Lifestyle Counselling Intervention to prevent Gestational Diabetes Mellitus

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CHAPTER 6:

Do physical activity and dietary changes mediate effects of a lifestyle intervention on gestational weight gain and glucose metabolism: Findings from the DALI randomised controlled trial

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To be submitted

Background: Evidence is needed for the relative effectiveness of different lifestyle intervention components during pregnancy in minimizing gestational weight gain (GWG) and improving antenatal glucose metabolism. The aim of this study was twofold: 1) to investigate the effect of the DALI lifestyle intervention on objectively measured physical activity and diet, and 2) to examine how these changes are related to GWG, fasting glucose and Homeostatic Model Assessment-Insulin Resistance (HOMA-IR).

Methods: Women with a pre-pregnancy BMI≥29 kg/m², from eleven European sites and without baseline gestational diabetes mellitus, were randomised into a healthy eating (HE), physical activity (PA), combined (HE+PA) or usual care groups. Participants allocated to the intervention arms received five face-to-face and four optional telephone sessions by a lifestyle coach trained in motivational interviewing. At baseline (<20 weeks), mid- (24-28 weeks) and late- (35-37 weeks) pregnancy, physical activity was measured with accelerometers and diet was assessed with three-day dietary records. Statistical analyses included longitudinal linear multilevel regression and multiple mediation models.

Results: A total of 436 women were included in the study, with 132 (30%) women providing valid physical activity data and 173 (40%) women providing dietary data at baseline and at either mid- or late-pregnancy. For physical activity, an effect on counts per min was found mid-pregnancy (β=53.1, 95% CI=0.2;105.9) in the PA group. For diet, overall dietary scores were improved in the HE group (β=6.8, 95% CI=2.0; 11.6) and the HE+PA group (β=5.7, 95% CI=0.7;10.7). The intervention did not seem to have a mediating effect through physical activity and dietary changes on GWG and glucose metabolism.

Conclusion: Irrespective of the use of stringent measurement methods, changes in physical activity and diet leading to a reduction in GWG might have been too subtle to detect in our study.

INTRODUCTION

In 2014, the estimated European prevalence of obesity (BMI≥30) in adult women was 15% and reaching epidemic proportions [349]. Likewise, obesity prevalence in pregnancy is high, varying from 7 to 25% depending on the consulted study [81]. Maternal obesity puts women at risk for the development of many adverse health outcomes, including gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH, including preeclampsia), depression and preterm delivery. It also impedes labour and delivery by an associated increased risk for induction, prolonged labour, combined spinal epidural, instrumental deliveries and caesarean sections and further affects the postpartum period by increased risks for haemorrhages, infections, weight retention and breast feeding problems. Offspring of obese mothers are more likely to experience post-delivery respiratory problems, be large-for-gestational-age, macrosomic or be at risk of obesity and the metabolic syndrome in later life [142]. To minimize the risk for these adverse health outcomes, the Institute of Medicine (IOM) recommends obese women to pursue a gestational weight gain (GWG) range of 5 to 9 kilograms [155], especially since excessive GWG together abnormal glucose tolerance aggravates the obesity-related health effects in pregnancy [81].

Lifestyle modifications are the main option to avoid excessive GWG. Interventions can be based on behavioural change in diet and physical activity, targeted separately or in combination [1]. Currently, for obese pregnant women, no specific dietary recommendations are defined, other than the national dietary guidelines and the option of consulting a dietitian or other qualified person [155]. For physical activity, international guidelines recommend, irrespective of pre-pregnancy BMI, that sedentary women should build up their activity level to at least 30 minutes of at least moderate activity a day, while already active women should maintain or increase their activity level up to 30-60 minutes a day [15].

As a consequence of the lack of specific information and time to incorporate lifestyle advice in routine consultations with obstetricians and midwifes, many different lifestyle interventions with a wide variability in content and delivery methods have been offered to overweight and obese pregnant women in large multicentre randomised controlled trials. To illustrate, the LIMIT trial provided combined diet, physical activity and behavioural strategies in overweight and obese pregnant women. Dietary advice was based on a reduced intake of foods high in refined carbohydrates and saturated fats and an increased intake of fibres [87]. Women were encouraged to increase daily walking and incidental activities. In the UPBEAT study, obese pregnant women were offered a behavioural intervention with the aim to increase the consumption of foods with a lower glycaemic index and to improve physical activity levels by increasing daily life activities and step count [262]. Effects on diet and physical activity levels were promising in most studies, based on self-reported data, however desired GWG and improvement in glucose metabolism were not always obtained compared to women receiving standard antenatal care [84,99,261].

Evidence relating to the effective intervention components for minimizing GWG and improving glucose metabolism remains inconsistent and contradictory. Several studies found that the combination of dietary and physical activity advice in a positive psychosocial climate gave the best results [16,249,255], while a meta-analysis by Thangaratinam et al. (2012) revealed that dietary interventions were more effective than exercise-based or combined interventions [319]. The identification of effective mediators on outcomes of interest can improve the development of future interventions, while on the other hand the identification of ineffective mediators can result in removal or necessary adaptations [124].

The European vitamin D and Lifestyle Intervention (DALI) study was developed to investigate the effects of different lifestyle interventions in overweight and obese pregnant women on GWG and glucose metabolism with the ultimate goal of GDM prevention. DALI is a randomised controlled trial based on a behavioural lifestyle intervention addressing healthy eating and/or physical activity in overweight and obese pregnant women [160]. Results from the main study illustrate reduced GWG but unchanged fasting glucose levels in the combined healthy eating and physical activity intervention arm compared to usual care [299]. The aim of the current paper is to examine the effect of the lifestyle interventions in the DALI lifestyle trial on objectively measured levels of physical activity and diet and investigate how these changes were related to the primary outcomes: GWG, fasting glucose, and insulin sensitivity.

METHODS

Design

The DALI study is a randomised controlled study with a 2x2x2 design. It consists of a vitamin D 2x2 trial and a lifestyle 2x2 trial. The current study is situated within the lifestyle trial that was conducted between March 2013 and August 2014. All relevant ethical committees approved the study and all participants gave written informed consent.

Participants and procedures

A detailed description with a visual illustration of this study can be found elsewhere [160]. In short, participants were recruited before 20 weeks of gestation at eleven study sites across nine European countries: Vienna (Austria); Leuven (Belgium); Odense and Copenhagen (Denmark); Galway (Ireland); Padova and Pisa (Italy); Poznan (Poland); Barcelona (Spain); Cambridge (United Kingdom) and Amsterdam (The Netherlands). Women were eligible for participation if they were 18 years or older, had no pre-existing diabetes, were able to walk at least 100 meter safely, did not require a specific diet, had no chronic medical conditions or psychiatric disease and spoke the language of the lifestyle coach. All women received a baseline assessment (<20 weeks of gestation) for GDM with a two hour 75 gram oral glucose tolerance test (OGTT). Participants with a fasting glucose ≥ 5.1mmol, 1 hour glucose ≥ 10.0 mmol or a 2 hour glucose ≥ 8.5 mmol were excluded [209].

Women without baseline GDM were allocated to one of the four intervention arms: Healthy eating (HE), physical activity (PA), combined (HE+PA) and a usual care arm offering local routine care. A computerised random number generator drew an allocation schedule pre-stratified for intervention site. Sealed opaque envelopes were prepared containing information on allocation. The lifestyle coaches were responsible for advising the participants of their allocated intervention. The involved research nurses, researchers and medical doctors were blinded to randomisation and participants were informed not to discuss their intervention with the DALI staff.

Intervention

The lifestyle intervention was offered between study entry and 35 weeks of gestation. It consisted of five face-to-face sessions (four prior to 24-28 weeks of OGTT) and four optional telephone counselling sessions with a personal lifestyle coach trained in motivational interviewing. The intervention goal was to improve diet and physical activity behaviours in order to limit GWG to the lower limit of 5 kilograms. All participants allocated to one of the three intervention groups received information about GDM, GDM risk factors and the targeted GWG. The HE intervention was based on seven key messages: 1) Replace sugary drinks; 2) Eat more non-starchy vegetables; 3) Increase fibre consumption; 4) Watch portion size; 5) Eat protein; 6) Reduce fat intake; 7) Eat less carbohydrates. General dietary information was provided with the DALI food triangle, a scheme of seasonal availability of fruits and vegetables and the interpretation of food labels. Participants in the HE intervention had the option to complete a dietary record and discuss this with her lifestyle coach. The PA intervention included five key messages: 1) Be active every day; 2) Sit less; 3) Be more active at weekends; 4) Take more steps; 5) Build your strength. General information on physical activity was provided by the American College of Obstetricians and Gynecologists (ACOG) supporting exercise model including information about frequency, intensity, time and type of exercise advised in normal pregnancy. Intervention tools, such as a pedometer, elastic dynaband, CD-ROM with suggested strength exercises and an exercise diary were offered only to women in the PA intervention. The women in the usual care arm did not receive any intervention other than the information on GDM, physical activity and diet provided in usual care (in the form of existing general leaflets).

Outcome measures

At baseline (between 12-20 weeks), in mid- (24-28 weeks) and in late- (35-37 weeks) pregnancy women underwent an OGTT whenever they had not been diagnosed of diabetes previously. At 0, 60 and 120 minutes after glucose ingestion blood samples were collected. Blood samples were processed locally and stored at -20º or -80º until further analysis in the central trial laboratory in Graz, Austria, certified according ISO 9001 standards. Homeostatic Model

Assessment-Insulin Resistance (HOMA-IR) was calculated as [fasting glucose*fasting insulin] / 22.5 [201].

Maternal body weight was measured by calibrated electronic scales (SECA 888; SECA 877) while participants wore only indoor clothes and no shoes. GWG was defined as the change in weight from baseline to late-pregnancy.

Dietary measure

Dietary assessment was undertaken by use of three-day dietary records at baseline, mid- and late-pregnancy. Information on food type and amount was collected through an open entry format, where each day was divided into breakfast, morning snack, lunch, afternoon snack, dinner and late-evening snack. All dietary records were translated into the English language by the research nurses and lifestyle coaches to facilitate analysis, except for the Dutch and Belgium dietary records. The consumed food and beverages were classified into 46 different food groups, based on the Flemish Food Based Dietary Guidelines [98] and DALI Food Triangle. Afterwards, these 46 food groups were combined into nine main food categories: 1) water and non-sugary drinks, 2) sugary drinks, 3) fruit, 4) vegetables, 5) carbohydrates (potatoes, rice, pasta, bread) 6) meat, meat products, poultry, fish, eggs and vegetarian products, 7) milk, milk products and cheese, 8) spreads and cooking fats and finally 9) the rest category. Portion size of the consumed foods and beverages were determined on the basis of “Measures & Weights” of the Belgian Superior Health Council [20]. A standard portion was considered in the case of missing detailed information on portion size. The average intake of the different food categories was calculated as the mean of the 3-day intake period. A DALI Diet Quality Index (DQI), based on the nine main food categories, was developed, using the same principles as previously developed DQIs [148,151,339]. The total DQI score is the main dietary outcome and is calculated as the mean of the quality, diversity and equilibrium sub-scores. The quality score informs whether a person generally consumed foods of the preference, mean or rest group. The diversity score informs about the degree of variation in food consumption and the equilibrium score considers the balance between minimum (~dietary adequacy) and maximum (~dietary moderation) recommended food intake (Jans et al. submitted).

Physical activity measure

Physical activity was measured by use of accelerometers (Actigraph: GT1M, GT3X+; Pensacola, Florida, USA) at the same time points participants completed the dietary records. They were instructed by the coach to wear the meters for three days on an elastic belt positioned over the right hip during waking hours, removing the device only for water-based activities (e.g. showering or swimming). Date, time and reason of removal were recorded in an activity diary, as well as the total time spent swimming. Raw data was recorded in 1-minute epochs and cleaned manually based on the activity diary. Periods of consecutive strings of zero-count epochs lasting more than 90 minutes were considered as non-wear time [58,165]. The vertical-axis was used for analysis [166]. A valid day was defined as at least 480 minutes of wear time [93] and only data from women with three valid days were considered in the analyses. Raw data was analysed in mean counts per minute (CPM), which were converted in minutes in sedentary, light, moderate and vigorous intensity using the Actilife software version 6.8.1 based on the Freedson cut-off points [106]: sedentary <100 CPM; light between 100-1951 CPM; moderate between 1952-5724 CPM; vigorous more than 5727 CPM. Swimming was added to the objective recording of physical activity as vigorous minutes and counts [91] (swimming is 7.0 metabolic equivalent of task (MET) [7] representing 6994 counts/min in an adult population according the formula METs value = 1.439008 + (0.000795 counts/min) [106]). Moderate and vigorous activity was summed and presented as moderate and vigorous physical activity (MVPA). Light activity and MVPA were combined to derive total physical activity. Sedentary, light and total physical activity were presented as percentage of total wear time. MVPA was shown as minutes per day.

Covariates

Demographics and other covariates were determined. At baseline, maternal age, parity, ethnicity (Caucasian versus non-Caucasian), educational level (lower/middle or higher), employment (yes/no) and marital status were assessed by questionnaire. At baseline, maternal body height was recorded on bare feet with a stadiometer (SECA 206, SECA, Birmingham, UK). The body mass index (BMI) was calculated by dividing the measured weight (in kg) by the square of height (m^2).

Statistics

Socio-demographic characteristics of women providing HE or PA data at baseline and at either mid-pregnancy or late-pregnancy were compared to those not included in the study sample, using the Student t-test (normally distributed continues variables) or the Chi square test (categorical variables).

Effect analyses

Longitudinal linear multilevel regression analyses were used for the continuous outcome variables of the DALI-DQI and activity scores. Multilevel analyses were undertaken with a three level structure: time (mid-pregnancy (24-28 weeks), late-pregnancy (35-37weeks)), individual and site. This corrects for possible clustering effects as specific characteristics of a treatment centre could impact on the treatment. DQI and physical activity scores at mid- and late-pregnancy were corrected for baseline values (crude model) and the following confounders (corrected model): age, education, employment status, parity, BMI at baseline visit, and ethnicity. Time was added as interaction term to the model to obtain the separated effect for mid-pregnancy and late-pregnancy. All analyses were performed with multilevel analysis for

Windows (MLwiN version 2.22; Centre for Multilevel Modelling, University of Bristol, Bristol, UK). A P-value ≤ 0.05 was considered significant.

Mediation analyses

To test for a mediating effect of mid-pregnancy diet and physical activity levels (DQI and total physical activity) on changes in the primary outcome measures at late-pregnancy (GWG, fasting glucose, HOMA-IR), multiple parallel mediation models as described by Hayes [133] were tested. Multiple mediation models are preferred above simple mediation models as most effects operate through multiple mechanisms at once. Furthermore, this allows the determinations of the strongest indirect effect [133]. The PROCESS macro (version 2.15) was run in SPSS version 22 (IBM Corp, Armonk, New York, USA) to compute the following steps simultaneously: (1) estimation of the intervention effects on the mediators by regressing the mid-pregnancy mediator score on the baseline mediator score, confounders and intervention dummies (α-coefficient); (2) estimation whether changes in the mediators predict changes in the outcome variables by regressing the outcome variables onto the baseline outcome variables, baseline mediators, mediators, confounders and intervention dummies (β-coefficient); (3) estimation of the indirect effect (αβ-coefficient); (4) estimation of the direct effect when accounted for the indirect effect (τ'-path); (5) estimation of the total intervention effect (τ-path). The conceptual mediation model is illustrated in Figure 6.1.

6

Bias-corrected bootstrapped 95% asymmetric confidence intervals (based on 1,000 bootstrap samples) were computed for the indirect effect [133]. The indirect effect is statistically different from zero if the confidence interval does not straddle zero. PROCESS is run for each primary outcome variable with the same value for the random number seed attributed to each run. This is done to obtain results as if all the paths were estimated in one model with multiple dependent variables [133]. The intervention condition is a multi-categorical independent variable and is therefore analysed with dummy coding [135]. The following factors were considered as confounders: age, education, employment, parity, BMI at baseline, and ethnicity. In addition for the primary outcome GWG the following two additional confounders were added: number of weeks between measurements and diagnoses of GDM (yes/no) according to local diagnostic criteria at 24-28 weeks' gestation. In case of GDM diagnosis at mid-pregnancy, the values of fasting glucose and HOMA-IR measured at this moment were used as outcome measures. Log transformed data for HOMA-IR was used because of skewness.

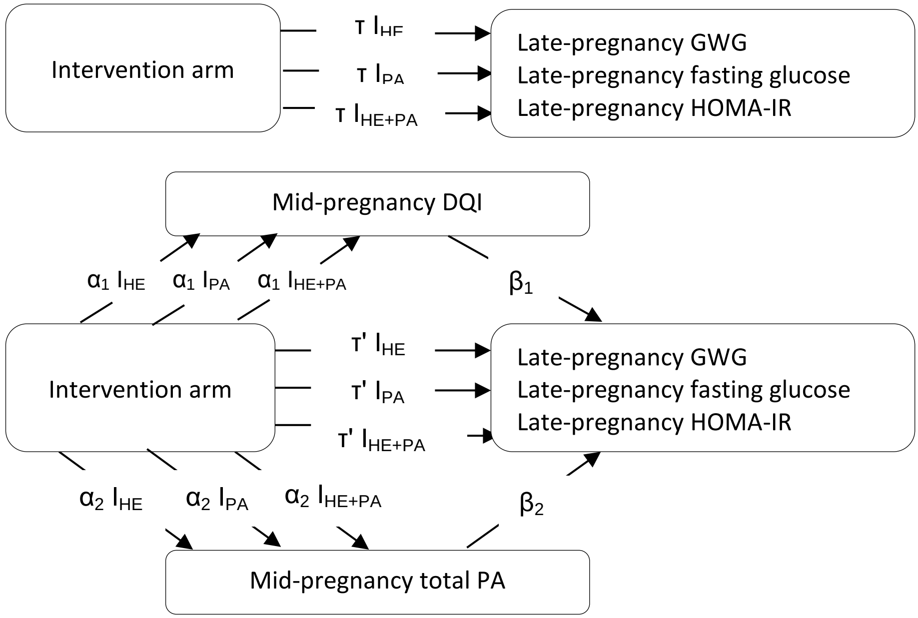


Figure 6.1: Conceptual mediation model

RESULTS

Participants

The flow diagram of the included participants for the dietary and exercise analyses is illustrated in Figure 6.2. The main reasons for exclusion to this study were the absence of baseline data (valid DQI and/or accelerometer), or baseline but no mid- or late pregnancy data availability. For the physical activity analyses, at 46%, 34% and 31% of randomised women (N=436) at baseline, mid-pregnancy and late-pregnancy provided valid accelerometer data. The main reasons for missing data were unavailability of accelerometers or non-attendance (38%); no data-recording as a result of non-wear, battery depletion or incorrect initialisation (10%); not enough valid weartime or days recorded (14%). For the dietary analyses, dietary records of 40% of the women at baseline and 36% of the women at mid- and late-pregnancy were used. Missing dietary records were a result of not being completed or returned by the participants.

Baseline characteristics of the women providing physical activity and dietary data are presented in Table 6.1. The mean BMI was 34.2 and 34.5 kg/m^2 for the participants included for the physical activity and dietary analyses, respectively. Participants were mostly Caucasian, employed and lived together with their partner. About half of the women had one or more children and had completed higher education. The women who provided either physical activity data or dietary data were not different from those who did not with respect to BMI, education, marital status and parity, although they were significantly older, more frequently employed and from non-Caucasian origin. Furthermore, women from the sites Austria, Denmark Copenhagen, The Netherlands and Spain were more represented in this subsample.

Table 6.1. Baseline characteristics

		Dietary record		Accelerometer	
	Total population (N=436)	(N=173)	P no dietary record vs available dietary record	(N=132)	P no valid accelerometer data vs valid accelerometer data
Age (years): Mean (SD)	32 (5.3)	32.8 (5.1)	**<0.001**	33.2 (5.3)	**<0.001**
BMI (kg/m^2): Mean (SD)	34.5 (4.0)	34.5 (4.0)	0.81	34.2 (3.5)	0.32
Gestational age at entry (weeks): Mean (SD)	15.3 (2.3)	15.2 (2.5)	0.33	14.9 (2.3)	**0.02**
Maternal ethnicity: *n* (%Caucasian)	378 (86.7)	138 (79.8)	**<0.001**	109 (82.6)	0.09
Education: *n* (%Higher)	239 (54.8)	91 (52.6)	0.45	76 (57.6)	0.45
Marital status: *n* (%With partner)	410 (94.0)	164 (94.8)	0.59	123 (93.2)	0.62
Parity: *n* (%Nulliparous)	215 (49.3)	85 (50.0)	0.95	68 (51.5)	0.54
Employment: *n* (%Working)	340 (78.0)	143 (82.7)	0.06	112 (84.8)	**0.02**

Notes: Bold numbers represent a significant difference of p<0.05 between the group with and without valid data.

***Notes**: Baseline refers to 12-20 weeks of gestation; T2: refers to mid-pregnancy (24-28 weeks of gestation); T3 refers to late-pregnancy (35-37 weeks of gestation); Abbreviations: ACC: Accelerometer data; GDM: Gestational diabetes mellitus; HE: Healthy eating group; HE+PA: healthy eating and physical activity group; LTFU: Lost to follow up; OGTT: Oral glucose tolerance test; PA: Physical activity group*

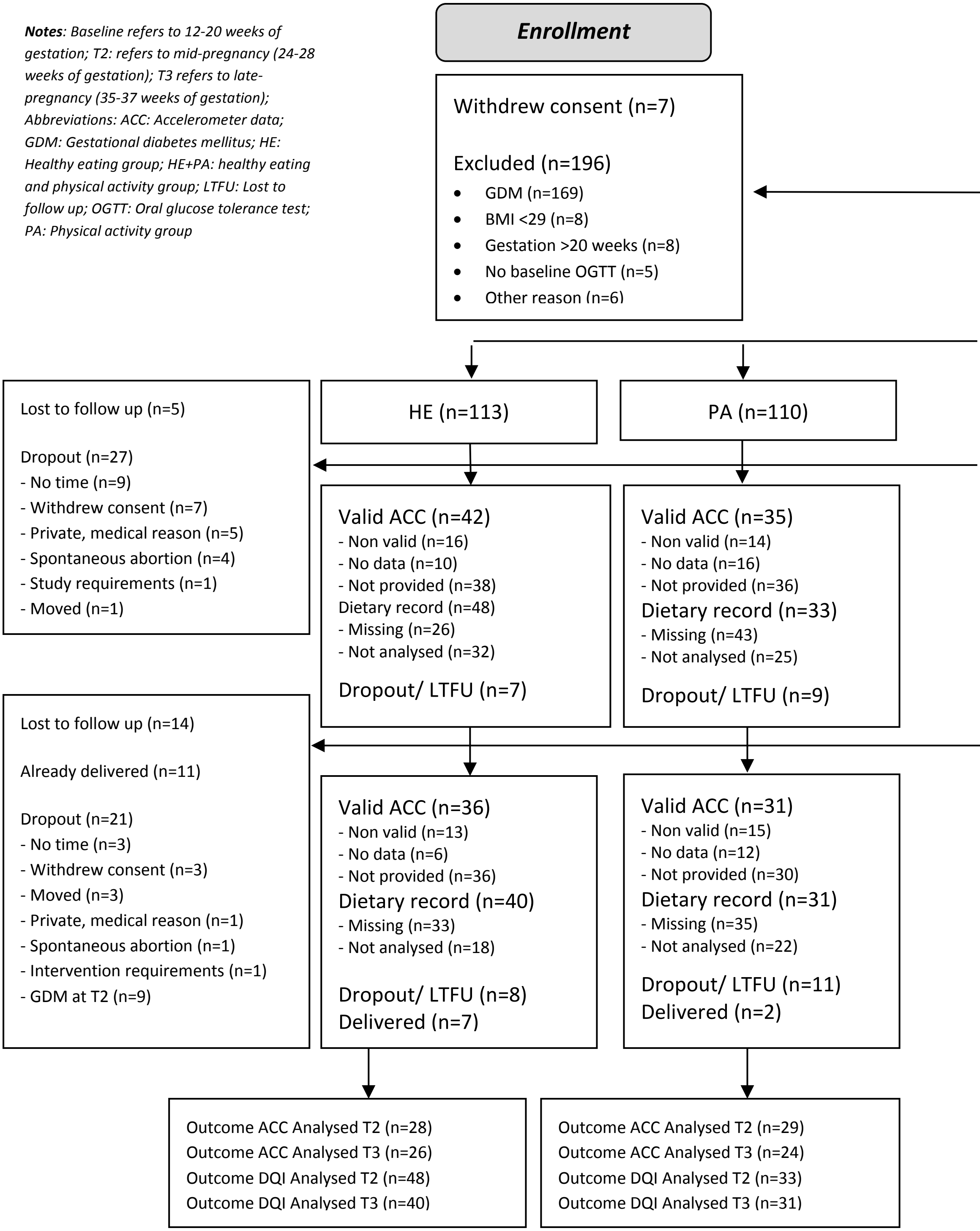
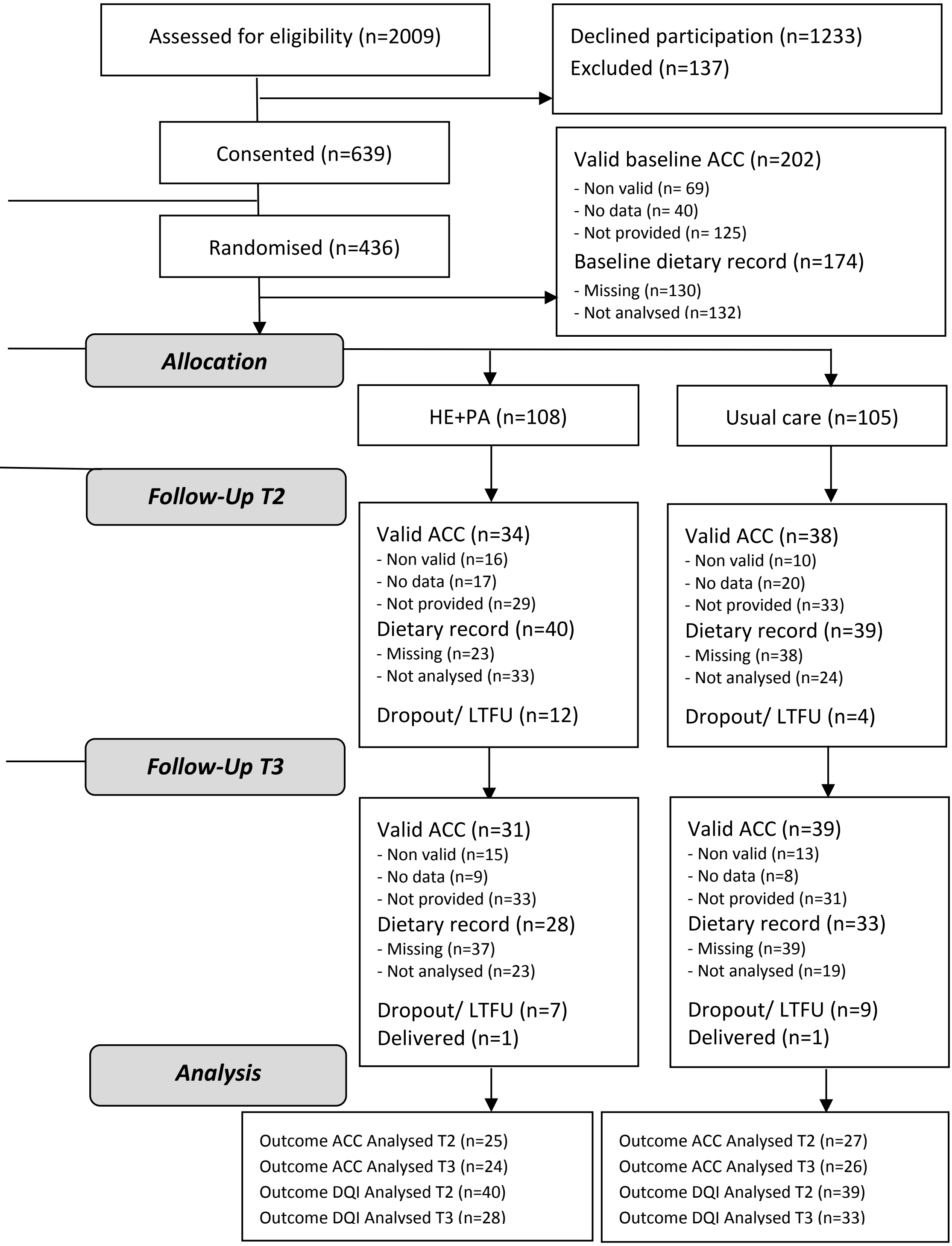


Figure 6.2: Consort diagram


Assessed for eligibility (n=2009)
Declined participation (n=1233)
Excluded (n=137)
Consented (n=639)
Valid baseline ACC (n=202)
- Non valid (n= 69)
- No data (n= 40)
- Not provided (n= 125)
Baseline dietary record (n=174)
- Missing (n=130)
- Not analysed (n=132)
Randomised (n=436)
Allocation
HE+PA (n=108)
Usual care (n=105)
Follow-Up T2
Valid ACC (n=34)
- Non valid (n=16)
- No data (n=17)
- Not provided (n=29)
Dietary record (n=40)
- Missing (n=23)
- Not analysed (n=33)
Dropout/ LTFU (n=12)
Valid ACC (n=38)
- Non valid (n=10)
- No data (n=20)
- Not provided (n=33)
Dietary record (n=39)
- Missing (n=38)
- Not analysed (n=24)
Dropout/ LTFU (n=4)
Follow-Up T3
Valid ACC (n=31)
- Non valid (n=15)
- No data (n=9)
- Not provided (n=33)
Dietary record (n=28)
- Missing (n=37)
- Not analysed (n=23)
Dropout/ LTFU (n=7)
Delivered (n=1)
Valid ACC (n=39)
- Non valid (n=13)
- No data (n=8)
- Not provided (n=31)
Dietary record (n=33)
- Missing (n=39)
- Not analysed (n=19)
Dropout/ LTFU (n=9)
Delivered (n=1)
Analysis
Outcome ACC Analysed T2 (n=25)
Outcome ACC Analysed T3 (n=24)
Outcome DQI Analysed T2 (n=40)
Outcome DQI Analysed T3 (n=28)
Outcome ACC Analysed T2 (n=27)
Outcome ACC Analysed T3 (n=26)
Outcome DQI Analysed T2 (n=39)
Outcome DQI Analysed T3 (n=33)

Effect of the DALI lifestyle interventions on maternal physical activity levels and diet
The means and standard deviations of the different physical activity and healthy eating outcomes at baseline, mid- and late-pregnancy are shown for each intervention group in Table 6.2. Furthermore, the crude and corrected effect outcomes of the different lifestyle interventions on activity and dietary levels are presented. Only the corrected effects will be discussed.

For physical activity, significantly more CPM were found in the PA group compared to the usual care group (β=53.1, 95% CI=0.2;105.9) in mid-pregnancy. However, no differences in total activity, sedentary behaviour, light activity and MVPA after adjustment for baseline and for possible confounders were found in any of the intervention groups compared to the usual care group measured in mid- and late-pregnancy.

For the maternal diet, the overall DQI was higher at mid-pregnancy compared to baseline for the HE (β=6.8, 95% CI=2.0; 11.6) and the HE+PA (β=5.7, 95% CI=0.7;10.7) intervention groups. This is reflected by higher quality (β=18.0, 95% CI=8.4;27.5 and β=13.6, 95% CI=3.7;23.6), moderation (β=5.8, 95% CI=2.7;8.9 and β=5.4, 95% CI=2.2;8.7) and equilibrium (β=5.8, 95% CI=1.2;10.3 and β=5.3, 95% CI=0.6;10.0) scores respectively for the HE and HE+PA intervention groups at mid-pregnancy. Late-pregnancy effects were noticed for dietary adequacy and moderation. The adequacy score was lower (β=-6.7, 95% CI=-12.0;-1.5) and the increase in moderation score at mid-pregnancy continued to late-pregnancy (β=5.7, 95% CI=2.4;9.1) in the HE group compared to the usual care group.

Effects of the DALI lifestyle intervention on GWG, fasting glucose and HOMA-IR
Overall intervention effects on GWG, fasting glucose and HOMA-IR have been reported elsewhere [299] . In summary, In the HE+PA group, but not HE or PA alone, women achieved less GWG than usual care group at 35-37 weeks (β=2.02 kg, 95% CI= -3.58;-0.46)). There were no differences in fasting glucose or HOMA-IR between intervention groups. Similar results were obtained in the mediation models. The total effect (τ-path) for the HE+PA group was a reduction in GWG of -3.07 kg (95% CI= -6.07;-0.07). No significant effects for the HE or PA interventions alone on GWG were found, either for fasting glucose or HOMA-IR in any of the intervention groups.

Mediation effects of total physical activity and DQI in mid-pregnancy on the primary outcomes GWG, HOMA-IR and fasting glucose in late-pregnancy
From the multiple parallel mediation models (Table 6.3), it was clear that the three lifestyle interventions did not indirectly influence GWG, fasting glucose or HOMA-IR through their effect on total physical activity or DQI (α*β path). Participants allocated to the HE+PA intervention group were able to increase their DQI in mid-pregnancy compared to those in the usual care group (α=12.4, 95% CI=4.5;20.3); due to missing outcome data the α-path is slightly

different from the models of fasting glucose (α=11.9, 95% CI=3.9;19.9) and HOMA-IR (α=11.9, 95% CI=4.0;19.9). A direct significant effect of the HE+PA intervention on GWG in late-pregnancy was seen, independent of the effect of the proposed mediators (τ'-path, τ'=-3.5, 95% CI=-6.8;-0.3). No effect of the mediators on GWG, fasting glucose and HOMA-IR were observed (β-path).

Table 6.2 (next pages): Notes: longitudinal linear multilevel analysis adjusted for time (mid- and late-pregnancy) and site, the usual care group was used as reference group; Bold numbers represent a significant effect of $p<0.05$. [a] crude model: adjusted for baseline value of the outcome; [b] corrected model: crude model adjusted for age, employment, education, parity, ethnicity, and body mass index at baseline; [c] Total physical activity is defined as all activities above 100 counts. Abbreviations: 95%CI: 95% confidence interval; DQI: Dietary Quality Index; HE: healthy eating; PA: physical activity; HE+PA: healthy eating and physical activity; MVPA: moderate and vigorous physical activity.

Table 6.2: The effectiveness of the three lifestyle interventions on physical activity and diet in mid- and late-pregnancy.

Mean (SD) or n		Baseline (<20weeks)	Mid-pregnancy (24-28wks)	Late-pregnancy (35-37 wks)	Mid-pregnancy				Late-pregnancy			
					crude model [a]		corrected model [b]		crude model [a]		corrected model [b]	
					ß	95% CI	ß	95% CI	ß	95% CI	ß	95% CI
Physical activity, *n*		132	109	100								
Total physical activity (% weartime)	HE	28.4 (8.4)	26.2 (7.6)	29.8 (7.6)	1.3	[-1.7; 4.4]	0.9	[-2.2; 4.0]	2.7	[-0.4; 5.8]	2.4	[-0.7; 5.6]
	HE+PA	27.8 (9.3)	25.8 (7.5)	25.9 (7.0)	1.1	[-2.0; 4.2]	1.1	[-2.0; 4.2]	-2.0	[-5.2; 1.2]	-2.0	[-5.1; 1.2]
	PA	31.2 (9.7)	28.6 (9.7)	25.5 (6.1)	1.9	[-1.2; 4.9]	1.7	[-1.3; 4.7]	-1.9	[-5.1; 1.3]	-1.7	[-4.9; 1.4]
	Usual care	27.3 (9.3)	25.1 (7.2)	25.6 (8.2)								
MVPA (min/day)	HE	47.6 (26.4)	41.1 (22.4)	37.7 (26.1)	5.8	[-5.2; 16.7]	6.4	[-4.6; 17.4]	0.5	[-10.7; 11.8]	1.0	[-10.4; 12.4]
	HE+PA	39.2 (21.3)	39.8 (25.7)	30.0 (18.9)	7.1	[-4.1; 18.4]	7.4	[-3.7; 18.5]	-4.7	[-16.1; 6.7]	-4.2	[-15.6; 7.2]
	PA	49.5 (25.8)	45.1 (31.5)	33.2 (23.2)	9.6	[-1.3; 20.6]	10.0	[-0.9; 20.9]	-8.5	[-20.0; 3.0]	-8.7	[-20.1; 2.7]
	Usual care	44.2 (32.6)	36.2 (17.7)	36.7 (24.1)								
Light intensity (% weartime)	HE	22.7 (7.4)	21.1 (6.5)	25.1 (7.5)	0.6	[-2.1; 3.4]	0.3	[-2.4; 3.0]	2.8	[-0.03; 5.6]	2.7	[-0.1; 5.5]
	HE+PA	22.9 (8.3)	20.8 (7.3)	22.1 (5.7)	0.2	[-2.6; 3.0]	0.2	[-2.5; 3.0]	-1.4	[-4.3; 1.4]	-1.3	[-4.1; 1.5]
	PA	25.3 (9.3)	23.0 (10.2)	21.2 (6.2)	0.6	[-2.1; 3.4]	0.6	[-2.1; 3.2]	-1.0	[-3.9; 1.8]	-0.7	[-3.5; 2.1]
	Usual care	22.1 (7.5)	20.7 (6.9)	21.1 (7.3)								
Sedentary (% weartime)	HE	71.6 (8.4)	73.8 (7.6)	70.2 (7.6)	-1.3	[-4.4; 1.7]	-0.9	[-3.9; 2.2]	-2.7	[-5.8; 0.4]	-2.4	[-5.6; 0.7]
	HE+PA	72.3 (9.2)	74.2 (7.5)	74.1 (7.0)	-1.1	[-4.3; 2.0]	-1.1	[-4.2; 1.9]	2.0	[-1.2; 5.1]	1.9	[-1.2; 5.0]
	PA	68.8 (9.7)	71.4 (9.7)	74.5 (6.1)	-1.8	[-4.9; 1.2]	-1.7	[-4.7; 1.3]	1.9	[-1.3; 5.1]	1.7	[-1.4; 4.9]
	Usual care	72.7 (9.3)	74.9 (7.2)	74.4 (8.2)								
Counts/min	HE	338.9 (148.7)	301.8 (119.1)	318.1 (129.3)	30.6	[-22.1; 83.4]	27.8	[-25.5; 81.2]	16.9	[-37.4; 71.2]	12.7	[-42.5; 67.9]
	HE+PA	307.0 (148.8)	284.6 (109.6)	257.0 (109.1)	24.5	[-29.5; 78.5]	24.4	[-29.3; 78.2]	-39.9	[-94.9; 15.1]	-41.9	[-97.0; 13.1]
	PA	358.7 (128.8)	330.9 (133.2)	265.7 (93.3)	**55.9**	**[3.0; 108.8]**	**53.1**	**[0.2; 105.9]**	-50.6	[-106.0; 4.9]	-55.4	[-111.1; 0.2]
	Usual care	307.3 (149.7)	273.8 (88.9)	288.1 (132.2)								

Table 6.2: continued

Mean (SD) or n		Baseline (<20weeks)	Mid-pregnancy (24-28wks)	Late-pregnancy (35-37 wks)	Mid-pregnancy crude model [a]		Mid-pregnancy corrected model [b]		Late-pregnancy crude model [a]		Late-pregnancy corrected model [b]	
					ß	95% CI	ß	95% CI	ß	95% CI	ß	95% CI
Diet, *n*		173	160	132								
Diet Quality Index (%)	HE	57.5 (12.3)	59.8 (12.9)	58.9 (10.2)	**6.8**	**[1.9; 11.6]**	**6.8**	**[2.0; 11.6]**	0.7	[-4.5; 5.9]	0.7	[-4.5; 5.9]
	HE+PA	53.0 (14.3)	56.2 (13.9)	50.8 (13.7)	**5.4**	**[0.4; 10.5]**	**5.7**	**[0.7; 10.7]**	-5.5	[-11.1; 0.1]	-5.2	[-10.8; 0.4]
	PA	55.0 (11.6)	56.6 (10.2)	55.2 (12.8)	4.4	[-0.8; 9.7]	4.4	[-0.9; 9.6]	-2.5	[-8.0; 3.0]	-2.6	[-8.1; 2.9]
	Usual care	53.0 (12.6)	50.4 (14.3)	56.5 (14.3)								
Quality (%)	HE	14.2 (27)	22.3 (25.4)	18.5 (22.6)	**17.2**	**[7.5; 26.9]**	**18**	**[8.4; 27.5]**	5.5	[-4.9; 15.9]	6.0	[-4.3; 16.3]
	HE+PA	7.3 (31.6)	14.1 (27.5)	1.8 (30.0)	**12.9**	**[2.9; 23]**	**13.6**	**[3.7; 23.6]**	-8.5	[-19.7; 2.8]	-7.8	[-18.9; 3.4]
	PA	7.4 (25.7)	11.6 (22.6)	9.4 (25.8)	9.2	[-1.3; 19.7]	9.9	[-0.5; 20.3]	-2.4	[-13.5; 8.6]	-2.4	[-13.3; 8.6]
	Usual care	5.2 (26.6)	-1.1 (28.9)	10.7 (29.6)								
Diversity (%)	HE	92.7 (9.6)	90.2 (10.7)	91.8 (10.2)	-2.3	[-6.2; 1.6]	-2.6	[-6.4; 1.3]	-3.7	[-8.0; 0.5]	-4.0	[-8.2; 0.2]
	HE+PA	90.4 (9.9)	89.6 (10.2)	90.3 (9.6)	-2	[-6.1; 2.1]	-1.8	[-5.8; 2.2]	-4.2	[-8.8; 0.5]	-3.7	[-8.3; 0.8]
	PA	94.5 (7.8)	95.7 (6.7)	94.0 (10.9)	2.9	[-1.4; 7.2]	2.8	[-1.5; 7.0]	-1.8	[-6.3; 2.7]	-2.0	[-6.4; 2.5]
	Usual care	92.7 (9.5)	92.3 (10.3)	94.8 (8.6)								
Adequacy (%)	HE	75.0 (11.3)	72.5 (15.3)	72.1 (13.6)	-0.7	[-5.6; 4.3]	-0.8	[-5.6; 4.1]	**-6.7**	**[-12.1; -1.4]**	**-6.7**	**[-12; -1.5]**
	HE+PA	71.3 (14.3)	71.2 (13.7)	70.2 (13.0)	-0.7	[-5.9; 4.5]	-0.4	[-5.5; 4.7]	**-6.1**	**[-11.9; -0.3]**	-5.4	[-11.1; 0.3]
	PA	77.2 (12.9)	74.8 (12.6)	74.0 (12.6)	0.2	[-5.3; 5.6]	0.2	[-5.2; 5.5]	-5.1	[-10.8; 0.6]	-5.1	[-10.7; 0.6]
	Usual care	72.2 (14.5)	72.5 (11.1)	77.1 (11)								
Moderation (%)	HE	85.1 (8.4)	88.4 (7.7)	88.2 (8.2)	**5.9**	**[2.7; 9.0]**	**5.8**	**[2.7; 8.9]**	**5.8**	**[2.4; 9.2]**	**5.7**	**[2.4; 9.1]**
	HE+PA	83.6 (8.0)	87.3 (7.8)	83.5 (8.8)	**5.3**	**[2.0; 8.6]**	**5.4**	**[2.2; 8.7]**	1.1	[-2.6; 4.8]	0.9	[-2.8; 4.5]
	PA	80.8 (8.3)	82.1 (8.7)	82.4 (7.2)	1.3	[-2.1; 4.7]	1.5	[-1.9; 4.9]	1.3	[-2.3; 4.9]	1.3	[-2.3; 4.8]
	Usual care	82.7 (9.5)	81.3 (9.3)	81.8 (8.1)								
Equilibrium (%)	HE	65.7 (10.2)	67.0 (12.5)	66.5 (10.7)	**5.9**	**[1.2; 10.5]**	**5.8**	**[1.2; 10.3]**	1.0	[-3.9; 6.0]	1.0	[-3.9; 5.9]
	HE+PA	61.3 (10.5)	64.9 (11.6)	60.3 (13.1)	**5.0**	**[0.2; 9.8]**	**5.3**	**[0.6; 10.0]**	-3.6	[-9.0; 1.8]	-3.2	[-8.5; 2.1]
	PA	63.1 (10.7)	62.5 (10.0)	62.2 (10.1)	2.0	[-3.0; 7.0]	2.1	[-2.8; 7.0]	-2.3	[-7.6; 2.9]	-2.4	[-7.5; 2.8]
	Usual care	61.1 (11.0)	59.9 (12.2)	64.0 (11.9)								

Table 6.3: Multiple mediation analysis

Mediator variable	Intervention effect on mediator (α-path)			Effect of the mediator on the outcome (β-path)	Indirect effect (path α*β)			Direct intervention effect on the outcome (τ'-path)		
	Estimate (95% CI)			Estimate (95% CI)	Estimate (95% CI)			Estimate (95% CI)		
	HE	HE+PA	PA		HE	HE+PA	PA	HE	HE+PA	PA
Multiple mediation model with GWG as outcome (n=81)										
Total physical activity	2.2 (-1.9;6.3)	2.5 (-1.6;6.7)	1.7 (-2.4;5.7)	0.02 (-0.2;0.2)	0.04 (-0.4;0.8)	0.04 (-0.5;0.9)	0.03 (-0.3;0.8)	-1.3 (-4.4;1.7)	**-3.5 (-6.8;-0.3)**	0.2 (-2.8;3.2)
DQI	5.5 (-2.3;13.4)	**12.4 (4.5;20.3)**	4.6 (-3.1;12.3)	0.03 (-0.1;0.1)	0.2 (-0.3;1.9)	0.4 (-0.8;2.1)	0.2 (-0.2;1.4)			
Multiple mediation model with fasting glucose as outcome (n=79)										
Total physical activity	2.5 (-1.5;6.5)	1.7 (-2.3;5.7)	0.6 (-3.5;4.7)	0.01 (-0.01;0.02)	0.02 (-0.01;0.1)	0.01 (-0.01;0.1)	0.004 (-0.02;0.1)	0.2 (-0.1;0.4)	-0.1 (-0.4;0.2)	-0.2 (-0.5;0.1)
DQI	6.9 (-1.1;14.9)	**11.9 (3.9;19.9)**	4.4 (-3.8;12.5)	0.001 (-0.01;0.01)	0.01 (-0.05;0.01)	0.01 (-0.1;0.1)	0.01 (-0.03;0.07)			
Multiple mediation model with HOMA-IR as outcome (n=78)										
Total physical activity	1.9 (-2.2;6.0)	2.0 (-1.9;6.0)	1.2 (-2.8;5.3)	0.003 (-0.01;0.02)	0.01 (-0.02;0.11)	0.01 (-0.02;0.09)	0.01 (-0.02;0.10)	0.2 (-0.1;0.4)	-0.1 (-0.4;0.2)	-0.01 (-0.3;0.3)
DQI	7.4 (-0.7;15.5)	**11.9 (4.0;19.9)**	4.2 (-4.0;12.3)	0.004 (-0.004;0.013)	0.03 (-0.03;0.22)	0.05 (-0.05;0.25)	0.02 (-0.02;0.18)			

Notes: Multiple mediation analysis with 1000 bootstrapping confidence intervals. Bold numbers represent a significant effect of $p<0.05$. Abbreviations: DQI: Dietary Quality Index; GWG: gestational weight gain; HE: healthy eating; HE+PA: healthy eating and physical activity; HOMA-IR: Homeostatic model assessment- insulin resistance; PA: physical activity.

DISCUSSION

The present study found that the lifestyle intervention offered within DALI was effective in increasing counts per minute and improving dietary scores (expressed in DQI and component scores) at mid-pregnancy. However, these lifestyle modifications did not mediate any effect of the intervention on GWG and glucose metabolism in late-pregnancy.

The effects of the present intervention on maternal physical activity and diet approximate those of most other counselling intervention trials targeting the same population. No substantial changes in objectively measured physical activity were established in the UPBEAT study [136]. In the LIMIT study, on the other hand, an antenatal lifestyle intervention was effective in increasing total physical activity measured by questionnaire in the second and third trimester of pregnancy [84], Hawkins et al. (2014) showed that their exercise intervention in the BABY study had a smaller decline in total physical activity mid-pregnancy compared to a health and wellness intervention [131], and in the Finnish RADIEL study self-reported leisure time physical activity improved by 15 minutes compared to the control group [171]. However, self-reported questionnaires are biased, representing the individual's perception of her activity, and therefore frequently over-estimate physical activity levels [270]. Furthermore, it is possible that women in the intervention group are more likely to report changes, because of having received the intervention message, but without a true change in behaviour. Therefore, objective measures are preferred such as the accelerometer data used in the present [21]. Clinically important is that the DALI intervention countered the expected reduction in physical activity in a progressing pregnancy as women were still able to be active according the ACOG guidelines of 30 minutes of MVPA a day in late-pregnancy. Therefore, it could be expected that women remained fitter with less pregnancy-related physical complaints (e.g. low back pain) as a result of the intervention [263]. The literature is more straightforward when it comes to dietary effects. Overall, lifestyle interventions carried out during pregnancy result in substantial improvements in different aspects of the maternal diet, including nutrients, food groups, measures of diet quality and eating habits [84,121,132,171,248,253,262,267]. The DALI intervention effects on the DQI and component scores particularly apply from baseline to mid-pregnancy, but not to late-pregnancy. A possible explanation could be related to a reduction in individual counselling intensity, as only one face-to-face contact (around 30 weeks of pregnancy) and one optional telephone session (around 34 weeks of pregnancy) were offered after the mid-pregnancy measurement. Also symptoms arising from the expanding uterus could impact dietary habits, such as heartburn which affects up to 80% of the women in their third trimester. Such symptoms often lead to a restriction in food intake, mostly of high-fat foods but also of fruits, vegetables and milk products [74].

We performed mediation analyses to examine the effect of the DALI lifestyle intervention on the primary outcomes of GWG, fasting glucose concentrations and HOMA-IR. The concept of mediation analysis is to understand causal mechanisms by establishing why and how an independent variable (lifestyle intervention) influences a dependent variable (e.g. GWG) through one or multiple mediating factors (changes in physical activity and DQI) [133]. We showed that the lifestyle interventions offered did not seem to indirectly influence GWG or glucose metabolism in overweight and obese pregnant women through modifications in maternal total physical activity and dietary quality scores. However, it is worth mentioning that even though multiple mediation models provide the most precise results [133], the total sample size for these three models was relatively small (n=81, 79 and 78), resulting in limited statistical power, and a higher risk of not finding a mediation effect that is actually present (type 2 error). Not finding evidence for mediation effects does not mean they are not present. For example, it is possible that 'small changes' in physical activity (e.g. 10% increase in step counts per week) and diet (e.g. reduction of 100 kcal a day by replacing sugary drinks for non-sugary drinks) are too small to be detected, but do result in (gestational) weight changes in the long-term [146]. However, based on our results, alternatives need to be considered. It might be that other (latent) biopsychosocial (e.g. genetics, social economic factors [248], the timing of weight gain [248]) or environmental factors (e.g. social support) may play a more prominent role in total GWG and changes in glucose metabolism during pregnancy, which requires further research.

The HE and HE+PA interventions within DALI were found to produce effects on diet within the longitudinal linear multivariate and the mediation models, with a slight preponderance of the HE arm. Interventions predominantly based on dietary modifications are globally accepted as the more effective intervention for overweight and obese women due to various reasons that may also apply for the DALI trial [319]: 1) the net benefit from interventions is probably linked to how the lifestyle advice is delivered. Correctly applying counselling skills (e.g. motivational interviewing) might especially be important in delivering physical activity advice which requires more skilled practitioners (chapter 5). Furthermore, in combined interventions, the dietary advice might not be delivered to the same standards compared to studies offering dietary advice alone, as the lifestyle coach has to shift between two distinct behaviours; 2) compliance to HE interventions might be easier to incorporate into one's life because of its relative simplicity and perceived safety in contrast to physical activity in pregnancy. Especially in late-pregnancy, more pregnancy-related barriers (e.g. back pain) might make compliance to physical activity advice more difficult; and 3) benefits of specific components of the diet are generally more known and accepted than the benefits of physical activity during the course of pregnancy [319]. This being said, it needs to be emphasized that this is not an advocacy for a dietary alone intervention, especially we showed that the HE+PA intervention in DALI was most effective in changing GWG. However, an opportunity remains to increase the physical activity part in lifestyle interventions.

This study has some strengths and limitations. The dietary quality and level of physical activity were measured at three different time points with highly valid measurement instruments within a European randomised controlled trial conducted in overweight and obese pregnant women. The use of dietary records is accepted as a valid method for measuring actual dietary intake in a setting with cultural and country-specific differences in foods and diets. Despite this, both the completion of dietary records by participants and the analysis of the records by researchers is very time-consuming and is therefore often seen as an important reason for not using dietary records in large research settings [344]. The dietary outcome refers to the level of foods and beverages. A more detailed level of macro- and micronutrients analysis was considered but was found less appropriate in light of the delivered dietary health messages and the lack of specific detail of the obtained dietary data. Accelerometers, used for measuring physical activity levels objectively, are a valid measurement tool outside pregnancy [259]. Although a limitation in the use of accelerometers can be found in the inadequate and incorrect measurement of stationary exercise, upper body movements and water-based activities [93]. Therefore, if women incorporate strength training exercises during pregnancy (e.g. at home with the dynaband) this is not reflected in total physical activity. Furthermore, swimming is an easy to perform exercise for pregnant women as the water partly supports the body (in this study 10% of the women swam or started to swim during pregnancy). The use of waterproof wearable monitors may provide a solution for this limitation [177], instead of the subjective addition of self-reported swimming activity. Obtaining objective longitudinal dietary and physical activity data is impeded as participants' compliance generally decreases over time [136,281]. A low compliance over time not only diminishes the sample size and statistical power for dietary and physical activity research, but also involves a certain degree of selection bias. Participants being more compliant to the study measurements are in general more motivated and more likely to benefit from the study intervention than the less compliant participants [225].

The present study shows that in the DALI lifestyle study dietary counselling is an effective component for dietary modifications in obese pregnant women. However, in an attempt to explain the working mechanisms of excessive GWG prevention and improved glucose metabolism, no mediating factors were found. Physical activity and dietary improvements associated with a reduction in GWG might have been too small to detect. Furthermore, other biopsychosocial and environmental factors should be explored.