1)	61.0 (40.5, 129.7)	49.3 (32.8, 83.7)	59.5 (36.7, 107.1)	**125.8 (60.6, 174.8)**	**<0.001**
HOMA	2.76 (1.81, 3.66)	2.26 (1.56, 3.72)	2.75 (1.87, 3.50)	2.65 (1.76, 3.60)	2.49 (1.79, 4.40)	0.58
Leptin (ng/mL)	42.4 ±18.5	42.8 ± 17.7	38.9 ± 18.1	41.5±18.0	46.4±18.0	0.11

Data are mean ± SD or median (interquartile range) unless otherwise indicated. No baseline differences were found between intervention groups.
The boldface data indicate statistically significant differences. Differences tested with Mann-Whitney U test.

Table 4.3: Maternal outcomes in the DALI lifestyle pilot three intervention groups

	n	HE	*n*	HE+PA	*n*	PA	Adjusted difference or OR (95% CI) HE vs HE+PA	*P*	Adjusted difference or OR (95% CI) HE vs PA	*P*	Adjusted difference or OR (95% CI) HE+PA vs PA	*P*
Glucose metabolism 24-28 weeks												
Fasting glucose (mmol/L)	40	4.3 ± 0.3	42	4.4 ± 0.4	41	4.5 ± 0.4	-0.001 (-0.1; 0.1)	0.99	-0.1 (-0.2; 0.1)	0.20	-0.1 (-0.3; 0.03)	0.13
1 hour glucose (mmol/L)	37	7.2 ± 1.6	39	7.2 ± 1.4	39	7.6 ± 1.7	0.2 (-0.4; 0.9)	0.43	-0.1 (-0.8; 0.5)	0.69	-0.5 (-1.1; 0.2)	0.17
2 hour glucose (mmol/L)	36	5.6 ±1.3	39	6.1 ± 1.5	40	6.1 ± 1.3	-0.3 (-0.9; 0.3)	0.37	-0.5 (-1.0; 0.1)	0.10	-0.2 (-0.7; 0.4)	0.53
Fasting insulin (mU/L)	40	17.9 (12.0, 20.6)	42	13.1 (10.9, 20.2)	43	15.4 (11.9, 19.7)	0.05 (-0.1; 0.2)	0.60	0.004 (-0.2; 0.2)	0.97	-0.04 (-0.2; 0.1)	0.66
1 hour insulin (mU/L)	36	157.6 (97.2, 194.7)	40	139.0 (74.7, 185.8)	41	117.4 (79.7, 183.2)	0.1 (-0.2; 0.4)	0.39	0.1 (-0.2; 0.3)	0.47	-0.1 (-0.3; 0.2)	0.53
2 hour insulin (mU/L)	35	66.0 (49.1, 132.6)	40	91.0 (44.7, 144.6)	42	92.2 (51.1, 136.8)	-0.1 (-0.4; 0.3)	0.70	-0.2 (-0.6; 0.1)	0.17	-0.2 (-0.5; 0.2)	0.32
HOMA	40	3.30 (2.25, 4.08)	42	2.63 (2.18, 3.65)	41	2.98 (2.11, 4.28)	-0.01 (-0.9; 0.9)	0.98	-0.4 (-1.4; 0.5)	0.36	-0.4 (-1.4; 0.5)	0.38
Leptin (ng/mL)	40	42.7 ± 20.4	42	39.7 ± 17.9	41	41.5 ± 17.3	1.5 (-4.8; 7.9)	0.63	-1.6 (-7.8; 4.7)	0.62	-3.2 (-9,4; 3.1)	0.32
Glucose metabolism 35-37 weeks												
Fasting glucose* (mmol/L)	37	4.3 ± 0.4	39	4.4 ± 0.5	42	4.6 ± 0.4	-0.2 (-0.3; 0.03)	0.09	**-0.3 (-0.4; -0.1)**	**0.01**	-0.2 (-0.3; 0.05)	0.16
1 hour glucose* (mmol/L)	33	7.9 ± 1.4	37	7.8 ± 1.5	38	8.1 ± 1.6	0.4 (-0.3; 1.0)	0.28	0.1 (-0.6; 0.8)	0.79	-0.3 (-1.0; 0.4)	0.41
2 hour glucose* (mmol/L)	31	6.3 ± 1.5	36	6.7 ± 1.3	38	6.7 ± 1.0	-0.3 (-1.0; 0.4)	0.35	-0.6 (-1.2; 0.01)	0.06	-0.3 (-0.9; 0.3)	0.39
Fasting insulin* (mU/L)	38	21.8 (14.8, 28.4)	37	17.9 (14.5, 27.4)	40	18.1 (14.7, 24.2)	0.1 (-0.2; 0.4)	0.47	0.01 (-0.3; 0.3)	0.95	-0.1 (-0.4; 0.2)	0.47

Table 4.3: continued

	n	HE	*n*	HE+PA	*n*	PA	Adjusted difference or OR (95% CI) HE vs HE+PA	*P*	Adjusted difference or OR (95% CI) HE vs PA	*P*	Adjusted difference or OR (95% CI) HE+PA vs PA	*P*
1 hour insulin* (mU/L)	33	177.6 (115.3, 269.1)	37	192.5 (136.3, 220.9)	39	175.4 (119.9, 230.0)	0.1 (-0.3; 0.4)	0.71	0.1 (-0.2; 0.5)	0.47	0.03 (-0.3; 0.4)	0.87
2 hour insulin* (mU/L)	31	115.2 (56.5, 187.7)	36	152.3 (99.6, 207.2)	39	156.4 (100.0, 206.6)	-0.2 (-0.7; 0.2)	0.33	**-0.4 (-0.8; -0.02)**	**0.04**	-0.2 (-0.5; 0.2)	0.37
HOMA*	36	3.90 (2.73, 5.54)	37	3.44 (2.80, 5.57)	40	3.60 (2.29, 5.25)	-0.7 (-3.0; 1.7)	0.60	-2.3 (-5.6; 1.0)	0.17	-1.8 (-5.1; 1.5)	0.29
Leptin (ng/ml)	36	43.7 ± 22.3	37	42.3 ± 15.0	40	43.5 ± 17.2	2.0 (-6.6; 10.7)	0.64	-2.6 (-10.3; 5.2)	0.51	-4.5 (-12.4; 3.4)	0.26
GDM at 35-37 weeks (%)	36	10 (28%)	35	11 (31%)	41	15 (42%)	0.84 (0.30; 2.33)	0.74	0.67 (0.25; 1.75)	0.41	0.79 (0.31; 2.07)	0.64
Weight gain												
Weight gain T1-T2** (kg)	42	3.5 ± 3.9	42	4.3 ± 3.5	46	5.2 ± 3.1	-0.8 (-2.4; 0.7)	0.29	**-2.6 (-4.9; -0.2)**	**0.03**	-0.7 (-3.0; 1.6)	0.55
Weight gain T1-T3**,§ (kg)	31	7.6 ± 5.3	30	8.5 ± 4.2	34	9.6 ± 4.3	-1.0 (-3.4; 1.4)	0.39	**-1.6 (-3.0; -0.2)**	**0.02**	-0.8 (-2.3; 0.6)	0.24
Weight gain T2-T3**,§ (kg)	31	3.9 ± 2.7	30	3.9 ± 2.0	34	4.5 ± 2.8	-0.1 (-1.4; 1.1)	0.85	-0.5 (-1.7; 0.87	0.43	-0.2 (-1.5; 1.0)	0.72
Weight gain <5kg**,§ (%)	31	9 (29%)	30	4 (13%)	34	6 (18%)	2.98 (0.87; 10.20)	0.08	1.86 (0.63; 5.52)	0.26	0.59 (0.17; 2.03)	0.40

Data are mean ± SD or median (interquartile range) unless otherwise indicated. For continuous outcome variables: adjusted differences from mixed models, with two levels (coach and individual), adjusted for baseline values of the outcome. For dichotomous outcome variables: logistic regression models, adjusted for baseline values of the outcome. Natural log-transformed values of insulin were used in the mixed models. Numbers in each column vary with completeness of data. The boldface data indicate statistically significant differences.

*Value of 24–28 weeks carried forward to 35–37 weeks for women who had GDM at 24–28 weeks.

**Adjusted for BMI at baseline and number of weeks between measurements: T1–T2 is weight gain between baseline and 24–28 weeks; T1–T3 is weight gain between baseline and 35–37 weeks; T2–T3 is weight gain between 24–28 weeks and 35–37 weeks. §Women with GDM at 24–28 weeks were excluded from analyses.

DISCUSSION

Procedures generally worked well, although recruitment overshot (to 150 women) due to the lag between baseline data collection, receiving OGTT results/confirming eligibility and informing all sites that recruitment was completed. There was no expectation that the study would be large enough to show a difference in the primary outcomes comparing different interventions. The significant differences in GWG, fasting glucose and 2-hour insulin levels (albeit trivial) between HE and PA were therefore surprising, although even with the DALI interventions, 32% of women developed GDM. The data suggest that the HE intervention was more efficacious than the PA intervention in reducing GDM risk, although the higher GWG in PA may reflect an increase in muscle mass, not necessarily in adiposity.

Previous RCTs initiated before 20 weeks' gestation have largely shown no impact on GDM prevalence, fasting glucose [189,247,249,271] or insulin concentrations. Exceptions are the BAMBINO physical activity intervention pilot [43], which saw a reduction in fasting glucose by 28 weeks' gestation, but with GWG unreported; and the Lifestyle in Pregnancy (LiP) study, which showed lower insulin concentrations at 28-30 weeks in the intervention group, but no significant reduction in fasting glucose [336].

The LiP study showed a GWG difference of only 1.4 kg between intervention and control women despite a very ambitious intervention programme including repeated visits to a dietitian, weekly fitness class and fitness centre membership. Thus, a time-consuming programme might be less effective than a simple one. One of the key issues with lifestyle interventions in general has been their limited impact on GWG when compared with control subjects. Several of the RCTs did have lower GWG in the intervention group [189,271,335], but controls had a lower GWG than anticipated, resulting in a lesser difference between the groups. A meta-analysis showed that differences between intervention and control groups across 10 RCTs achieved a mean difference in GWG of -2.21 kg [249]. In spite of this, few reported a significant reduction in glycaemia or GDM. The study by Quinlivan et al. (*n*=124) [266] was the only trial in the meta-analysis that achieved a significant reduction in GDM (odds ratio (OR) 0.18) and achieved a 6.8 kg GWG difference. The study by Thornton et al. (*n*=232) [323] also achieved a substantially lower GWG (-9.07 kg) but with a nonsignificant reduction in GDM (OR 0.53).

Our findings of more/better effects of diet alone are in line with a previous review, finding larger effects of dietary intervention alone on GWG, compared with PA or a combined approach [319]. We speculate that a combined intervention might dilute the message or require too much change, and then be demotivating. Another interpretation would be that a combined intervention does not mean "complete" but "partial" HE and PA; PA intervention being less effective, HE+PA ranks intermediate between HE and PA. The lack of effect of the PA interventions does not imply no effect of PA on pregnancy and offspring outcomes per se, as this pilot had no control subjects. Interventions to increase PA in pregnancy are well known to be difficult [246] especially in the third trimester. Although we are being as careful as possible

to avoid the kinds of GWG convergence seen in some other major RCTs, it might be difficult to prevent a low GWG in the control group among women motivated to come into a lifestyle trial. Including multiple European cultures might generate a range of lifestyle responses in control subjects as well as intervention participants. Such differences between sites, with their very different underlying cultural landscapes (and climates) and associated differences in nutrition and physical activity habits will be of interest in the main trial. At this point, it would appear that our generic approach to the lifestyle change messages (Table 4.1) has been successful. These were originally based on an intervention among New Zealand Maori [301] and hence expected to be cross cultural to some extent. We found the motivational interviewing approach to be well suited to the intervention. Even so, only 29% of participants in the HE group of the pilot achieved the <5 kg GWG goal, a proportion comparable to those in other RCTs (e.g. [335]).

One other difference in the DALI approach from other RCTs is the exclusion of women with GDM by WHO 2013 criteria (22%) prior to recruitment. It may be that in the other trials, it was never possible to reverse pre-existing GDM in these women. However, there is debate over the validity of the new criteria in early pregnancy [348] which were built around data at 24-28 weeks gestation [69]. Data from China suggest that a significant proportion of women with GDM on the fasting glucose in early pregnancy, have no GDM using the new criteria at 24-28 weeks [353].

The study has a number of weaknesses. It was established as a pilot to a full RCT of 440 women, and hence there were no power calculations performed to decide on the number of participants required and there was no untreated control group. As a pilot, the expertise of the intervention coaches would have improved over time, in preparation for the main trial. Numbers were still too small to look for adherence to lifestyle change or adverse pregnancy outcomes. The main trial will report on accelerometer and dietary record data. We have not adjusted the significance level for multiple comparisons; however, the comparisons followed our a priori statistical analysis plan, and the difference in GWG is in line with other RCTs, which speaks against the role of chance.

In conclusion, an HE intervention among obese European women led to lower GWG, fasting glucose, and 2-hour insulin concentrations by 35-37 weeks' gestation than a PA intervention or a combination of HE and PA. Although a larger trial is still clearly needed, these pilot findings are promising, and support the use of early HE interventions in obese pregnant women.