From efficacy to effectiveness: Two randomized controlled trials of lifestyle intervention postpartum

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”Verklig visdom är att förstå vidden av sin egen okunskap”

Confucius

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ABSTRACT

The overall aim of this thesis was to evaluate if, and how, weight loss can be achieved in women with overweight and obesity after pregnancy by combining results from two randomized controlled trials; LEVA (Lifestyle for Effective Weight loss during Lactation) and LEVA in Real Life. In the LEVA trial, a 12-week diet intervention based on the Nordic Nutrition Recommendations produced a weight loss of 9%, which was sustained at 10% after 1 year, among 68 lactating women. However, important aspects of the dietary changes contributing to this weight loss remained to be examined. Therefore, in the first two papers, eating frequency and food choice in the LEVA trial are reported. In the following two papers, the short and long term effectiveness of the diet treatment to produce weight loss among 110 postpartum women within a primary health care setting were examined through the LEVA in Real Life trial.

At baseline, LEVA women reported an eating frequency of 5.9 intake occasions per day (paper I). During the intervention, a positive association was found between change in eating frequency and change in energy intake. Also, women who received diet treatment reduced their eating frequency more during the intervention than did women not receiving it. Furthermore, results from paper II show that LEVA women had a high intake of sweets and salty snacks and an intake of fruit and vegetables below the recommendations at baseline. During the intervention, women receiving diet treatment reduced their intake of sweets and salty snacks and caloric drinks, and increased their intake of vegetables, more than did women not receiving it. At 1 year, only the difference in increased vegetable intake remained between the groups. Thus, findings from papers I and II suggest that dietary changes in line with current dietary guidelines can help women with overweight and obesity to achieve weight loss after pregnancy.

In the LEVA in Real Life trial, women randomized to the diet group achieved greater weight loss after 12 weeks (6.7% vs 2.0%) and 1 year (11.6% vs 5.1%) compared to the control group (paper III). Preliminary data after 2 years show that the diet group has had a greater weight regain from 1-2 year compared to the control group such that the observed difference in weight loss at 1 year was not maintained at 2 years (7.5% vs 5.8%). In sum, the combined results from papers III and IV provide evidence that diet treatment delivered within a primary health care setting can produce clinically relevant weight loss among postpartum women with overweight and obesity. However, the results also highlight the difficulty of maintaining weight lost during the first year postpartum.

Keywords: postpartum, weight loss, RCT, diet intervention, women, eating frequency, food choice, efficacy, effectiveness

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SAMMANFATTNING PÅ SVENSKA

Forskning visar att utveckling av övervikt och fetma bland kvinnor ofta sker i samband med barnafödande. Detta förklaras till stor del av betydande viktökning under graviditet och retention av graviditetsvikt efter förlossning. På kort sikt medför denna viktutveckling en ökad risk för komplikationer under kommande graviditeter och på lång sikt bidrar den till ökad risk för insjuknande i fetmarelaterade följdsjukdomar.

Det övergripande syftet med denna avhandling var att undersöka om, och hur, hållbara livsstilsförändringar kan uppnås bland kvinnor med övervikt och fetma efter graviditet genom att kombinera resultat från två kliniska försök; LEVA (Livsstil vid Effektiv Viktminskning under Amning) och LIV (LEVA i Vardagen). I LEVA-studien bidrog kostbehandling enligt de Nordiska Näringsrekommendationerna till en viktminskning på 9 % efter tolv veckor, vilket utökades till 10 % efter ett år, bland 68 ammande kvinnor. Frågor som kvarstod att besvaras var genom vilka förändringar i kostintag som denna viktminskning hade uppnåtts (delarbete I och II). I den efterföljande LIV-studien undersöktes om kostbehandling efter graviditet kan bidra till viktminskning även när den ges inom ordinarie verksamhet i Närhälsan bland 110 kvinnor med övervikt och fetma (delarbete III och IV).

I delarbete I har måltidsfrekvens studerats. Vid studiestart hade LEVA-kvinnorna en måltidsfrekvens på 5.9 intagstillfällen per dag. Det fanns ett positivt samband mellan minskad måltidsfrekvens och minskat energiintag under interventionen. Kvinnor som mottog kostbehandling minskade sin måltidsfrekvens mer än kvinnor som inte mottog den. I delarbete II har livsmedelsintag studerats. Vid studiestart hade LEVA-kvinnorna ett högt intag av sötsaker och salta snacks och ett lågt intag av frukt och grönsaker. Under interventionen minskade intaget av sötsaker, salta snacks och energigivande dryck, medan intaget av grönsaker ökade, mer hos kvinnor som mottog kostbehandling jämfört med kvinnor som inte mottog den. Endast skillnaden i ökat grönsaksintag kvarstod mellan grupperna ett år efter studiestart. Sammanfattningsvis visar delarbete I och II att kostförändringar i linje med rådande näringsrekommendationer kan hjälpa kvinnor med övervikt och fetma att uppnå viktminskning efter graviditet.

I LIV-studien uppnådde kvinnor som mottagit kostbehandling större viktminskning efter tolv veckor (6.7 vs 2.0 %) och ett år (11.6 vs 5.1 %) jämfört med kvinnor som enbart erhöll en broschyr kring hälsosamma levnadsvanor (delarbete III). Preliminära resultat från delarbete IV visar att kostgruppen har haft större viktökning mellan 1-2 år jämfört med broschyrgruppen och att det inte kvarstår någon skillnad i viktminskning mellan grupperna vid två år (7.5 vs 5.8 %). Sammanfattningsvis visar delarbete III och IV att även kostbehandling som ges inom ordinarie verksamhet kan bidra till klinisk relevant viktminskning bland kvinnor med övervikt och fetma efter graviditet. LIV-studien belyser dock svårigheten att bibehålla denna viktminskning i ett långtidsperspektiv.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Huseinovic E, Winkvist A, Bertz F, Bertéus Forslund H, Brekke HK. Eating frequency, energy intake and body weight during a successful weight loss trial in overweight and obese postpartum women.
European Journal of Clinical Nutrition 2014;68(1):71-6.

II. Huseinovic E, Winkvist A, Bertz F, Brekke HK. Changes in food choice during a successful weight loss trial in overweight and obese postpartum women.
Obesity (Silver Spring) 2014;22(12):2517-23.

III. Huseinovic E, Bertz F, Leu Agelii M, Johansson Hellebö E, Winkvist A, Brekke HK. Effectiveness of a weight loss intervention among postpartum women: results from a randomized controlled trial in Primary Health Care.
American Journal of Clinical Nutrition 2016;104(2):362-70.

IV. Huseinovic E, Bertz F, Brekke HK, Winkvist A. Two-year follow-up of a weight loss intervention among postpartum women: results from a randomized controlled trial in Primary Health Care.
In manuscript.

CONTENT

Abbreviations

BMI	Body Mass Index
D-groups	Study groups receiving diet treatment in the LEVA trial
E%	Percent of total energy intake
FAO	Food and Agriculture Organization of the United Nations
IOM	Institute of Medicine
LEVA	Swedish: Livsstil vid Effektiv Viktminskning under Amning; English: Lifestyle for Effective Weight loss during Lactation
ND-groups	Study groups not receiving diet treatment in the LEVA trial
NNR	Nordic Nutrition Recommendations
PAL	Physical Activity Level
SD	Standard Deviation
WHO	World Health Organization

1 INTRODUCTION

This thesis concerns the issue of maternal weight development in women with overweight and obesity after pregnancy. It is based on the combination of an efficacy trial, the LEVA (Swedish for Lifestyle for Effective Weight loss during Lactation) trial, that focused on maximum effect of a treatment when implemented under ideal conditions and an effectiveness trial, the LEVA in Real Life trial, examining the maximum effect obtained when a treatment is implemented within real world settings.

The aim of the LEVA trial was to fill an identified knowledge gap on what treatment program may help lactating women with overweight and obesity to obtain sustainable lifestyle changes to lose weight following pregnancy. The results showed that diet behavior modification treatment provided clinically relevant and sustainable weight loss (1), but important aspects of the dietary changes contributing to this weight loss remained to be explained. However, results from controlled efficacy trials such as LEVA do not constitute sufficient basis to launch new treatment programs within health care because studies of implementation in real life are necessary to translate research findings into clinical practice. Therefore, the LEVA in Real Life trial was initiated to evaluate the effectiveness of the diet treatment program to produce weight loss among postpartum women when conducted within the primary health care setting. Thus, the aim of this thesis was to 1) identify changes in dietary intake reported by women receiving diet treatment in the LEVA trial, and 2) evaluate the short and long term effectiveness of the diet treatment program to produce weight loss when implemented within a real world setting in the LEVA in Real Life trial.

2 BACKGROUND

2.1 Overweight and obesity

2.1.1 Definition

Overweight and obesity are defined as conditions of abnormal or excessive accumulation of body fat to the extent that health might be impaired (2). Body mass index (BMI), calculated as weight in kilograms divided by square of height in meters, is commonly used to classify overweight and obesity according to the cut offs set by the World Health Organization (WHO). The classification system is based on studies on comorbidity risks associated with BMI and body-fat accumulation and is independent of sex or age, see Table 1. The risk of serious complications is markedly increased as BMI exceeds 30 kg/m^2 (2).

Table 1. Classification of adult underweight, normal weight, overweight and obesity according to BMI (2)

Classification	**BMI (kg/m^2)**
Under weight	<18.50
Normal weight	18.50-24.99
Overweight	25.00-29.99
Obese	≥30.00
Obese class 1	30.00-34.99
Obese class 2	35.00-39.99
Obese class 3	≥40.00

Research has shown that central localization of excess body fat, i.e. abdominal adiposity, contributes to higher risks of obesity-related comorbidities than do peripheral localization, and that changes in central fat accumulation predict changes in risk factors for comorbidity better than does BMI (3). Therefore, measure of waist circumference is recommended as an additional method of identifying overweight and obesity by the WHO. In women, a waist circumference above 80 cm indicates increased risk of obesity-related metabolic complications, and a waist circumference above 88 cm indicates substantially increased risk. The corresponding cut offs in men are 94 cm and 102 cm, respectively (2).

2.1.2 Prevalence

Globally, the proportion of adults with overweight and obesity has increased at an alarming rate during the last decades and the situation has been described as an epidemic, and lately also a pandemic, affecting both richer and poorer societies (4). The rise of the obesity epidemic seems to have begun in high-income countries in the 1970s and 1980s. Worldwide, the proportion of women with a BMI of 25 kg/m^2 or greater increased from 29.8% in 1980 to 38.0% in 2013. The corresponding increase in men was from 28.8% to 36.9% (5). In 2014, the reported global prevalence of adult obesity was 14.9% in women and 10.8% in men, and this is estimated to reach 21% in women and 18% in men by 2025 if the trend from previous years continue (6). In Sweden, the prevalence of overweight in 2014 was 29% in women and 42% in men, with an additional 14% having obesity among both sexes (7).

2.1.3 Etiology

In simple terms, the fundamental cause of excess weight is a chronic positive energy balance where energy intake must exceed energy expenditure for weight gain to occur. However, the etiology of overweight and obesity is much more complex, as it involves interaction of multiple and diverse factors such as environmental, behavioural, social, genetic, and cultural (2, 8).

Epidemiological trends in obesity indicate that the primary cause of the global obesity problem lies in environmental and behavioural changes caused by industrialization, urbanization and economic transition (2, 4, 9). The unlimited access and variety of foods available, especially high-fat, energy-dense foods, the reduction in physical activity and the concurrent increase in sedentary behaviour are thus thought to play a major role (4, 10). In an expert consultation report by WHO in 2003, key factors that might promote or protect against weight gain and obesity were listed (9). Among the promoting factors, there was convincing evidence for a sedentary lifestyle and a high intake of energy-dense micronutrient-poor foods and probable evidence for a high intake of sugars-sweetened soft drinks and fruit juices. In addition, there was possible evidence for large portion sizes. Among the protective factors, there was convincing evidence for regular physical activity and a high intake of dietary fibre and probable evidence for infants to be breastfed. Also, there was possible evidence for consumption of low glycaemic index foods and insufficient evidence for increased eating frequency. Similarly, in 2007, the World Cancer Research Fund/American Institute of Cancer Research published a systematic review on food, nutrition, physical activity and cancers, which resulted in public health goals and personal recommendations

for cancer prevention. Although this report mainly focused on cancer prevention, recommendations on several behaviours were given due to their potential effect on prevention of weight gain as maintenance of a healthy weight was concluded to be one of the most important ways to protect against cancer (11). These recommendations included being physically active, limiting consumption of energy-dense foods, avoiding sugary drinks and eating at least five portions of vegetables and fruits every day.

In the most recent update of the Nordic Nutrition Recommendations (NNR) from 2012 (12), it was concluded that diets rich in vegetables, root vegetables, pulses, fruits and berries, nuts and seeds, whole grains, fish and sea food, vegetable oils and low-fat dairy products are associated with lower risk of chronic disease, including obesity, compared to Western-type dietary patterns characterized by high consumption of processed meat and foods with low nutrient-density but high fat and sugar content. The effect of these foods on obesity prevention was mainly mediated by a low energy density. Furthermore, diets rich in meat, refined grains, sweets, sugar-rich drinks, and desserts were found to predict weight gain and larger waist circumference. Consequently, dietary changes recommended in NNR 2012 that could potentially promote energy balance and health were, among others, an increased intake of vegetables and fruits, exchange of high-fat dairy with low-fat dairy and limited intake of beverages and foods with added sugar.

In addition to the focus on food choice for the prevention of weight gain, a growing body of evidence also suggests that meal patterns may be a significant predictor of body weight (13, 14). This hypothesis is based on the concurrence of the obesity epidemic and the loosening of traditional meal patterns which is thought to dissolve collective norms guiding temporal eating (15, 16). For example, in an examination of the relative contribution of energy density, portion size, and the number of eating and drinking occasions to changes in daily energy intake in the U.S. between 1977-2006, increases in portion size and number of eating occasions were found to contribute the most (17). Furthermore, a recent review concluded that, while both portion sizes and eating frequency have increased in the population over the past 35 years, the latter may be contributing more to the positive energy balance and therefore be more problematic for weight gain (13). Nevertheless, there is a lack of consistency in the current literature examining the importance of meal patterns for weight management (18). As an example, early epidemiological studies have reported an inverse relationship between adiposity and overall eating frequency, indicating that a high eating frequency would be preferable in obesity prevention (19, 20). On the contrary, more recent studies demonstrate higher eating frequency in women with obesity compared to

normal weight (21, 22), and a positive relation between eating frequency and energy intake (21, 23). Hence, this suggests that transition to a higher eating frequency might increase the risk of over-consuming energy intake. As a likely consequence of these heterogeneous results, in the latest revision of NNR from 2012, the guideline on meal pattern from 2005 proposing three meals and 1-3 snacks per day was withdrawn without comment (24). Thus, the importance of eating frequency as determinant of energy intake and weight still remains unclear.

Even though the obesity epidemic to a large extent is driven by environmental and societal factors that override our physiological regulation of energy balance, genetics also play a strong role in determining the susceptibility to an obesogenic environment. Estimates of heritability from family and twin studies range from 30 to 70%, with the typical estimate at 50%, indicating that one-half of the variation in body weight within a population could be a result of inherited factors (8, 25). Furthermore, research has shown that the susceptibility to weight gain might be increased during certain critical time periods throughout life such as the fetal and postnatal period, and early adulthood (2). In women, one such critical time period also is pregnancy (26, 27). This was demonstrated in a Stockholm obesity clinic where 73% of female patients identified pregnancy as an important trigger of their obesity and the majority reported a weight retention of more than 10 kg after each pregnancy when asked about their weight history (28, 29). The importance of pregnancy for maternal weight development will be further described in section 2.2.

2.1.4 Consequences

Excess body weight is recognized to increase the risk of numerous adverse health effects and all-cause mortality (30, 31). The health burden of overweight and obesity is largely driven by an increased risk of cardiovascular diseases (32), type 2 diabetes (33), and several forms of cancers, e.g., stomach, large intestine, pancreas, kidney and postmenopausal breast (34). Many of the comorbidities associated with excess body weight are in turn mediated by insulin resistance, impaired glucose metabolism, dyslipidemia, and hypertension (8). Previous literature has shown that median survival is reduced by 2-4 years at BMI 30-35 kg/m^2 and by 8-10 years at BMI 40-45 kg/m^2 when compared with BMI in the normal weight range (31). Furthermore, overweight and obesity also contribute to several non-fatal but disabling disorders such as osteoarthritis, infertility, asthma, chronic back pain and sleep apnea (35, 36). These conditions lead to reduced health-related quality of life and are often the primary reason for obesity-

related contact with the health care system (37, 38). However, most of these conditions can be improved by modest weight loss (2).

Along with the increased risk of morbidity and mortality for the individual, overweight and obesity are also related to substantial health care costs for the society. In a systematic review of the economic burden of obesity worldwide, Withrow et al reported that obesity alone accounts for 0.7–2.8% of a country's total health-care expenditures. When costs associated with having overweight are added, the upper limit of this range reaches 9.1% of total health care expenditure (39). The authors further found that individuals with obesity have medical costs that are 30% greater than those of normal weight individuals. This increased expenditure was mainly attributed to the influence of obesity on coronary heart disease, hypertension and type 2 diabetes. In addition to the medical costs, society also incurs substantial indirect costs from obesity as a result of decreased years of disability-free life, increased mortality before retirement, early retirement, disability pensions, and reduced productivity (35).

2.1.5 Treatment

Weight loss is the most effective treatment of obesity-related morbidity. According to guidelines from the American College of Cardiology/American Heart Association from 2013, weight loss treatment is indicated for 1) individuals with obesity and 2) individuals with overweight with more than one indicator of increased cardiovascular risk e.g. type 2 diabetes, hypertension, dyslipidaemia or elevated waist circumference (40). Numerous studies have shown that modest intentional weight loss of 5-10% can produce clinically relevant improvements in risk factors for metabolic disease such as glucose control, plasma lipid profile, and blood pressure. This amount of weight loss has also been reported to prevent and reverse type 2 diabetes and hypertension in individuals with overweight and to produce significant improvements in sense of well-being and self-esteem (40-43). In fact, even weight loss of 3-4% can result in clinically meaningful benefits with respect to reducing triglycerides and blood glucose levels, and decreasing the risk of type 2 diabetes (40).

A wide variety of treatments for overweight and obesity are available today, including dietary modification, physical activity, pharmacological drugs and bariatric surgery. Dietary change represents the most conventional treatment and a variety of energy-reduced dietary approaches can produce weight loss in adults with overweight and obesity (44). In a systematic review and meta-analysis by Franz et al, individuals receiving diet intervention were found to

achieve a mean weight loss of 4.9 kg (5%) after six months. After 12, 24 and 48 months, mean weight loss was 4.6, 4.4 and 3.0 kg, respectively (45). Behavioural weight management programs which combine diet, exercise and cognitive strategies are recommended for long-term success (46). These programs produce weight loss of approximately 8% during the initial intervention period, with weight plateaus after approximately six months. Thereafter, participants typically experience weight regain of 1-2 kg per year, with faster regains closer to treatment termination. To improve weight loss maintenance, face-to-face or telephone-delivered weight loss maintenance programs that provide regular contact (at least monthly) with a trained interventionist to help participants engage in high levels of physical activity (200–300 min per week), monitor body weight regularly (at least weekly), and consume a reduced-calorie diet are recommended (44). Still, only 20% are successful at long-term weight loss when defined as ≥10% loss of initial body weight maintained for at least one year (47).

In 2013, the Swedish Agency for Health Technology and Assessment and Assessment of Social Services published a report on the scientific evidence of dietary recommendations for individuals with obesity (48). One of the main findings from the report was that a range of advice on dietary modification can result in weight loss and that there are no differences in long-term weight loss after consuming diets with different macronutrient compositions or framing (e.g. Mediterranean diet, low glycaemic index diet etc.). This conclusion is supported by other researchers demonstrating that the adherence to a prescribed diet, and the calorie restriction per se, are far stronger predictors of weight loss outcomes than is the diet composition itself (49, 50). Furthermore, the 2013 report found strong scientific evidence that physical activity as a supplement to dietary modification with energy restriction has no significant additive value for weight reduction in individuals with obesity (48). Although regular physical activity is an important modifier of morbidity, and has positive effects on physiological functions and quality of life (9), compensatory mechanisms are believed to explain the lack of effect on weight loss among individuals with obesity. These mechanisms include a lower degree of physical activity throughout the rest of the day, increased hunger and less of a sense of satiety in connection with meals (48).

Weight reduction can also be achieved through pharmacological drugs and bariatric surgery. Even though several drugs have been shown to facilitate weight loss, many of them are associated with severe side effects and have been withdrawn during recent years (51). At the moment, Orlistat is one of the few drugs approved in Europe. This is a pancreatic lipase inhibitor that

reduces intestinal fat uptake with approximately 30% which, in combination with lifestyle treatment, has been shown to result in greater weight loss compared with lifestyle change alone (52, 53). Finally, bariatric surgery is considered to be the most effective method to achieve long-term weight loss. In most county councils in Sweden, individuals with BMI ≥40 kg/m^2, or BMI ≥35 kg/m^2 with concurrent obesity-related comorbidity, may be considered for surgery (54). In the Swedish Obese Subjects Study, individuals who had undergone bariatric surgery achieved a weight loss of 23.4% after two years compared to a weight increase of 0.1% in the control group receiving lifestyle intervention only. After ten years, weight change from baseline was -16.1% and +1.6% in the two groups, respectively (55). Thus, bariatric surgery is highly effective in lowering body weight and hence reducing negative metabolic and cardiovascular consequences of obesity. However, it is of invasive nature, costly and associated with several surgical complications and life-long supplementation of micronutrients.

2.2 Weight development during reproduction

2.2.1 The reproductive cycle

The reproductive cycle can be divided into four component parts of varying length: pregnancy, full lactation, partial lactation, and non-pregnancy and non-lactation (56). During these phases, women experience physiological and metabolic changes, including changes in body weight. Epidemiological data show that women retain weight with each pregnancy, beyond that of non-pregnant women (26, 27). In addition, during the lactation phase, weight gain is observed in some women (26, 57). Thus, the reproductive period is a critical life stage for women that may result in weight gain and development of overweight or obesity. The focus of this thesis is on weight development during the latter part of the reproductive cycle, i.e. after pregnancy, defined as the postpartum period. Below, the consequences of maternal weight before, during and after pregnancy are presented as they all contribute to the net weight change following a reproductive cycle.

2.2.2 Pre-pregnancy weight

As a consequence of the obesity epidemic, a growing number of women are entering pregnancy with excess body weight (58, 59). This is worrying as maternal pre-pregnancy overweight and obesity is the most common high-risk obstetric condition and an independent predictor of several maternal and perinatal complications. These complications include gestational diabetes, hypertension, pre-eclampsia, caesarean delivery, large-for-gestational-age-

infants, stillbirth, infant mortality and an increased risk for offspring development of overweight and obesity later in life (60-62). In addition, pre-pregnancy BMI has been found to be a predictor of excessive gestational weight gain (63) and postpartum weight retention (64).

Due to practical problems with study design and recruitment of women prior to conception, no randomized controlled trial has yet assessed the effect of pre-conceptional weight loss intervention in women with overweight and obesity on pregnancy outcomes (60, 65). Instead, registry-based studies examining interpregnancy weight change have been conducted. In one such study by Boegerts et al, the association between change in pre-pregnancy BMI from the first to the second pregnancy and the risk of adverse outcomes in the second pregnancy was examined (66). The authors found an increased risk of gestational diabetes for interpregnancy weight increases of ≥2 BMI units, and an increased risk for pregnancy-induced hypertension with an increase of ≥3 BMI units in women with pre-pregnancy normal weight. Also, the risk for large-for-gestational-age infants was found to be halved if women lost ≥1 BMI unit between pregnancies. The same association was examined by Villamor and Cnattingius in a nationwide Swedish study of approximately 151 000 women (67). They found that, compared to women who had weight changes of <1 BMI unit, the odds for adverse pregnancy outcomes for those who gained ≥3 BMI units was increased for most outcomes. The same authors also recently showed that, compared with women with a stable BMI between the first and second pregnancy, the risk for women who gain ≥4 BMI units is significantly increased for stillbirth and infant mortality (68). They also found that, in overweight women, pre-conceptional weight loss reduced the risk of neonatal mortality and conclude that these findings support that pre-pregnancy weight loss should be promoted in women with overweight. In fact, in the U.S, weight loss in women with pre-pregnancy overweight and obesity has been described as a cornerstone for achieving optimal pregnancy outcomes and individualized pre-conceptional dietary counselling for weight loss is recommended in the American guidelines on weight development during pregnancy provided by the Institute of Medicine (IOM) (69).

2.2.3 Gestational weight gain

During pregnancy, women gain weight to support the growth and development of the foetus. Gestational weight gain comprises the products of conception, i.e. the foetus, placenta and amniotic fluid; increases of maternal tissues, i.e. the uterus, breasts, blood, and fluids; and increases in maternal fat stores (70). The increased maternal fat accumulation during pregnancy is

positively related to gestational weight gain and is predominantly accumulated centrally (26). As a consequence of the increased body mass, energy requirements during pregnancy are increased. Among normal weight women, the increased energy requirement has been estimated to be negligible in the first trimester, 350 kcal per day in the second trimester, and 500 kcal per day in the third trimester (71).

In 2009, IOM re-examined the American guidelines on gestational weight gain originally released in 1991 (69). The aim of the 2009 report was to provide recommendations on pregnancy weight gains associated with minimal risk of negative health consequences of inadequate or excessive weight gains for the infant and the mother. For the infant, outcomes such as foetal growth, gestational duration, morbidity and mortality were considered while outcomes for the mother included complications of pregnancy, labour, postpartum weight retention and lactational performance (69). The recommendations provide ranges of optimal weight gain based on pre-pregnancy BMI and emphasize larger weight gains for lower pre-pregnancy BMI categories, see Table 2. Weight gains that exceed the IOM recommendations increase the risk of gestational diabetes, pre-eclampsia, caesarean sections, large-for-gestational-age infants and childhood development of overweight and obesity. In addition, excessive gestational weight gain is a risk factor for postpartum weight retention (64, 72, 73). More specifically, the rate of gestational weight gain in the first trimester has been found to be more strongly associated with postpartum weight retention compared to weight gain in the second or third trimesters, regardless of pre-pregnancy BMI (74). This is likely explained by the fact that early pregnancy weight gain mainly represents maternal fat deposition, rather than fetal or placental tissue or fluid.

Table 2. Recommendations for gestational weight gain from the Institute of Medicine according to pre-pregnancy BMI category (69).

Pre-pregnancy BMI (kg/m^2)	**Total weight gain (kg)**	**Rate of weight gain in 2nd and 3rd trimester (kg/week)***
<18.5	12.5-18.0	0.51
≥18.5 to <25.0	11.5-16.0	0.42
≥25.0 to <30.0	7.0-11.5	0.28
≥30.0	5.0-9.0	0.22

*Calculations assume a total weight gain of 0.5–2.0 kg in the first trimester.

Still, many women gain outside the recommended range and in the U.S, 37.3% of women with normal weight, 64.1% with overweight and 63.5%

with obesity gain more than recommended during pregnancy (75). Predictors of excessive gestational weight gain are high pre-pregnancy BMI (75), smoking session (75), primiparity (26), increased food intake (76), intake of caloric drinks, sweets and salty snacks (77) and decreased physical activity (78). However, a recent Cochrane review, including 65 randomized trials, concluded that there is high-quality evidence to indicate that diet or exercise, or both, during pregnancy can reduce the risk of excessive gestational weight gain (79).

2.2.4 Lactation

For women who breastfeed after delivery, energy requirements are increased compared to pre-pregnant levels as production of breast milk is an energy requiring process. A distinction is usually made between exclusive breastfeeding, i.e. consumption of breast milk as the sole energy source, and partial breastfeeding, i.e. consumption of breast milk in combination with formula and/or other foods (80). Energy cost of lactation is determined by the amount of milk produced, the energy content of the milk and the energetic efficiency of milk synthesis. Butte et al used a milk production of 749 g per day during exclusive breastfeeding, an energy density of milk of 0.67 kcal per g and an energetic efficiency of 0.80 to estimate the energy cost of exclusive breastfeeding through the first five months postpartum to be 670 kcal per day. In well-nourished women, this may be subsidised by energy mobilisation from tissue stores corresponding to approximately 170 kcal per day (70, 81), which would result in a net increase of approximately 500 kcal in total daily energy requirement compared to the non-lactating state. As for partial lactation, the associated energy cost depends on the amount of complementary feeding and therefore varies greatly among women. Total energy requirements during lactation can also be estimated from the sum of measured total energy expenditure (inclusive of the energetic efficiency of milk synthesis) plus milk energy output, i.e. milk production*energy density, while allowing for energy mobilisation from tissue stores using the following equation (70):

Energy requirements during lactation = Total energy expenditure + milk energy output – energy mobilisation from tissue stores

Several maternal characteristics have been associated with initiation and duration of lactation, including higher education, multi-parity, attitudes toward breastfeeding, older age, non-smoking and gestational weight gain below and above the IOM recommendations (82-84). Furthermore, a strong negative association with pre-pregnancy BMI has been found such that

women with obesity are less likely to intend to breastfeed and have a decreased initiation and shorter duration of breastfeeding compared with women of normal weight (84, 85). Reasons for this are most likely multifactorial, including biological, behavioural and/or cultural (86, 87). This is unfortunate given the numerous well-documented health benefits of breastfeeding, including reduced risk of offspring development of overweight and obesity (88, 89).

2.2.5 Postpartum weight retention

Historically, the postpartum period has been defined as up to six weeks post-delivery because most of the pregnancy-related adaptations in e.g. uterus size and blood volume are reverted to the non-pregnant state during this time (90, 91). However, it has also been used to describe the time period up to one year after delivery as a result of other pregnancy-related physiological changes that occur during this period, including lactation and changes in body weight (26, 91). Postpartum weight retention is commonly defined as the difference between postpartum and pre-pregnancy weight (27). At 6-18 months after delivery, an average postpartum weight retention of 0.5-3.0 kg is commonly reported (90, 92, 93); however, large variations in weight development are observed in most studies and 14-25% of women experience a weight retention of ≥5 kg by 6-18 months postpartum (94, 95).

Determinants of postpartum weight retention

During the postpartum period, potential determinants of maternal body weight changes are diet, physical activity and lactation. For women who breastfeed, the additional energy cost of lactation can be met by increased energy intake, decreased energy expenditure and/or mobilisation of fat stores (81, 96). Thus, in theory, lactation can cause weight loss during the postpartum period if not compensated for by increased energy intake and/or decreased energy expenditure.

In reality, the influence of breastfeeding on postpartum weight change is unclear, with some systematic reviews demonstrating a positive association with postpartum weight loss while others find little or no impact (97, 98). Among the studies that show a positive association, it tends to be relatively weak and often confounded by factors such as gestational weight gain, pre-pregnancy weight and physical activity (99). In a systematic review from 2014, the authors conclude that there is currently insufficient evidence to suggest that breastfeeding is directly associated with postpartum weight change (100). They also found that limited number of studies adjusted for food intake, physical activity or time of measurement, and that several studies

did not adjust for any confounding factors at all. Thus, possible reasons for the heterogeneous results from observational studies might be unadjusted confounding factors, but also variation in intensity and duration of lactation, definition of breastfeeding, sample size, study population, time of measurement, and use of measured or self-reported body weight. Also, in studies that do adjust for potential confounders, the risk for residual confounding or reverse causality cannot the ruled out. As for randomized trials, these are greatly lacking as randomization on breastfeeding on an individual level is unethical. However, in 2013, Oken et al published a cluster-randomized trial comparing differences in adiposity in women randomly assigned to an intervention to promote prolonged and exclusive breastfeeding or usual care. At follow-up 11.5 years after pregnancy, a statistical significant, but clinical irrelevant, mean BMI difference of 0.27 units was found between the two groups (101).

Although lactation increases energy requirements of postpartum women, research has shown that lactating women, when possible, increase their energy intake rather than increase mobilisation of fat stores to meet the extra energy cost (29, 102, 103). Furthermore, during pregnancy, women have been found to decrease their physical activity and, during the postpartum period, delay the return to their pre-pregnant exercise practice (104). In addition, lactating women may be predominately sedentary and spend a large amount of time sitting and nursing their infant (96). Thus, if postpartum women adapt to lactation by increased energy intake and decreased energy expenditure, the common assumption that the extra energy cost of lactation should be added to pre-pregnant energy requirements is delusive. In other words, women seem to be just as susceptible to the laws of energy balance during the postpartum period as during other time periods in life, and a negative energy balance, caused by lactation and/or lifestyle modification, seems vital for preventing retention of gestational weight after pregnancy.

As for dietary determinants of postpartum weight retention, results from the Norwegian Mother and Child Cohort Study show that adherence to the NNR 2004 during the first 4-5 months of pregnancy is associated with lower postpartum weight retention six months after delivery, irrespective of gestational weight gain (105). Furthermore, in the Active Mothers Postpartum trial, determinants of postpartum weight change from 6 weeks to 24 months postpartum were assessed among 450 U.S women with overweight and obesity. In that study, postpartum weight loss was associated with lower intake of junk food (i.e. servings of sodas, sweetened drinks, French fries, chips, and fast food) and greater intake of healthy foods (i.e. servings of milk, fruit, and vegetables) (106). Finally, in the Stockholm

Pregnancy and Weight Development Study, risk factors for postpartum weight retention were identified by studying the weight development of 1423 women prospectively from pregnancy until one year postpartum. Weight retention one year postpartum was found to be greater in women with increased snack frequency postpartum compared to pre-pregnant practices (107). Other non-dietary maternal determinants of postpartum weight retention that have been reported include younger age, primi-parity, lower educational level, smoking cessation, and short interpregnancy interval (<12 months) (90, 96, 108, 109).

Long-term implication of postpartum weight retention

For many women, postpartum weight retention contributes to cumulative weight gain with each reproductive cycle which can increase the risk of complications during subsequent pregnancies (68, 110) and influence long-term maternal health (93, 111). Previous observational data show that failure to lose pregnancy weight by six months postpartum is a predictor of long-term maternal weight development (111), and parity has been positively associated with maternal BMI (98) and waist circumference (112). For example, Rooney and Schauberger found that women who did not return to pre-pregnancy weight by six months postpartum had gained 8.4 kg at 8.5 years after pregnancy, compared with 2.4 kg in women who did (113). Likewise, in the Stockholm Pregnancy and Women's Nutrition study, women who had developed overweight at follow-up 15 years after index pregnancy were those who had retained more weight at one year postpartum and had had steeper weight gain from 1 to 15 years after pregnancy, compared to women not developing overweight (114). Also, weight retention one year postpartum in the first pregnancy has been found to predict weight development in the subsequent pregnancy (115).

There are several methodological challenges in studying the long-term implication of pregnancy on maternal weight development. Some of these include weight changes over time also in non-pregnant women, use of self-reported pre-pregnancy weight, lack of information on relevant confounders, and problems in identifying the optimal time point when the overall impact of pregnancy should be evaluated (29). Furthermore, the postpartum period may be a time when women not only retain gestational weight, but gain additional weight (27). Gunderson et al reported that women with overweight and obesity have greater risk of gaining ≥2 kg from six weeks to two years postpartum than have women with normal weight (116). Likewise, Lipsky et al found the odds of weight gain from one to two years postpartum to be higher for women with obesity in early postpartum compared to women with normal weight (57). This is a problem in observational studies as repeated

measures of postpartum weight are rarely obtained to differentiate between retention of pregnancy weight and subsequent postpartum weight gain (26). Therefore, it has been suggested that postpartum weight retention only should be defined within a limited time period of up to 12-18 months postpartum as other lifestyle-related factors may influence changes in body weight thereafter (27). Also, this implies that the long-term effects of pregnancy on maternal body weight from observational studies should be interpreted with caution.

A window of opportunity

The postpartum period has been described as a "teachable period" to promote healthy lifestyle behaviours among women (117). The term is usually used to indicate naturally occurring life transitions or health events thought to motivate individuals to spontaneously adopt risk-reducing health behaviour (118). During the postpartum period, several contextual factors converge which contribute to making this time period a unique opportunity to support lifestyle changes. These facilitators include increased energy requirement during lactation (70), motivation to return to pre-pregnancy weight (119), desire to serve as a parental role model (120), and an established contact with health care professionals. In addition, in Sweden, women can benefit from a generous parental leave which enables parents to be on paid parental leave until the child is 1.5 years old. Thus, this could provide opportune conditions to initiate lifestyle changes.

High willingness to participate in postpartum weight programs has been reported (117, 119, 121). Ohlendorf et al found that 50% of women with normal weight and 80% of women with overweight or obesity have plans to seek weight loss information from health care providers by four months postpartum (122). The most frequently desired information was specific strategies to lose weight postpartum. As the family environment, including attitudes towards eating habits and physical activity, lay the foundation for children's health-related behaviours, intervening when women enter parenthood may increase the reach of interventions and provide spill-over effects on the offspring. Furthermore, postpartum interventions might positively impact maternal weight development during subsequent pregnancies. Thus, the postpartum period might be an ideal time window to implement lifestyle changes in women to influence the short- and long-term health of the mother and her child.

2.3 Postpartum weight loss

Despite growing understanding of the impact of pregnancy on maternal weight development, no ideal time to return to pre-pregnancy weight has been established in the literature (91). Current evidence suggests that women who do not lose pregnancy weight by the first 6-12 months postpartum are at higher risk of developing overweight or obesity (93, 113, 123). However, while energy restriction and physical exercise may promote weight loss in the general population, there has been concern that lactating women might not adequately adapt to a negative energy balance during lactation by increasing fat mobilization such that milk content and production, and consequently infant growth, could be impaired.

2.3.1 Postpartum trials

One of the first experiments conducted to examine the effect of energy restriction in lactating women was performed by Strode et al in 1986 (124). In that study, 22 well-nourished exclusively lactating women who had gained ≥11 kg during pregnancy were recruited between 6-24 weeks postpartum. Women were given the choice to be included in an experimental group, where energy intake was to be reduced by 20-30%, or a control group, where normal intake was maintained, during one week. The authors found no adverse effects on milk composition or milk intake among infants of mothers whose energy intake was greater than 1500 kcal per day, either during the first or second week following energy restriction. A couple years later, Dewey et al conducted a randomized controlled trial to assess the effect of exercise on lactation performance (125). At 6-8 weeks postpartum, 33 exclusively lactating women were randomly assigned to an exercise group, to perform aerobic exercise for 45 min per day during 5 days per week, or a control group. After 12 weeks, no adverse effects on lactation performance or infant weight gain were found. However, no difference in maternal weight change was observed between the two groups which was explained by a concurrent increase in energy intake among women in the exercise group.

In 2000, Lovelady et al conducted a randomized trial among lactating women with overweight to examine whether postpartum weight loss through energy intake restriction and physical exercise affects infant growth (126). At four weeks postpartum, 40 exclusively lactating women were randomized to either a diet and exercise group, instructed to restrict energy intake by 500 kcal per day and exercise for 45 min per day, 4 days per week, or a control group. After 10 weeks, the intervention group had lost 4.8 kg compared to 0.8 kg in the control group with no difference in gain in infant weight or length. The authors concluded that weight loss of 0.5 kg per week in exclusively lactating

women with overweight does not affect the growth of their infants. The year before, McCrory et al had reached the same conclusion after having induced an 11-day long energy deficit of 35% in exclusively lactating women with no adverse effects on milk volume, composition, energy output or infant growth (127). In that trial, three study groups were evaluated: diet, diet plus exercise, and control. The authors suggested that weight loss through a combination of diet and exercise is preferable to diet only to preserve maternal lean body mass but that longer-term studies were needed to confirm these findings. Thus, once lactation is established, it seemed that postpartum women with overweight may restrict energy intake by 500 kcal per day and perform exercise several times per week to promote a weekly weight loss of 0.5 kg.

2.3.2 The LEVA trial

In 2007, our research group set out to examine, whether, among exclusively lactating women with overweight and obesity, dietary modification, physical exercise, or a combination of both, leads to a significantly greater weight loss over a 1-year period, compared to women not receiving any intervention (1). The trial utilized a 2 by 2 factorial design to enable examination of the separate and interactive effects of the interventions. In addition to changes in body weight, the trial aimed to evaluate the effect of the interventions on maternal body composition, infant growth, breast milk composition, cardiovascular fitness, cost-effectiveness and dietary intake. The design and methods of the trial, with the acronym LEVA, are described in detail in section 4.1. In Table 3, a short summary of the weight outcome is presented. The authors found that the diet treatment produced clinically relevant and sustainable weight loss with no adverse effects on infant growth. Also, the combined diet and physical exercise treatment did not yield significant weight or body composition changes beyond those of diet treatment alone.

Table 3. Changes in body weight after 12 weeks and 1 year in women randomized to the diet, exercise, diet and exercise or control group in the LEVA trial (1). Values are mean±SD.

	Diet (n=15)	**Exercise (n=16)**	**Diet and exercise (n=16)**	**Control (n=15)**
Change after 12 weeks (kg)	-8.3±4.2	-2.4±3.2	-6.9±3.0	-0.8±3.0
Change after 1 year (kg)	-10.2±5.7	-2.7±5.9	-7.3±6.3	-0.9±6.6

2.3.3 Environmental toxins in breast milk

In addition to the concern of impaired breast milk production during weight loss in lactating mothers, questions have been raised about the impact of postpartum weight loss on milk content of persistent organic pollutants. This is based on the fact that secretion of breast milk is a major way of eliminating environmental toxins found in maternal adipose tissue and the notion that concentration of these substances in breast milk might be positively associated with maternal weight loss (128).

Persistent organic pollutants are synthetic chemicals with some produced to be used as pesticides and solvents while others are by-products of the industry. In addition, there are naturally occurring environmental pollutants, including mercury, lead and cadmium. They all have in common that they are persistent to degradation in the environment and can exert harmful negative effects on human cognitive, endocrine and immune functions (128). The main source of exposure is food, especially inland lake fish and fatty fish from the Baltic Sea, which may contain raised levels of mercury, dioxins and polychlorinated biphenyl (129). As persistent organic pollutants are lipophilic, they bind to fat-rich tissues and can accumulate in the food chain and in the human body. During lactation, when fat is mobilized from maternal adipose tissue to assist breast milk production, persistent organic pollutants can be transferred from mother to infant via the breast milk. Infant exposure is mainly dependent on the duration of lactation, maternal age and parity (128, 130).

In a recent collaboration between the authors of the LEVA trial and the Swedish National Food Agency, the association between weight loss during lactation and concentration of persistent organic pollutants in breast milk was examined. It was found that the breast milk concentration of several chlorinated pollutants increased with increasing weight loss percentage during the intervention period. However, the absolute exposure remained stable due to decreased infant consumption of breast milk when complementary foods were introduced and a lower energy demand per kg body weight of infants at 24 weeks (i.e. intervention termination) compared to at 12 weeks of age. The authors conclude that it is unlikely that the balance between benefits and risks of breastfeeding will change if weight loss is restricted to 0.5 kg per week (131). This is in line with the conclusions drawn by the Swedish National Food Agency in 2008 after reviewing the literature on maternal weight loss during lactation, breast milk content of toxins and risks for the infant (128). Also, in a more recent assessment of the risks and benefits of breastfeeding conducted by the Norwegian Scientific Committee

for Food Safety in 2013, it was concluded that the possible risks from high exposure to organic pollutants from breast milk are clearly outweighed by the beneficial effects of breastfeeding (132).

2.3.4 Official recommendations

In the U.S, the guidelines on weight gain during pregnancy from 2009 state that counselling on diet and physical activity should be offered to all postpartum women to help eliminate postpartum weight retention (69). In the original guidelines from 1991, IOM stated that a postpartum weight loss of up to 2 kg per month had been found to be consistent with maintaining an adequate milk volume (80). In Sweden, the National Food Agency recommends women to return to pre-pregnancy weight within one year postpartum and not to lose more than 0.5 kg per week during lactation (133). They also recommend mothers with overweight to try to achieve normal weight after pregnancy and ask for help from a dietitian at their health care centre. In order to meet the nutrient requirements of lactation, women are advised to consume 500 g fruit and vegetables daily, to eat according to the plate model, and to choose skimmed milk and/or natural low-fat yoghurt (~0.5 l per day), low-fat margarine and wholegrain alternatives when consuming cereals. In addition, advice is given to eat breakfast, lunch and dinner as well as one or two snacks as "this makes it easier to keep away from soft drinks, cakes, ice-cream, sweets and treats" (133).

2.4 Pregnancies and lactation in Sweden

Since 1973, the Swedish Medical Birth Register has collected data on deliveries in Sweden with a reach of 97% of all deliveries today. In 2014, approximately 114 000 deliveries were reported to the registry (134). Between 1973 and 2014, the mean age of childbearing women increased from 26.0 to 30.0 years. The mean age of primiparous women increased from 23.7 to 28.5 years during the same period, with higher maternal age in urban compared to rural areas. Furthermore, the prevalence of pre-pregnancy overweight and obesity has increased significantly in Sweden during the recent decades. Between 1992 and 2014, the proportion of women with overweight or obesity at registration for antenatal care increased from 25% to 38%. In 2014, 25.4% of all women had overweight and 13.1% had obesity at registration (134). However, there are great socio-economic differences in pre-pregnancy BMI. In a recent study among 163 000 Swedish women, weight development among women who had their first and second singleton birth in 1982-2010 was examined. The results show that women with low education were more likely to start their pregnancies at an unhealthy weight.

Also, these women experienced the greatest interpregnancy weight gain (135). In addition to this educational gradient, pre-pregnancy BMI also varies across different regions with lower BMI in urban compared to rural areas (134). For example, in 2010, the age-standardized prevalence of pre-pregnancy obesity in Sweden was highest in Sörmland and Gotland (15.1%) and lowest in Stockholm (7.3%) (136). As for gestational weight gain, 63% of Swedish women with overweight and 57% with obesity have excessive gestational weight gain according to the IOM guidelines. Among women with pre-pregnancy normal weight, those with low education have higher risk of excessive weight gain compared to women with high education (59).

Sweden has adopted the WHO recommendation of exclusive breastfeeding up to six months of age, with continued breastfeeding along with complementary food thereafter (135). In addition, the Swedish National Food Agency states that there is no harm in giving small samples of food to children after four months of age if the child also is breastfed (137). Since the mid-1990s, breastfeeding rates in Sweden have decreased slightly; however, from 2010, this decrease seems to have levelled off (138). Between 2010 and 2013, the proportion of infants being exclusively breastfed during the first six months increased from 11% to 15%, although there are great regional differences in breastfeeding patterns. In 2013, 96% of infants were breastfed to some extent at one week postpartum with the corresponding proportions at 2, 4 and 6 months being 86%, 75% and 63%, respectively. At 12 months, 19% reported breastfeeding.

2.5 Summary of background

Overweight and obesity contribute to increased morbidity and mortality worldwide. The weight changes that occur during reproduction make women especially susceptible to excessive weight gain during this life stage. These weight gains can have adverse effects in subsequent pregnancies and negative long-term consequences for maternal health. The postpartum period is a unique period in life when the convergence of several contextual facilitators may contribute to making this an opportune time to promote healthy lifestyle behaviours. Previous efficacy trials have demonstrated that postpartum lifestyle intervention can produce safe weight loss in lactating women. In the LEVA trial, diet behaviour modification treatment was found to produce clinically relevant and sustainable weight loss among postpartum women; however, important aspects of the dietary changes that contributed to this weight loss remain to be examined. Likewise, the short and long term effectiveness of the diet intervention to produce postpartum weight loss when implemented within ordinary care warrants further investigation.

3 AIM

The overall aim of this thesis was to evaluate if, and how, weight loss can be achieved among postpartum women with overweight and obesity by combining results from the LEVA trial and the LEVA in Real Life trial. More specifically, the aim was to identify changes in dietary intake reported by women receiving diet treatment in the LEVA trial and to evaluate the short and long term effectiveness of the diet treatment to produce postpartum weight loss when implemented within a real world setting in the LEVA in Real Life trial.

The specific aims were to:

Paper I — Investigate the effect of the diet treatment on eating frequency and examine associations among eating frequency, energy intake and body weight at baseline as well as associations among changes in these variables during the intervention period in the LEVA trial.

Paper II — Describe food choices at baseline and changes in food choice after 12 weeks and 1 year in the LEVA trial.

Paper III — Examine the 12-week and 1-year effectiveness of a diet treatment to produce weight loss among postpartum women when conducted within the primary health care setting in the LEVA in Real Life trial.

Paper IV — Evaluate 2-year outcome in the LEVA in Real Life trial and examine factors associated with successful long-term outcome.

4 SUBJECTS AND METHODS

4.1 The LEVA trial

4.1.1 Subjects

Between 2007 and 2010, eligible women were recruited during pregnancy or up to 8 weeks postpartum from 15 antenatal clinics in Gothenburg, Sweden. Inclusion criteria included a self-reported pre-pregnancy BMI of 25-35 kg/m^2, non-smoking, singleton term delivery, intention to breastfeed for six months, providing <20% of infant energy intake as complementary foods, birth weight of infant >2500 g, and no illness in the mother or infant. The upper BMI criterion was set at 35 kg/m^2 to limit the inclusion of women who might be unable to participate in the exercise treatment or who might be at risk of obesity-related conditions that may require additional medical treatment. The study was approved by the regional ethical committee in Gothenburg and written informed consent was obtained from all women.

4.1.2 Study design

Women attended the research clinic for baseline measurements at 8-12 weeks postpartum. At 10-14 weeks postpartum, women were randomly assigned to four study groups; diet behavior modification treatment, physical exercise behavior modification treatment, combined diet and physical exercise behavior modification treatment or control treatment (i.e. lactation only). Women were stratified on the basis of pre-pregnancy BMI <28.0 and ≥28.0 kg/m^2 and a blocked randomization (block size of four) was used within each stratum. Group allocation was concealed to all women until completion of baseline measurements. Study measurements were conducted at baseline, intervention termination (indicated as 12 week) and 9 months later (indicated as 1 year), see Figure 1. All groups received routine postnatal care at the maternal health care clinics and were offered the treatment and material of the alternative study groups after final follow-up. The primary outcomes of the LEVA trial were changes in body weight and body composition.

4.1.3 Study groups

Women randomized to diet behaviour modification treatment received treatment by a dietitian, and women randomized to physical exercise behaviour modification treatment received treatment by a physical therapist, for a total of 2.5 hours of individual behaviour modification counselling. This was delivered during 1.5 hour at the start of the intervention and 1 additional

hour at a follow-up home visit after six weeks of intervention. Women randomized to the combined diet and physical exercise behaviour modification treatment received treatment by both the dietitian and physical therapist of a total of five hours. During the 12-week intervention period, women were contacted bi-weekly with cell-phone text messages to report body weight in the diet group, number of brisk walks in the exercise group, and both body weight and number of brisk walks in the combined diet and exercise group. Through the text messages, women received personalized feedback on their performance and encouragements to adhere to the treatment(s) by the dietitian. Women randomized to the control group received no treatment, text messages or home visit. During the intervention, women in all four groups were asked not to engage in other lifestyle-modification programs.

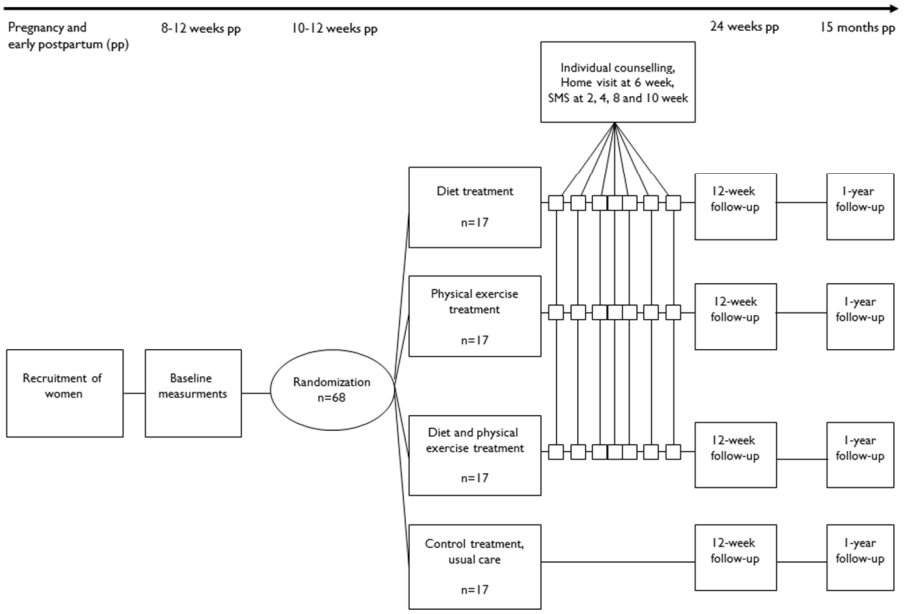

Figure 1. Study design of the LEVA trial.

Diet behaviour modification treatment

Women randomized to diet treatment met individually with the dietitian at the research clinic and were instructed to implement a diet modification plan in order to achieve a reduction in energy intake of 500 kcal per day and a nutrient composition according to NNR 2004 (24). These recommendations emphasized a diet composition of total fat <30% of energy intake (E%), protein 10-20 E%, carbohydrate 50-60 E%, saturated fat ≤10 E%, and fiber

≥12.5 g per 1000 kcal. The diet plan was communicated in terms of foods and consisted of four key dietary principles to be implemented one at a time, according to a step-wise body weight-determined plan in order to achieve the weekly weight loss goal of 0.5 kg and the goal of 6 kg after 12 weeks. In addition, women were advised and monitored not to exceed a weekly weight loss of ≥1 kg while breastfeeding. Women were provided with an electronic body scale and instructed to self-weigh ≥3 times per week and to use body weight as a proxy for energy balance in order to adjust the energy intake during the intervention by a step-wise introduction of the key dietary principles.

The four key dietary principles to be introduced were: [1] limit consumption of sweets, salty snacks and caloric drinks to one day a week and a maximum of 100 g, [2] substitute regular foods with low-fat and/or low-sugar alternatives marked with the "green keyhole," a voluntary labelling symbol for food producers provided by the Swedish National Food Agency indicating foods that contain less sugar, fat and salt and more whole grains and fiber, [3] cover one-half of the plate with vegetables at lunch and dinner by applying the "plate model," an illustration of the proportions between the meal components, and [4] reduce portion sizes (Figure 2). Women were provided with suggestions of concrete changes in food choice to the reported baseline diet in accordance with the four key dietary principles and calculations on the weekly and 12-week weight loss that would be achieved if the principles were implemented. Initially, the energy reduction of 500 kcal per day was achieved by implementing dietary changes suggested by the dietitian and jointly agreed upon. Thereafter, negative energy balance was sustained by implementing dietary changes conceived and experienced as functional by the woman herself as measured by changes in body weight through the self-weighing routine. Women were told to evaluate each key dietary principle for at least two weeks before introducing the next principle in order to secure that all dietary modifications were implemented and given enough time to be evaluated.

The diet plan was presented in a printed booklet covering safety issues regarding weight loss during lactation, instructions on how regular self-weighing can substitute calorie counting, presentation of the four key dietary principles, and space for individualizing the plan to reduce personal barriers to change identified by the woman. The booklet also included checklists for documenting weekly achievements in weight loss and successful introduction of the key dietary principles. During the counselling sessions, the dietitian aimed to create a working relationship by establishing agreement on the goals and strategies, being personal, empathic, non-judgmental, and expressing a

true belief in the woman's capacity to succeed. Reflective listening and joint solution seeking were used to establish strategies to overcome barriers to change and dietary concerns identified during counselling.

During the second counselling after six weeks of intervention, the diet plan was followed up with a 24-h recall at the women's home and feedback was provided on the current diet. In addition, strategies to reduce intake of saturated fat and maintain or reduce intake of unsaturated fats, depending on baseline diet, were introduced.

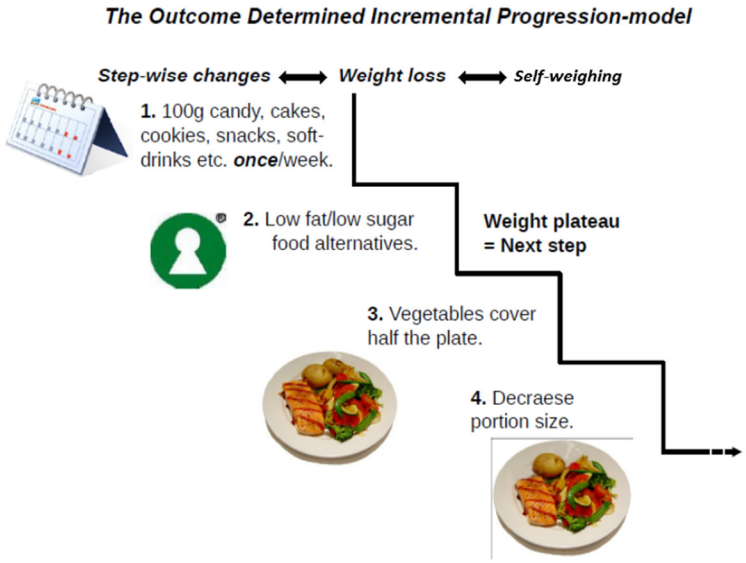

Figure 2. IIllustration of the four key dietary principles from the printed diet booklet provided to women receiving diet treatment in the LEVA trial. Reprinted with permission (139).

Physical exercise behaviour modification treatment

Women randomized to exercise treatment met individually with the physical therapist at the woman's home. The physical therapist designed a structured exercise plan to provide the same style of step-wise implementation of exercise, a goal-level of exercise, self-monitoring, support and follow-up, as was used in the diet treatment. The exercise plan aimed to implement a 45-min brisk walk 4 days per week, at 60-70% of maximum heart rate, with the number and duration of walks gradually increased during the first four weeks.

Women were provided with a heart-rate monitor (Polar FS2C; Polar Electro Oy, Kempele, Finland), and an activity dairy for self-monitoring. The exercise plan was presented with a printed booklet covering health benefits of exercise, safety issues regarding exercise technique, and basic information on diet and hydration. The booklet also included instructions on how to self-monitor using the heart-rate monitor and space for individualizing the plan to reduce barriers to change. Furthermore, the booklet included checklists to document weekly achievements in exercise implementation. Women were advised to perform the walks with the baby in a stroller. During the second counselling session after six weeks of intervention, the exercise plan was followed up with a discussion on the achievements of the exercise goals.

Post intervention
During the 9-month period after the intervention, women were instructed to live their lives as they themselves chose. The women were contacted once after six months and were asked about their health status and whether they still intended to attend the 1-year follow-up.

4.1.4 Measurements

Anthropometry
Body weight was determined after an overnight fast to the nearest 0.1 kg by using an electronic scale (MC 180 MA; Tanita, Tokyo, Japan), with women wearing light underclothing. Height was measured to the nearest 0.5 cm with a wall-mounted stadiometer. BMI was calculated from weight in kilograms divided by the square of height in meters. Pre-pregnancy BMI was calculated as self-reported pre-pregnancy weight divided by the square of measured height. Waist circumference was measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest using a measuring tape. Body composition was measured at all three study visits using dual-energy X-ray absorptiometry (Lunar Prodigy, GE Lunar Corp, Madison, Wisconsin, USA). Total energy expenditure was measured at baseline and 12 week using the doubly labelled water method. Resting energy expenditure was measured using a Deltatrac II Metabolic Monitor ventilated hood system (Datex-Ohmeda, Helsinki, Finland).

Dietary intake
Dietary intake was assessed at baseline, 12 week and 1 year using a weighed diet record during four consecutive days, preferably Wednesday through Saturday. Women were provided with an electronic kitchen scale and instructed to register all foods and beverages in as much detail as possible and to weight the amounts to the nearest one gram. Women were told not to

divert from their usual food choices or habits as their diet record would be used to construct the diet plan if they were randomized to the diet treatment. Dietary intake was calculated using the software Dietist XP (version 3.2, Kost och Näringsdata, Bromma, Sweden), based on the Swedish Food Database 2010 and data from food manufacturers.

Physical activity
Physical activity level (PAL) was calculated as measured total energy expenditure divided by measured resting energy expenditure. Daily step counts were measured with a multi-sensor arm-worn accelerometer SenseWear Armband (SWA Pro2, BodyMedia, Inc., Pittsburgh, Pennsylvania, USA) during seven consecutive days. Step counts were analysed using InnerView Professional software 5.1.

4.2 The LEVA in Real Life trial

4.2.1 Subjects

Between 2011 and 2014, 110 women with a self-reported BMI of ≥27 kg/m^2 at 6-15 weeks postpartum were recruited through midwives and flyers at antenatal and child care clinics as well as via advertisements in shopping centres, web journals, social media sites and newspapers in Gothenburg and seven surrounding municipalities in Sweden. The BMI criterion of 27 kg/m^2 was used to allow women to reach the intervention weight-loss goal of 6 kg without over-treating normal-weight women. Exclusion criteria included serious disease in woman or child, participation in another weight trial and inability to assimilate written study material in Swedish. The study was approved by the regional ethical committee in Gothenburg and written informed consent was provided by all women.

4.2.2 Study design

The LEVA in Real Life trial was a two-arm randomized controlled trial with women attending the primary health care clinic for baseline measurements and group allocation at 6-15 weeks postpartum. Following baseline measurements, women were randomized to the diet behaviour modification treatment group or the control group through a simple randomization procedure using numbered and sealed envelopes generated through a random number table. Women were told they would be randomized to one of two groups involving different types of communication of dietary advice, either through a dietitian or a brochure, but they were not provided with details of the alternative group. Study measurements were conducted at baseline, at

intervention termination (indicated as 12 week) and 1 and 2 years after baseline, see Figure 3. All study measures and administration of diet intervention were completed by two dietitians at the primary health care clinics. Both study groups received routine postnatal care at the maternal health care clinics and were offered the treatment and material of the alternative study group and a cinema voucher upon completion of the 2-year follow-up. The primary outcome of the LEVA in Real Life trial was change in body weight.

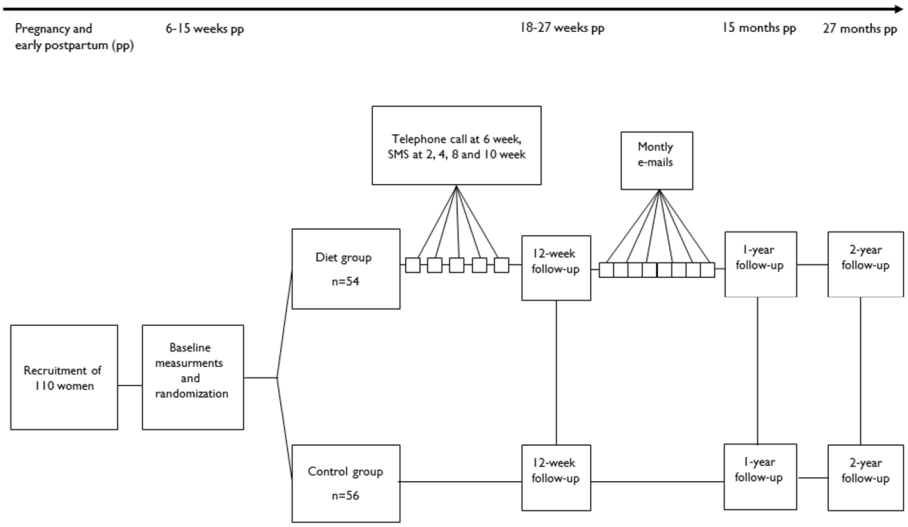

Figure 3. Study design of the LEVA in Real Life trial

4.2.3 Study groups

Diet group

Women randomized to the diet group were instructed to complete a diet record during four consecutive days following the baseline visit, preferably during three weekdays and one weekend day. Women were told to include method of preparation, brand names, fat percentages etc. and asked not to divert from their usual food choices or habits as their diet record would be used to construct the weight loss diet plan. Within 1-2 weeks of the baseline visit, women again met with the dietitian at the primary health care clinic for 1.5 hour of structured individual diet behaviour modification treatment. The diet treatment was adapted from the LEVA trial and aimed to achieve a weekly weight loss of 0.5 kg and a goal of 6 kg after 12 weeks through an

energy reduction of 500 kcal per day by implementing the four key dietary principles as described above and presented in Figure 2.

The diet plan was presented with the printed booklet from the LEVA trial, covering the key dietary principles and instructions to self-weight ≥3 times per week and to use body weight as a proxy for energy balance in order to adjust energy intake during the intervention. Strategies to manage barriers to change identified by the woman were established jointly between the woman and the dietitian and noted in the booklet during counselling. For example, such strategies could be to avoid keeping sweets and salty snacks at home to limit access to easily accessible energy-dense snacks or to prepare lunch boxes to avoid meal skipping while keeping busy with the baby. Finally, the booklet covered some general advice to increase physical activity with encouragements to set a specific exercise goal such as taking brisk walks with the stroller 4 days per week.

During the 12-week intervention period, women were contacted bi-weekly by the dietitian with standardized cell phone text messages to report current body weight. In addition, they were provided with personalized reinforcement and feedback on their progress. The text message after six weeks of intervention was replaced with a telephone call to allow for questions and more thorough feedback.

Control group

Women randomized to the control group received no diet treatment, text messages or telephone call but were given a brochure on healthy eating at the baseline visit. This group was intended to approximate a usual care condition; however, in concern that offering no treatment would limit participant motivation to complete the study, a brochure was given to women in the control group. The brochure included information on regular meal patterns, the plate model, selecting low-fat foods labelled with the green keyhole, reducing intake of energy-containing beverages and a recommendation to aim for a weight-loss rate of 0.5 kg per week.

Post intervention

During the 9 months following intervention termination, monthly e-mails were sent to women in the diet group to increase the likelihood of establishing sustainable lifestyle changes. The e-mails included information on the four key dietary principles, physical activity, how to deal with the return to work following maternity leave, and strategies for long-term weight-loss maintenance. Women were also asked to report their current body weight and provided with reinforcement and feedback by the dietitian through the e-

mail correspondence. Women in the control group did not receive any e-mails. No contact was provided to any of the groups between the 1- and 2-year follow-up.

4.2.4 Measurements

Anthropometry

Weight was measured to the nearest 0.1 kg and body fat was estimated with bioelectrical impedance using an electronic scale (Omron BF508, Hoofddorp, The Netherlands (140)), with the women wearing light clothing. Height was measured without shoes via a wall-mounted stadiometer to the nearest 0.1 cm at the baseline visit. Waist circumference was measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest. Hip circumference was measured around the widest portion of the buttocks. Pre-pregnancy BMI was calculated as self-reported pre-pregnancy weight divided by the square of measured height and gestational weight gain was obtained by self-report at baseline.

Dietary intake

An unannounced telephoned 24-h recall was performed with all women a few days prior to the study visits at baseline, 12 week and 1 year. First, the women were asked to recall all foods and beverages consumed from midnight to midnight the preceding day in an uninterrupted and free approach. This was followed by detailed and probing questions about each food and beverage including cooking methods, brand names, fat percentages etc. Participants were asked to specify type of ingredients and cooking method for mixed dishes and homemade recipes. Foods and beverages were quantified using weights and volumes, household measures or a booklet of 2-D photographs of different portion sizes of foods (Portionsguiden, Livsmedelsverket, Uppsala, Sweden), issued to the women before each study visit. Finally, a multi-item list with easily overlooked foods and beverages was reviewed to allow for addition of items not remembered up to this point. The interviews covered dietary intake during Monday through Thursday. Dietary intake was calculated using the software Dietist XP (version 3.2, Kost och Näringsdata, Bromma, Sweden), based on the Swedish Food Database 2010 and data from food manufacturers.

Physical activity

Step counts were measured during seven consecutive days prior to the study visits at baseline, 12 week and 1 year using a pedometer (Omron Walking Style Pro HJ-720IT-E2, Hoofddorp, The Netherlands (141)), sent to the women before each study visit. Women were instructed to wear the

pedometer at the hip, in a pocket or hanging from the neck using a key chain cord, from the time they woke-up until bedtime and not to divert from their usual physical activity. Step counts were analysed using the Omron Health Management Software (Version E1.012, Omron Healthcare Co., Ltd).

Additional questions
At the follow-up after 12 weeks and 1 year, women in both groups were asked if they considered their trial participation to have changed their lifestyle habits and if they had made any "structured or organized" dietary changes on their own during the trial duration (e.g. subscribed to a weight loss program, kept food record regularly or made substantial dietary alterations beyond the material and treatment received through their trial participation).

4.3 Data analysis

Statistical analyses were performed using SPSS version 20.0 or 21.0 (IBM, Somers, New York, USA). Statistical significance was considered at $p<0.05$. Student's t-test and Mann Whitney U-test were used to compare continuous variables between two groups and paired samples t-test and Wilcoxon's signed-rank test was used to evaluate changes within groups. Pearson Chi-square test and Fisher's exact test were used to compare categorical variables between groups. Values are presented as mean ± SD, median (1^{st}; 3^{rd} quartile) and proportions. To investigate the effect of the diet treatment on eating frequency (paper I) and food choices (paper II) in the LEVA trial, the four original study groups were merged into two groups: diet treatment groups (diet + diet and exercise, D-groups) and non-diet treatment groups (exercise + control, ND-groups).

Paper I
Diet records from the LEVA trial were used to assess eating frequency, defined as the mean number of intake occasions during the four registered days at baseline and 12 week. An intake occasion was defined as an energy intake of ≥50 kcal, including foods and/or beverages and separated in time from the preceding and following intake occasion by at least 30 min. When reported foods were not available in Dietist XP, data on energy content were obtained from each food manufacturer's website. When information regarding the amount or weight was missing, standard servings in Dietist XP were used.

Multivariable linear regression was used to examine associations among eating frequency, energy intake and weight at baseline as well as associations

among changes in these variables during the intervention. The following variables were evaluated as confounders: education, parity, age, PAL, energy cost of lactation, weight, energy intake and change in relevant variables between baseline and 12 week. A variable was included in the multivariate model if the regression coefficient varied more than 10% when the variable was added to the model. However, PAL was considered crucial to adjust for and was included in all regression models. Energy cost of lactation was calculated according to Butte et al by using the following estimations: a milk production of 749 g per day during exclusive breastfeeding, an energy density of milk of 0.67 kcal per g and an energetic efficiency of 0.80 (70). To account for the fact that some women were partially breastfeeding, information on infants' energy intake from complementary feeding, assessed by questionnaires at baseline and 12 week, were included (see below). For the variable eating frequency, one outlier was excluded from all regression models.

*Energy cost of lactation = (749 g per day * 0.67 kcal per g)/0.8 – infant energy intake from complementary feeding*

Paper II

Diet records from the LEVA trial were used to examine changes in food choice from baseline to 12 week and 1 year. Food items were manually categorized into seven major food groups, mainly on the basis of underlying hypotheses related to the key dietary principles; [1] sweets and salty snacks, [2] caloric drinks, [3] fruit, [4] vegetables, [5] potatoes/pasta/bread, [6] meat and meat products and [7] dairy. In addition, energy density of dairy products was assessed to evaluate the recommendation to substitute regular foods with low-fat and low-sugar alternatives. Energy intake and quantity consumed from each food group were expressed as mean intakes during the four registered days. Percent of total energy intake contributed by each food group was calculated as the food group energy intake divided by the total daily energy intake, E%. In addition, the proportion of women reaching an intake of 500 g fruit and vegetables per day was assessed. This recommendation includes fruits, berries, juice (maximum 100 g per day), dried fruits, root vegetables and legumes. However, in line with the key dietary principles, juice was categorized as a "caloric drink" in paper II.

Multivariable linear regression was used to examine differences in change in food choice between D-groups and ND-groups, with change in food choice as dependent variable (ranks were created for non-normally distributed variables) and group assignment (D- and ND-groups) as independent variable. All regression models were adjusted for baseline intake of the

dependent variable and an estimate of the energy intake underreporting at 12 week and 1 year. This estimate has been developed for a previous assessment of macro- and micronutrient intakes in the LEVA trial (142). The calculations of the estimate are based on a table-derived estimated mean energy requirement of 32.5 kcal/kg/day from a report of a joint FAO/WHO/UNU expert consultation on human energy requirements (based on a mean female age of ≥30 years, a mean weight of ≥85 kg and a PAL of 1.75) (143). This was thereafter corrected for energy cost of lactation (as described above) and changes in body tissue energy stores as measured by dual energy x-ray absorptiometry, assuming that the energy equivalents of fat and fat-free mass are 9403 kcal per kg and 883 kcal per kg, respectively (144). A validation against underreporting calculated using measured total energy expenditure at 12 week showed a correlation of 0.9 ($p<0.001$) (139). Below, an example of the calculation of energy intake underreporting at 12 week is provided.

1. Calculation of daily energy requirement at 12 week:

*32.5 kcal/kg/day * weight at 12 week (kg) + energy cost of lactation*

2. Estimation of total energy cost of changes in body tissue energy stores between baseline and 12 week:

Δ *Fat mass (kg) * 9403 kcal/kg* + Δ *Fat free mass (kg) * 883 kcal/kg*

3. Calculation of daily energy cost of changes in body tissue energy stores:

Energy cost from step [2] / number of days between baseline and 12 week

4. Calculation of estimated daily energy requirement at 12 week:

Daily energy requirement from step [1] – daily energy cost of body weight change from step [3]

5. Calculation of energy intake underreporting at 12 week:

Estimated daily energy requirement– reported energy intake

Paper III

In paper III, anthropometric outcomes and treatment-related measures at 12 week and 1 year in the LEVA in Real Life trial are presented. Power calculations showed that a sample size of 106 women would have 90% statistical power (α=0.05, two-sided test) to detect a difference in weight loss

of 3.0 kg at 1 year (-5.0±4.0 kg in diet group and -2.0±4.0 kg in control group, based on results from the LEVA trial and accounting for a more heterogeneous sample), allowing for 30% attrition.

Linear mixed models were used to identify statistically significant differences in outcome measures between the two study groups across the three time points. The models included group, time and group by time interaction as fixed factors, controlling for baseline value of the outcome and lactation status (defined as exclusive, i.e., human milk only as energy source, partial or none). Time was treated as the repeated factor and the covariance matrix was modelled as unstructured. The difference in proportion of women in the diet group and the control group at (±1 kg) or below their pre-pregnancy weight was tested using a Chi-square test and logistic regression models adjusted for differences in postpartum weight retention at baseline. Differences in postpartum weight retention between the two groups were analysed using multivariable linear regression models adjusted for the baseline value.

Data were analysed using two different models: completers only analysis and intention to treat analysis. In the intention to treat analysis, missing values were replaced with the group-specific 1st and 3rd quartile value, respectively, for that specific variable. Thus, two different models were performed to test anthropometric outcomes given that women lost to follow-up were either a group-specific "success" or "failure". This strategy was used as postpartum women have natural fluctuations in weight and because weight gain following initial weight loss is expected which would not have been captured by baseline, or last, observation carried forward. Women ≥12 weeks pregnant at a follow-up visit were excluded from the analyses.

Paper IV

In paper IV, outcomes at 2 year in the LEVA in Real Life trial were analysed using the same strategy and statistical method as described for paper III, i.e. completers only analysis and intention to treat analysis using linear mixed models. Linear regression was used to examine the relation between percent weight change at 12 week and 2 year. Postpartum weight difference was defined as measured weight at each study visit minus self-reported pre-pregnancy weight. Weight regain from 1-2 year was defined as >1 kg gain.

Women ≥12 weeks pregnant at a follow-up visit were excluded from that specific time point but included at remaining time points when data were available. Women with a subsequent child born since study entry were included throughout if the full pregnancy occurred between two succeeding study visits. A sensitivity analysis excluding all women with a new

pregnancy during the trial duration will be performed when data are complete.

5 RESULTS

As the 2-year data of the LEVA in Real Life trial were not complete by the printing of this thesis, the results presented on the 2-year outcomes in paper IV are preliminary.

5.1 Study population

Papers I and II
Among the 68 randomized women in the LEVA trial, 62 (91%) completed the 12-week follow-up and 57 (84%) remained to complete the 1-year follow-up. During the intervention, one woman was excluded due to pregnancy and one woman due to prescription of a metabolism-affecting drug while four women dropped out for other reasons. Between the 12-week and 1-year follow-up, five women were excluded because of new pregnancies and none dropped out. In papers I and II, one additional woman at 12 week and two additional women at 1 year were excluded due to missing diet records. Thus, 61 women (90%) completed the diet record at baseline and 12 week and 54 of these women (79%) also completed the diet record at 1 year. Women who dropped out or were excluded at 12 week had higher parity, higher BMI and breastfeed partially to a higher degree compared to women who remained in the trial.

Baseline characteristics of women in the LEVA trial are presented in Table 4. There were no statistically significant differences in baseline characteristics between D-groups and ND-groups.

Papers III and IV
Among the 110 randomized women in the LEVA in Real Life trial, 100 (91%), 93 (85%) and 76 (preliminary data, 69%) women remained to complete the follow-up after 12 weeks, 1 year and 2 years, respectively. During the intervention, ten women dropped out. Between the 12-week and 1-year follow-up, seven additional women dropped out. In addition, eight women reported a subsequent pregnancy at 1 year of which four women were ≥12 week gestation and thereby excluded. Between the 1- and 2-year follow-up, three women dropped out, one woman reported pregnancy >12 week gestation and seven women reported a full pregnancy and delivery between 1-2 year. Consequently, 100 (91%), 89 (81%) and 75 (preliminary data, 68%) women were included in the main analysis at 12 week, 1 year and 2 years, respectively. Women who dropped out during the intervention were younger, had higher pre-pregnancy and baseline BMI and were less educated than

women who remained in the trial. Women who dropped out or were excluded due to pregnancy ≥12 week gestation at 1 year had higher pre-pregnancy and baseline BMI and lower parity compared to women who remained in the trial.

Baseline characteristics of women in the LEVA in Real Life trial are presented in Table 4. There were no statistically significant differences in baseline weight or BMI between the two groups; however, there was a difference in height (168.0 vs 165.4 cm, p=0.022). Also, the diet group had higher postpartum weight retention at baseline compared to the control group (8.1 kg vs 5.2 kg, p=0.023).

Table 4. Baseline characteristics of women in the LEVA trial and the LEVA in Real Life trial.

Variable	**The LEVA trial (n=68)**	**The LEVA in Real Life trial (n=110)**
Age, years	33.1 ± 4.2	32.2 ± 4.6
Parity, n	1.0 (1.0; 2.0)	2.0 (1.0; 2.0)
Primiparous, % (n)	51.5 (35)	38.2 (42)
Education, % (n)		
Short education at high school	7.4 (5)	0.9 (1)
≤3 y beyond high school	19.1 (13)	39.1 (43)
≥3 y beyond high school	73.5 (50)	60.0 (66)
Lactation, % (n)		
None	0 (0)	16.4 (18)
Partial	7.5 (5)	26.4 (29)
Exclusive[a]	92.5 (62)	57.3 (63)
Pre-pregnancy BMI[b], kg/m^2	28.4 (27.1; 30.8)	28.4 (26.0; 32.4)
<25.0, % (n)	1.5 (1)	11.8 (13)
25.0-29.9, % (n)	67.6 (46)	51.8 (57)
≥30.0, % (n)	30.9 (21)	36.4 (40)
Baseline BMI, kg/m^2	30.0 (27.8; 32.5)	31.0 (28.8; 33.6)
25.0-29.9, % (n)	50.0 (34)	39.1 (43)
≥30.0, % (n)	50.0 (34)	60.9 (67)
Weight, kg	86.9 (79.9; 92.7)	86.7 (79.5; 94.9)
Height, cm	168.8 ± 6.0	166.7 ± 6.0
Waist circumference, cm	95.0 (90.0; 101.3)	94.8 (89.9; 105.0)
Postpartum weight retention[c], kg	3.5 ± 5.5	6.6 ± 6.8
Energy intake[d], kcal/day	2644 ± 805	2250 ± 805
Step count[e], steps/day	8343 (7162; 10810)	6845 (5396; 8568)

Values are presented as mean ± SD, median (1st; 3rd quartile) and proportions (%). [a]Defined as human milk only as energy source. [b]Based on self-reported pre-pregnancy weight and measured height. [c]Defined as the difference between baseline and pre-pregnancy weight. [d]Assessed by 4-day diet records during weekdays and weekend days in the LEVA trial and by 24-h recalls during weekdays in the LEVA in Real Life trial [e]Assessed by 7-day Sensewear data in the LEVA trial and by 7-day pedometer data in the LEVA in Real Life trial.

5.2 Eating frequency in the LEVA trial

Eating frequency at baseline

Women in the LEVA trial had a mean eating frequency of 5.9±1.2 intake occasions per day at baseline, with the mean eating frequency ranging from 4 to 10 intake occasions, see Figure 4. Eating frequency was significantly higher during Monday-Friday compared to during Saturday-Sunday (6.0±1.4 vs 5.5±1.5 intake occasions per day, p=0.011).

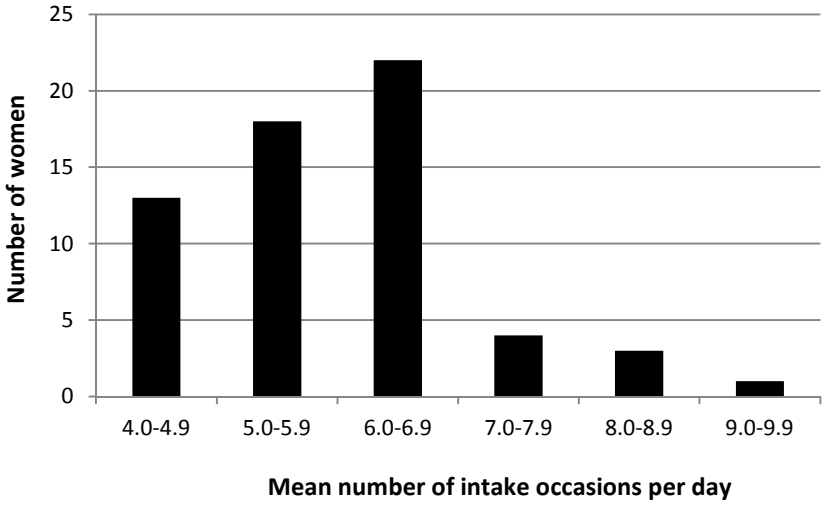

Figure 4. Eating frequency at baseline among women in the LEVA trial, n=61.

Changes in eating frequency during the intervention

During the intervention, eating frequency was reduced in both D-groups and ND-groups ($p<0.05$). However, women in D-groups reduced their eating frequency more than did women in ND-groups (-1.0 vs -0.5 intake occasion per day, p=0.001). As previously reported by Bertz et al (1), energy intake was also more reduced in D-groups than in ND-groups during the intervention (-661±463 vs -324±395 kcal per day, $p<0.001$).

Associations between eating frequency, energy intake and body weight

At baseline, a positive association was observed between eating frequency and energy intake ($p<0.001$, $R^2=42.6\%$), with an increase in daily energy intake of 307±46 kcal with each additional intake occasion, see Figure 5. However, no association was observed between eating frequency and body weight at baseline (p=0.187, $R^2=1.3\%$), although the association approached

statistical significance after adjustment for PAL and age at baseline (p=0.063, R^2=9.1%).

During the intervention, a positive association was found between change in eating frequency and change in energy intake in the crude model (β=212±64 kcal per day, p=0.002). The association was somewhat attenuated after adjustment for change in PAL and group assignment, such that daily energy intake was reduced by 169±69 kcal with each decrease in intake occasion (p=0.017). Furthermore, a positive association was found between change in eating frequency and change in body weight in the crude model (β=2.0±0.7 kg, p=0.003); however, the association became non-significant after adjustment for change in PAL, eating frequency at baseline and group assignment (β=0.9±0.7 kg, p=0.179).

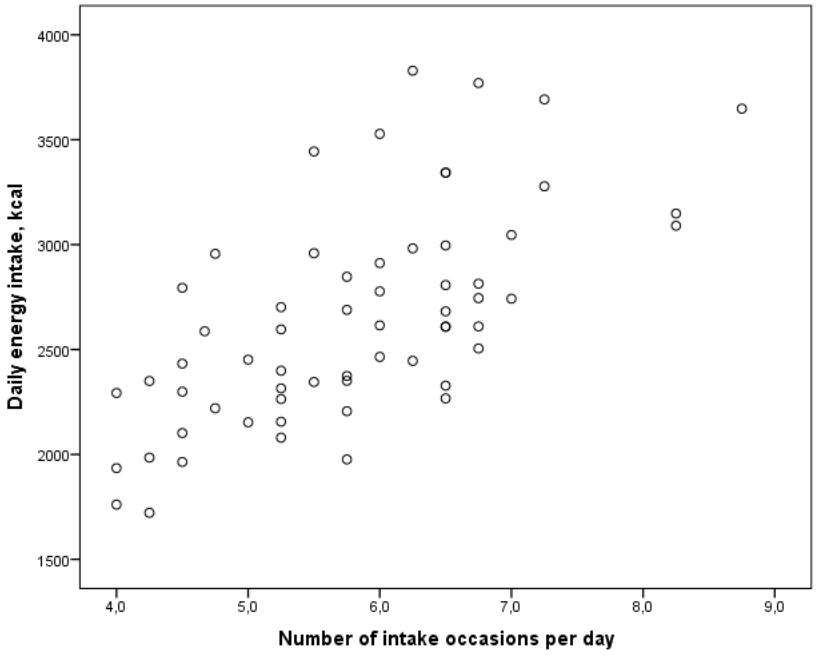

Figure 5. Association between eating frequency and daily energy intake at baseline among women in the LEVA trial (crude model), n=60.

5.3 Food choice in the LEVA trial

Food choice at baseline

At baseline, the food groups contributing the most to daily energy intake was sweets and salty snacks (21 E%) and potatoes, pasta and bread (19 E%). The women reported a mean intake of sweets and salty snacks of 153 g per day and a median intake of caloric drinks of 62 g per day at baseline. The mean intake of fruit and vegetables was 338 g per day, of which 174 g was fruit and 164 g was vegetables. The median intake of juice was 11 g per day. One in five women reached the recommended intake of 500 g fruit and vegetables per day at baseline.

Food choice at 12 week and changes in food choice between baseline and 12 week

At 12 week, sweets and salty snacks contributed 11 E% in D-groups and 21 E% in ND-groups ($p=0.001$). Women in D-groups had a mean daily intake of fruit and vegetables of 473 g while the corresponding intake was 320 g in ND-groups ($p=0.011$). The intake of fruit was 193 g and 173 g per day, and the intake of vegetables was 280 g and 147 g per day, in the two groups, respectively. More women in D-groups than in ND-groups reached the recommended daily intake of 500 g fruit and vegetables at 12 week (45% vs 17%, $p=0.016$). During the intervention, D-groups reduced their E% from sweets and salty snacks ($p<0.001$) and caloric drinks ($p=0.001$), and increased their E% from vegetables ($p<0.001$), more than did ND-groups. Also, the energy density of dairy products decreased more in D-groups than in ND-groups ($p=0.016$).

Food choice at 1 year and changes in food choice between baseline and 1 year

At 1 year, sweets and salty snacks contributed 14 E% and 18 E% in D- and ND-groups, respectively ($p=0.146$). Women in D-groups reported an intake of fruit and vegetables of 355 g per day while the corresponding intake was 293 g in ND-groups ($p=0.139$). The daily intake of fruit was 164 g and 159 g, and the daily intake of vegetables was 191 g and 134 g, in the two groups, respectively. At 1 year, 19% in D-groups and 7% in ND-groups consumed 500 g fruit and vegetables per day ($p=0.420$). Compared to baseline, women in D-groups reported a greater increase in E% from vegetables at 1 year than did ND-groups ($p=0.002$).

Figures 6 and 7 display changes in energy intake and quantity related to the changes in food choice reported at 12 week and 1 year.

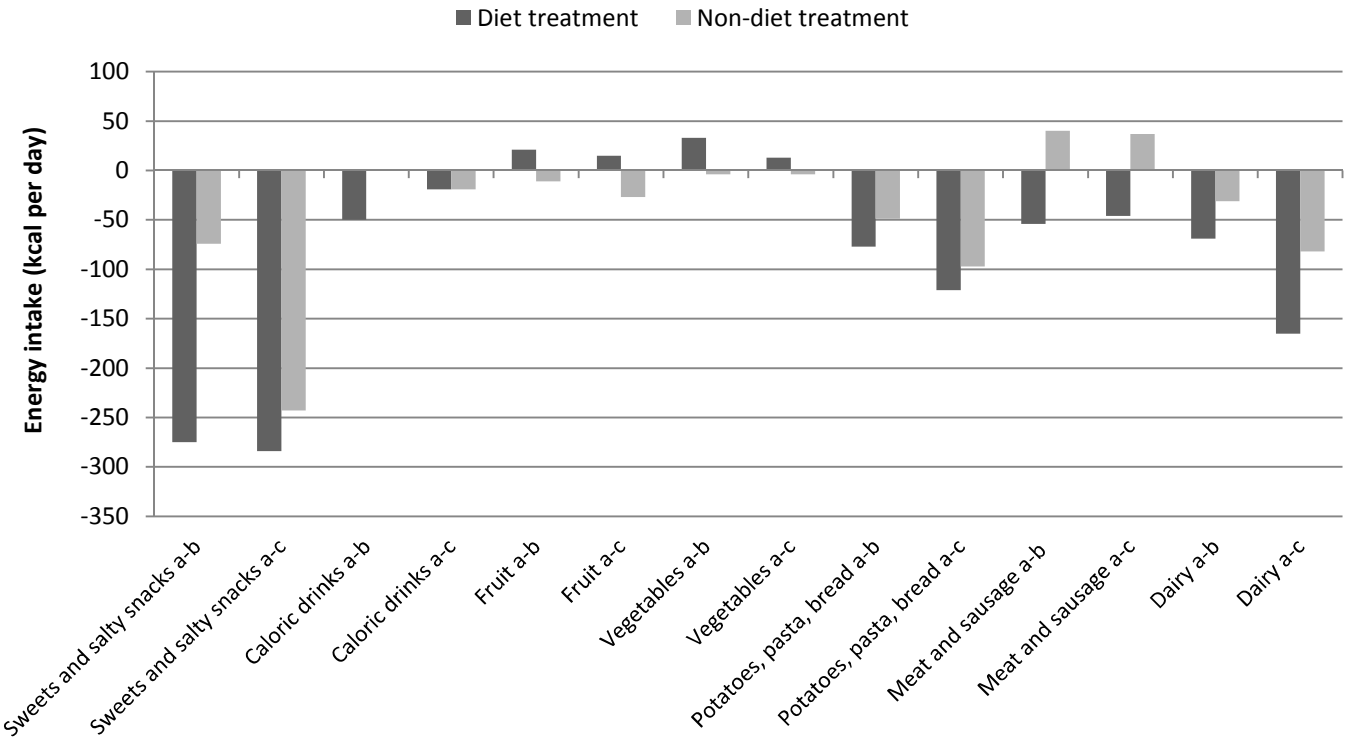

Figure 6. Changes in food choice (kcal per day) from baseline to 12 week (a-b) and 1 year (a-c) among women receiving diet treatment and women not receiving it in the LEVA trial, n=61 from a-b and n=54 from a-c. Median values are presented.

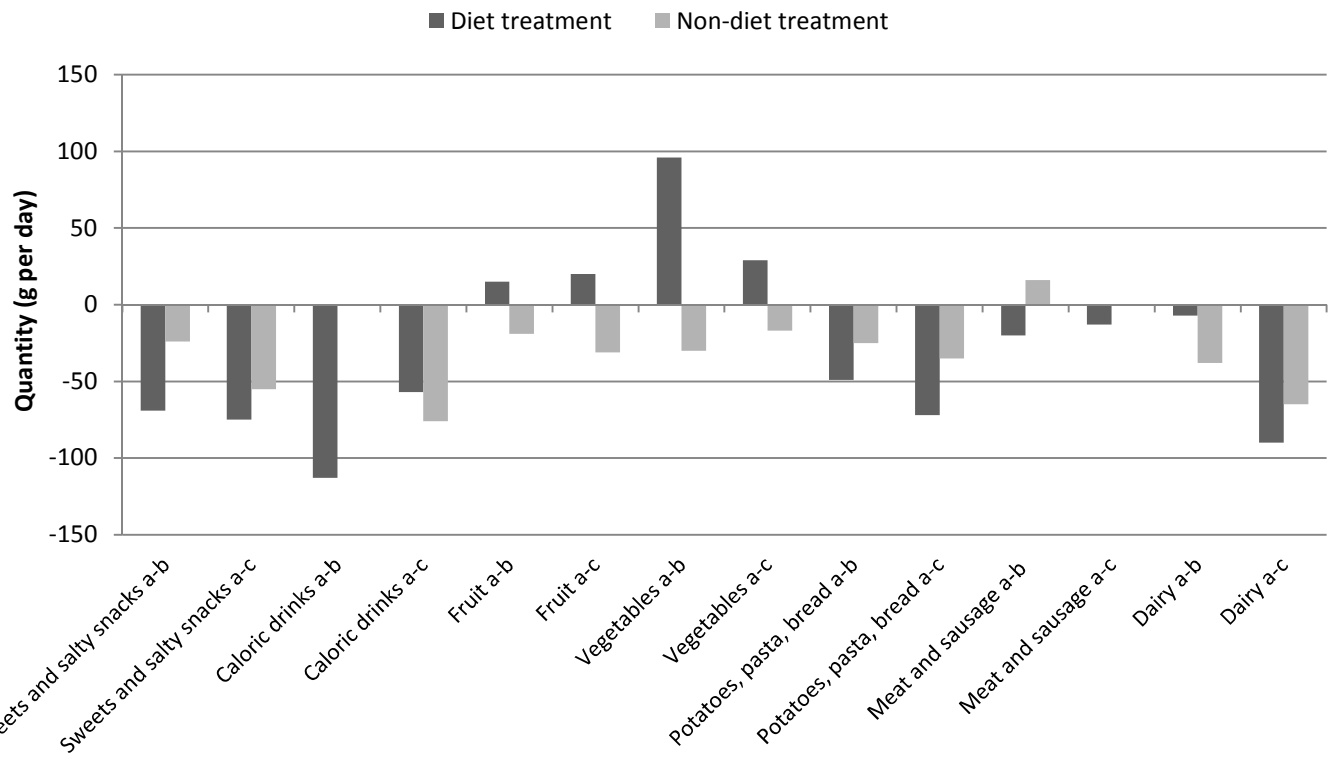

Figure 7. Changes in food choice (g per day) from baseline to 12 week (a-b) and 1 year (a-c) among women receiving diet treatment and women not receiving it in the LEVA trial, n=61 from a-b and n=54 from a-c. Median values are presented.

5.4 Effectiveness of the LEVA in Real Life trial

Anthropometric outcomes

There was a statistically significant main effect of time on weight in both the diet group and the control group at 12 week and 1 year ($p<0.001$), indicating that both groups lost weight. Furthermore, there was a statistically significant group by time interaction with the diet group achieving greater weight change at 12 week (-6.1 kg [-8.4; -3.2] vs -1.6 kg [-3.5; -0.4], $p<0.001$) and 1 year (-10.0 kg [-11.7; -5.9] vs -4.3 kg [-10.2; -1.0], $p=0.004$) compared to the control group. More women in the diet group than in the control group lost ≥5% of baseline weight by the 12-week follow-up (70% vs 23%, $p<0.001$) and ≥10% of baseline weight by the 1-year follow-up (59% vs 31%, $p=0.011$). The greater weight loss in the diet group was accompanied by larger reductions in BMI, waist circumference, hip circumference and body fat percentage compared to the control group at 12 week (all $p<0.01$) and 1 year (all $p<0.05$), see Figure 8 for BMI trajectories.

At baseline, the proportion of women with a BMI within the normal weight, overweight and obesity range was 0%, 41% and 59% in the diet group and 0%, 38% and 63% in the control group. The corresponding proportions at 12 week were 11%, 53% and 36% in the diet group and 2%, 47% and 51% in the control group. At 1 year, the proportions were 18%, 61% and 21% in the diet group and 16%, 52% and 32% in the control group. In Figure 9, weight trajectories among women with pre-pregnancy normal weight, overweight and obesity in the two groups are presented.

Lactation

At baseline, 82% in the diet group and 86% in the control group reported any breastfeeding. The corresponding proportions were 64% vs 72% at 12 week and 14% vs 9% at 1 year, respectively. As for exclusive breastfeeding, this was reported by 46% in the diet group and 68% in the control group at baseline. The proportions at 12 week were 0% vs 6%, respectively. No women practiced exclusive breastfeeding at 1 year.

In the diet group, weight change during the intervention was -6.8% in exclusively lactating, -5.8% in partially lactating and -10.5% in non-lactating women at baseline. Among exclusively lactating women, this corresponds to a weight loss of 6.1 kg and a mean weekly weight loss of 0.5 kg. Weight change at 1 year was -9.1% in exclusively lactating, -11.2% in partially lactating and -15.5% in non-lactating women in the diet group. In the control group, weight change during the intervention was -3.8%, -1.2% and -1.0% among women exclusively, partially and not lactating at baseline. The

corresponding weight change at 1 year was -7.2%, -4.7% and -5.2%, respectively.

Dietary intake

At baseline, women reported a weekday energy intake of 2250±805 kcal per day. The E% derived from fat, carbohydrates and protein was 34.8, 47.5 and 15.8, respectively. Moreover, the E% derived from saturated fats was 13.9 and the intake of fiber was 22 g per day.

In the diet group, there was a main effect of time on energy intake at 12 week ($p<0.001$), but not at 1 year ($p=0.072$). No main effect of time on energy intake was observed in the control group at any time point. Moreover, there was a statistically significant group by time interaction for energy intake at 12 week (-667 [-1176; -209] vs -180 [-543; +191] kcal per day, $p<0.001$), but not at 1 year (-630 [-1056; -150] vs -284 [-873; +278] kcal per day, $p=0.077$). As for macronutrients, the diet group reduced their E% of fat ($p=0.004$) and increased their E% of protein ($p<0.001$) more than did the control group at 12 week; however, only the increase in E% of protein remained at 1 year ($p=0.020$). Also, the diet group reduced their E% of saturated fat ($p=0.002$) and increased their intake of fiber ($p<0.001$) more than did the control group at 12 week, but not at 1 year ($p>0.05$).

Step count

At baseline, mean step count was 6878±1971 steps per day in the diet group and 7345±2864 steps per day in the control group. At 12 week and 1 year, step counts were 8008±2439 vs 6863±2676 and 7945±2098 vs 7742±2746 steps per day in the two groups, respectively.

In the diet group, there was a main effect of time on step count at 12 week ($p=0.037$), but not at 1 year ($p>0.05$). No main effect of time was observed in the control group. Furthermore, there was a statistically significant group by time interaction for step count at 12 week (+1187±2371 vs -542±2854 steps per day, $p=0.005$), but not at 1 year (+1053±2440 vs +394±2857 steps per day, $p=0.322$).

Additional questions

When women were asked if they considered the trial participation to have changed their lifestyle habits at 12 week, 98% in the diet group and 49% in the control group reported that it had. At 1 year, the corresponding proportions were 100% and 40%, respectively. Furthermore, when women were asked if they had made any “structured or organized” dietary changes (e.g. subscribed to a weight loss program, kept food record regularly or made

substantial dietary alterations beyond the treatment and material provided by trial) on their own at 12 week, 2% in the diet group and 11% in the control group reported that they had. At 1 year, the corresponding proportions were 7% and 27% in the two groups, respectively.

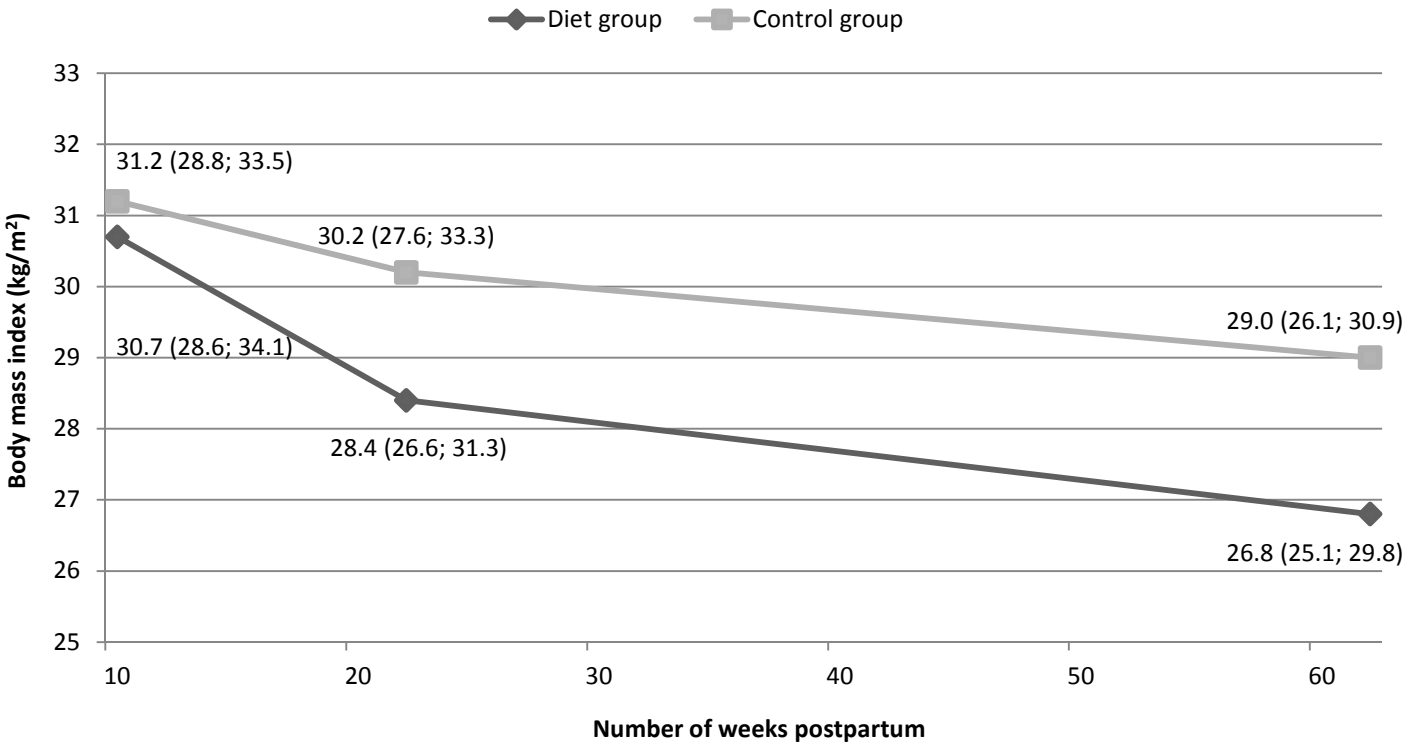

Figure 8. Body mass index at baseline, 12 week and 1 year among women randomized to the diet group and the control group in the LEVA in Real Life trial. N=110 at baseline, 100 at 12 week, and 89 at 1 year. Values are median (1st; 3rd quartile).

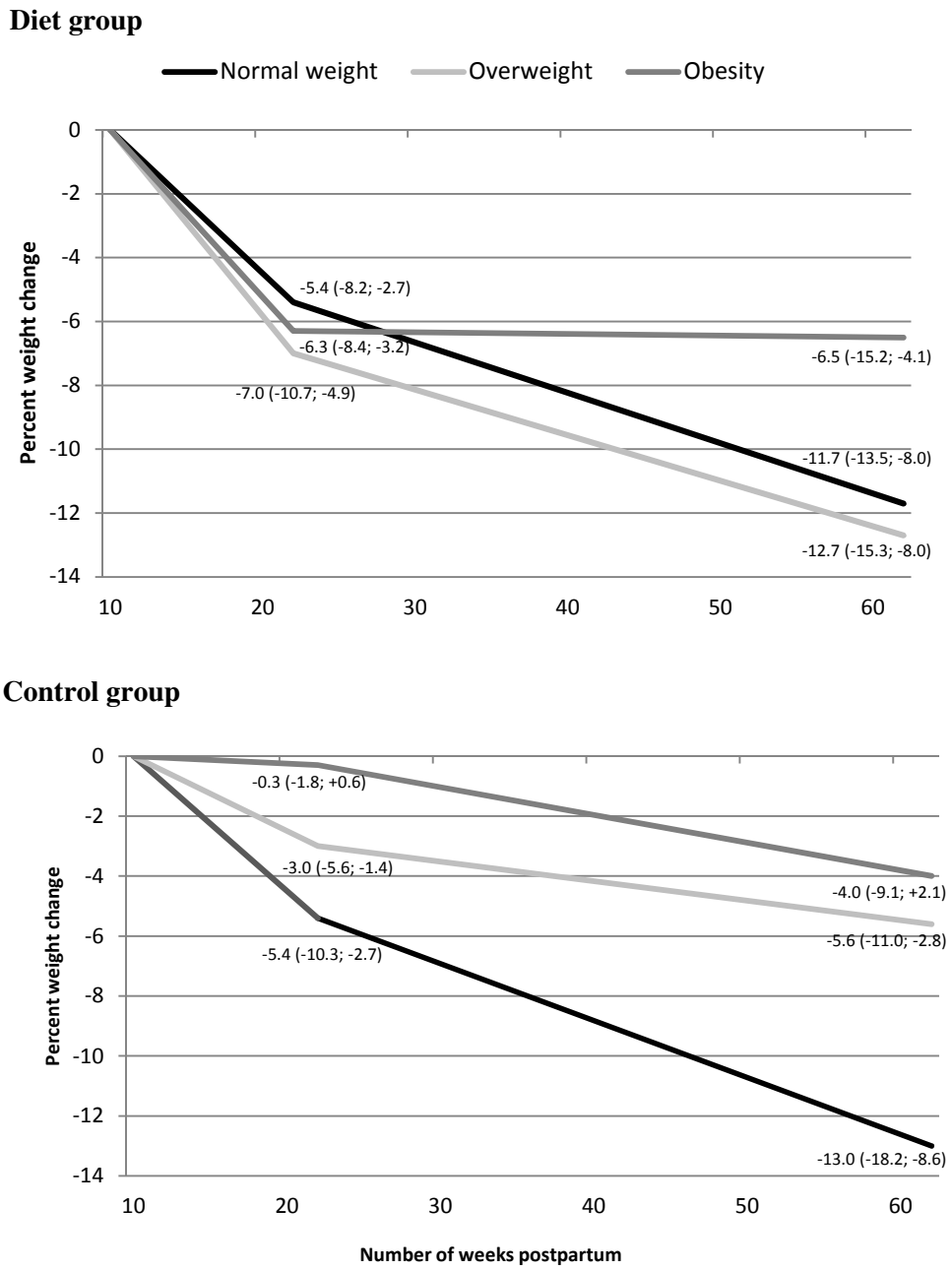

Figure 9. Weight trajectories among women with pre-pregnancy normal weight, overweight and obesity in the diet group (n=9, 27 and 18) and the control group (n=4, 30 and 22) in the LEVA in Real Life trial. Values are median (1st; 3rd quartile).

5.5 Two-year follow-up of the LEVA in Real Life trial

Anthropometric outcomes from 0-2 year
Median (1st; 3rd quartile) weight change at 2 year was -6.3 (-10.9; -1.7) kg in the diet group and -4.6 (-9.6; +0.9) kg in the control group. There was a main effect of time on weight, BMI, waist and hip circumference and percent body fat within both groups at 2 year (all $p<0.001$); however, no group by time interaction was observed for any variable (all $p>0.05$). Furthermore, the proportion of women at or below baseline weight (84% vs 76%, $p=0.399$) or meeting a weight loss of ≥5% (66% vs 51%, $p=0.245$) or ≥10% (40% vs 30%, $p=0.469$) of baseline weight did not differ between groups at 2 year, see Figure 10. The proportion of women with a BMI within the normal weight range at 2 year was 16% in the diet group and 11% in the control group.

When women with a full pregnancy and delivery between the 1- and 2-year follow-up were excluded (6 women in the diet group and 1 woman in the control group), weight change from 0-2 year was -7.6 (-11.0; -4.3) kg in the diet group and -4.9 (-9.8; +0.4) kg in the control group.

Weight change from 1-2 year
Mean±SD weight change from 1-2 year was +3.1±4.7 kg and +0.7±3.8 kg among all women in the diet and control group, respectively ($p=0.022$). Among women with weight loss at 1 year, 73% in the diet group and 57% in the control group were classified as weight regainers at 2 year ($p=0.199$). Furthermore, among women who lost ≥10% of baseline weight at 1 year, 58% and 73% maintained this loss at 2 year, respectively ($p=0.478$).

When women with a full pregnancy and delivery between the 1- and 2-year follow-up were excluded, weight change from 1-2 year was +2.6±4.6 kg and +0.6±3.8 kg in the two groups, respectively.

Association between percent weight change at 12 week and 2 year
Percent weight change at 12 week was positively associated with percent weight change at 2 year among all women in the LEVA in Real Life trial ($p<0.001$, $R^2=21.9\%$). The association remained after adjustment for new pregnancies during the trial duration ($p<0.001$, $R^2=23.9\%$). Also, the trend remained when the analysis was stratified by study group ($p=0.088$ in the diet group and $p<0.001$ in the control group).

Self-weighing frequency

At 2 year, 90% in the diet group and 81% in the control group reported use of body scale (p=0.341). The corresponding proportions were 98% and 85% at 12 week (p=0.034) and 96% and 81% at 1 year (p=0.052), respectively. Among women reporting use of a body scale at 2 year, there was no difference in proportion of women in the two groups reporting self-weighing at least weekly, 49% vs 41% (p=0.498). Furthermore, there was no difference in self-weighing frequency at 1 year between women who gained weight from 1-2 year and women who maintained or lost weight (p=0.233). However, there was a trend for a lower self-weighing frequency at 2 year among weight regainers compared to weight maintainers (0.3 times per week vs 0.5 times per week, p=0.066). Also, women who gained weight from 1-2 year reported larger decrease in self-weighing frequency between the 1- and 2-year follow-up compared to women who maintained or lost weight during this time period (-0.3 times per week vs 0.0 times per week, p=0.006).

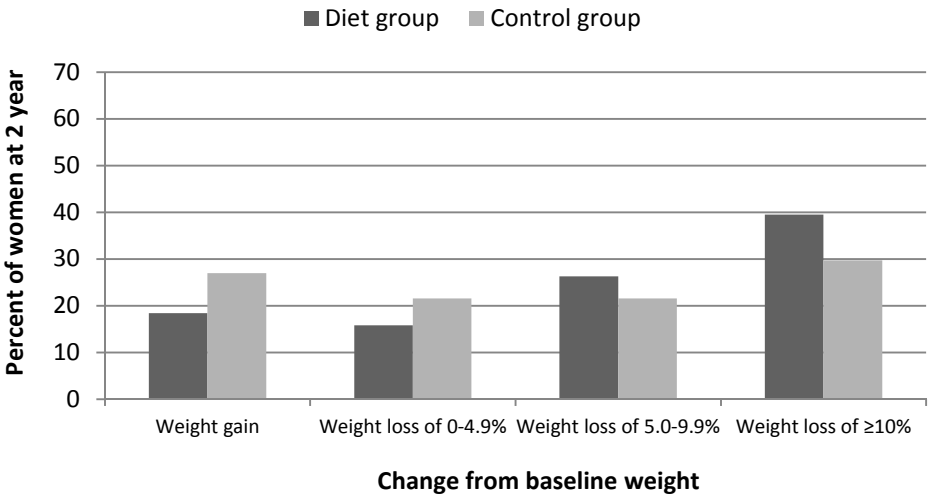

Figure 10. Percent weight change between baseline and 2 year among women in the diet group and the control group in the LEVA in Real Life trial. Preliminary data, n=75.

6 DISCUSSION

6.1 Results in relation to previous research

6.1.1 Paper I

In paper I, eating frequency in the LEVA trial was examined. At baseline, a mean daily eating frequency of 5.9 intake occasions was observed. Although eating frequency was not assessed in terms of meals and snacks, this suggests that women had an eating frequency above the recommended range for lactating women of three meals and one to two snacks provided by the National Food Agency (133). At 12 week, eating frequency was reduced to 4.7 and 5.7 intake occasions per day in D- and ND-groups, respectively. Interestingly, although the decrease in eating frequency in D-groups might be a consequence of the diet intervention, eating frequency in ND-groups was also reduced during the intervention, from 6.1 to 5.7 intake occasions per day. This may reflect an effect simply of taking part in a trial. Alternatively, this might indicate that women in early postpartum have a natural decrease in eating frequency over time, possibly due to changes in breastfeeding habits and related changes in energy requirements and diurnal rhythm. This speculation is supported by the findings from Durham et al, who found that exclusively breastfeeding women were more likely to consume snacks compared with partially, and non-, breastfeeding women (103).

Few studies have examined meal patterns during the postpartum period. In the Stockholm Pregnancy and Weight Development Study, meal pattern characteristics among 1423 Swedish women were examined using a trend method to identify predictors of postpartum weight retention among a number of pre-defined patterns of behaviour. The questions on meal pattern concerned self-perceived meal time regularity, frequency of main meals and self-perceived change in frequency of snacking. The only meal pattern factor related to postpartum weight retention at 1 year was increased frequency of snacking, from 0-2 snacks per day prior to pregnancy to ≥3 snacks per day postpartum (107). Moreover, in a longitudinal study among 163 pregnant Swedish women, 93-97% reported having three main meals (breakfast, lunch and dinner) daily during both pregnancy and postpartum. However, snack frequency was not assessed in this study (145). Finally, in an examination of eating habits among 321 Swedish women four years after pregnancy, 82% reported consuming breakfast, lunch and dinner, with or without 1-3 snacks, and 18% reported having irregular eating habits, defined as meal skipping or frequent snacking (146).

It has been suggested that high eating frequency may be a cause of obesity if frequent consumption of foods and energy-containing drinks lead to overconsumption of total energy intake (13, 147). This hypothesis is supported by findings demonstrating that snacks consumed ≥1 hour before a meal (148), or in a non-hungry state (149), do not elicit satiety and compensatory responses, or reduce appetite (150), at subsequent meals. On the contrary, some isocaloric experiments have suggested that dividing total energy intake into more frequent intake occasions could prolong satiety and decrease appetite at the following meal (151, 152). The cross-sectional results from paper I support the first hypothesis, demonstrating a positive association between eating frequency and daily energy intake at baseline. This is in agreement with several other studies (153-155). However, no significant association was found between eating frequency and body weight at baseline, although statistical significance was approached after adjustment for PAL and age. This is similar to the findings by Drummond et al who reported a positive association of eating frequency with energy intake, but not with BMI (156). The authors discuss that physical activity may be an important factor to adjust for as high levels of physical activity may promote high eating frequency to meet the increased energy requirement, without a concurrent increase in body weight. In support of an actual association between eating frequency and body size, a recent study among approximately 19 000 U.S adults found that eating frequency, meal frequency and snack frequency were all positively related with overweight and obesity after adjustment for underreporting of energy intake. Interestingly, when analyses were performed without adjustment for underreporting, all measures showed inverse or null association with body size. Just like in paper I, the authors only included intake occasions providing ≥50 kcal (157).

During the intervention, a positive association was found between change in eating frequency and change in energy intake; however, no association emerged between change in eating frequency and change in body weight after adjustment for confounders. Similarly, the association of snacking frequency with weight change was assessed in an ancillary study to a 12-month trial among 123 postmenopausal U.S women with overweight and obesity. In that study, no association was found between percent weight loss and snacking frequency at 12 months. However, a tendency for a positive association between snacking frequency and intake of fiber, fruit and vegetables was observed (158). Furthermore, in a trial by Bertéus Forslund et al, the effect of no snacks vs three snacks per day was examined on 1-year weight loss among 140 Swedish adults with obesity. After 1 year, energy intake and body weight had decreased in both groups; however, no between-group-differences emerged (159). Finally, Cameron et al examined if 3 meals+3 snacks could

produce greater weight loss than that obtained with only 3 meals under conditions of similar energy restriction. After 8 weeks of intervention, no difference in weight change or appetite between the groups was observed (160).

As displayed above, the relation of eating frequency with energy intake and weight is inconclusive. The conflicting results from previous cross-sectional, longitudinal and experimental studies are likely a consequence of the recurring methodological problems within the field, including a wide range of assessment methods used to examine meal patterns, heterogeneity in how meal patterns are defined and analysed and non-compliance in clinical trials (147, 161, 162). Furthermore, potential confounders such as physical activity, dietary restraint and misreporting of energy intake are not always adjusted for (13, 156). Finally, there may be effect inconsistencies across categories of age, gender, BMI and snack food choice (13, 163, 164).

6.1.2 Paper II

In paper II, food choices in the LEVA trial were examined. At baseline, a high intake of energy-dense and nutrient-poor foods, and a low intake of fruit and vegetables, was observed. In fact, only one in five women reached the recommended daily intake of 500 g fruit and vegetables at baseline. Still, this is comparable with data from the most recent national dietary survey among non-pregnant and non-lactating Swedish women, Riksmaten, where only 21% of women reached this recommendation (165). Among women aged 31-44 years in Riksmaten, daily intake of fruit and vegetable was 324 g, compared with 340 g in the LEVA trial. Furthermore, in the LEVA trial, sweets and salty snacks contributed with 21 E% and caloric drinks with an additional 2 E%. This is higher than the 15 E% contributed by sodas, candy, pastries, rolls and cookies in Riksmaten. For comparison, in Riksmaten, the proportion of women with overweight/obesity and high education was 42% and 47%, respectively. In the LEVA trial, the corresponding proportions were 100% and 74%, respectively.

Previous research has shown that the transition from pregnancy to postpartum may be associated with a negative influence on diet quality (104, 166). In a study by George et al, dietary intake during pregnancy and postpartum was examined among 149 U.S women. The authors found that, compared with pregnancy, intake of grains, fruit and vegetables all declined, while the E% from fat and added sugar increased, postpartum (167). Furthermore, Wennberg et al examined changes in food habits from pregnancy up to six months postpartum among 163 Swedish women. They found the reported

diet during pregnancy to be inadequate compared to the recommendations by the National Food Agency, with a tendency for an even poorer diet postpartum. The reduced diet quality was related to an increased intake of sweets, cakes, cookies, crisps, ice cream, and a decreased intake of fruit and vegetables (145). Thus, these results are in line with the baseline findings from paper II, demonstrating low diet quality among women with overweight and obesity in early postpartum.

During the intervention, women in D-groups reduced their E% from sweets, salty snacks and caloric drinks, and increased their E% from vegetables more than did ND-groups. At 1 year, only the greater increase in E% of vegetables remained between the two groups. Similarly, Lovelady et al examined changes in food choice among 48 postpartum U.S women randomized to a diet and exercise group or a control group at 4 weeks postpartum. After 10 weeks of intervention, women in the diet and exercise group had lost more weight, and reported consuming less fat, sweetened drinks, sweets and desserts and "snack foods", than did the control group (168). Likewise, Colleran et al randomized 27 U.S women to a diet and exercise group or a minimal care group at 4 weeks postpartum. After 16 weeks of intervention, the diet and exercise group had achieved more weight loss and reported greater increase in intake of whole fruit servings, and greater decrease in intake of saturated fat and E% from added sugar, than did the minimal care group (169). Finally, among 450 U.S women participating in the Active Mothers Postpartum trial, lower intake of "junk food", i.e. soda, sweetened drinks, chips and fast food, and higher intake of "healthy food", i.e. milk, fruit and vegetables, were found to predict weight loss from 6 weeks to 24 months postpartum (106).

The results from paper II also correspond to findings from the general population. For example, Hutchesson et al assessed food changes during a 12-week weight loss program among 268 Australian adults and found that successful weight losers reported greater reduction in E% of energy-dense, nutrient-poor foods and greater increase in E% of fruit and vegetables (170). Similarly, increased intake of fruit, vegetables and low-fat dairy, as part of an energy-reduced diet, has been associated with initial weight loss and subsequent weight loss maintenance among 828 U.S adults participating in the Weight Loss Maintenance trial (171). As for the effect of vegetable consumption on weight loss, this was assessed among 120 Australian adults with overweight in a trial examining two groups of energy restriction, differing only by doubling the portion sizes of vegetables. After 12 months, no between-group-difference in weight loss was observed; however, a

positive correlation was found between change in E% of vegetables and weight change (172).

6.1.3 Paper III

In paper III, the 12-week and 1-year outcomes of the LEVA in Real Life trial are presented. The results show that women randomized to the diet group achieved greater weight loss at both 12 week and 1 year than did women in the control group. Also, at 12 week, women in the diet group reported greater energy intake reduction and increase in step counts compared with the control group. However, no between-group-differences in change in energy intake or step counts were observed at 1 year.

In a Cochrane review from 2013 of randomized controlled postpartum trials, the effect of diet, exercise, or both, for weight loss in women after childbirth was examined (91). In total, 12 trials involving 910 women were included in the outcome analysis. The results show that both diet and combined diet and exercise interventions result in greater weight loss than that obtained with usual care; however, no effect was observed for exercise-only interventions. Also, no difference in the magnitude of weight loss between diet and combined diet and exercise interventions was found. Further, in a systematic review and meta-analysis from 2015, strategies for postpartum weight loss were examined (94). In total, 46 studies were included in the systematic review and 32 trials, including 1892 women, were eligible for meta-analysis. Most of the trials recruited women within the first 3 months postpartum and examined diet and exercise or exercise-only interventions. The meta-analysis showed that postpartum lifestyle interventions result in a mean body weight change of -2.3 kg (95% CI: -3.2, -1.4). The intervention duration ranged from 11 days to 36 months and the attrition rate ranged from 0-42%. Of the included trials, 18 provided the control group with usual care or instructions to maintain their usual diet or activity pattern, 4 provided a single lifestyle consultation or printed material at the baseline visit and 7 maintained contact beyond baseline via emails, phone calls or mailed material. In a sensitivity analysis excluding trials where the control group received some form of intervention, the effect size increased to -2.6 kg (95% CI: -3.5, -1.6). In sub-group analyses, trials including combined diet and exercise intervention, self-monitoring and an intervention duration of ≤6 months produced greater weight loss compared with trials including exercise-only interventions, no self-monitoring and an intervention duration of >6 months. However, no difference in weight loss was observed between individual or group setting, home-based or centre-based intervention delivery or the number of technology-based media used to provide support.

In the LEVA in Real Life trial, weight loss among women randomized to the diet group was 6.1 kg after 12 weeks and 10.0 kg after 1 year. This is in line with the LEVA trial, where women in D-groups had a weight loss of 7.6 kg after 12 weeks and 8.5 kg after 1 year (1). However, this amount of weight loss is greater than that observed in previous postpartum trials, where intervention groups have lost 0.9 kg (173), 1.6 kg (174), 1.9 kg (127), 2.3 kg (175), 3.1 kg (175), 4.8 kg (126), 5.8 kg (169), 7.3 kg (176), and 7.8 kg (177). Among women randomized to the control group, weight loss was 1.6 kg after 12 weeks and 4.3 kg after 1 year. This is somewhat higher than in the LEVA trial, where ND-groups achieved a weight loss of 1.5 kg after 12 weeks and 1.7 kg after 1 year (1). Also, this weight loss is greater than that reported in previous postpartum trials, where the control/minimal care groups have had weight changes of +0.2 kg (174), -0.2 kg (127), -0.36 kg (173), -0.8 kg (126), -1.3 kg (176), -1.6 kg (169), and -4.9 kg (177).

6.1.4 Paper IV

In paper IV, 2-year outcomes of the LEVA in Real Life trial are presented. To date, weight loss at the 2-year follow-up is 6.3 kg in the diet group and 4.6 kg in the control group. Also, so far, weight regain from 1-2 year is greater in the diet group than in the control group, such that the difference in weight loss observed between the two groups at 1 year is not maintained at 2 year.

As illustrated above, substantial weight regain occurred among women in the diet group from 1-2 year. Research has started to unravel the mechanisms that drive weight regain after substantial weight loss and it is now well known that powerful biological compensatory mechanisms hamper maintenance of lower weight after initial weight loss (178). Most importantly, total energy expenditure and activity-related energy expenditure decrease after weight loss, beyond that expected from losses of fat mass and fat-free mass, and these reductions persist during long-term maintenance of lower weight (178). Further, metabolic efficiency increase following weight loss and signals for appetite and satiety are altered to increase the rewarding value of food and to favour energy consumption (178). Thus, this creates optimal circumstances for weight regain. In addition to these biological mechanisms, weight regain is also believed to reflect a temporal decrease in adherence to the diet regime that initially produced weight loss. This is likely a major determinant of weight regain as studies show that adherence to a prescribed diet is a far stronger predictor of weight loss outcomes than is any diet itself (46).

Research demonstrates that weight loss maintenance interventions and extended care can improve long-term outcome after initial weight loss (179, 180). In a systematic review and meta-analysis of randomized controlled trials, behavioural interventions that focus on both diet and physical activity were found to produce a mean difference of 1.6 kg (95% CI: 2.3, 0.9) in weight regain compared with controls over a period of 12 months. If Orlistat was combined with the lifestyle intervention, the difference in weight regain increased to 1.8 kg (95% CI: 2.5, 1.1) (181). Although these effects were statistically significant, they suggest relatively small benefits. Also, results from the Weight Loss Maintenance trial suggest that the effect of continued intervention might be limited. In that trial, individuals randomized to monthly personal contact following weight loss regained less weight than did those in a self-directed group over 2.5 years (182); however, after an extended follow-up for an additional 2.5 years, the benefit of the personal contact found after 2.5 years was no longer observed after 5 years (183). Thus, long-term weight loss maintenance seems harder to achieve than initial weight loss and appears to be the greatest current challenge in obesity treatment.

The key components contributing to successful lifestyle intervention have not yet been confirmed. However, in postpartum women, trials including self-monitoring have been reported to produce weight loss three times that in trials without (94). Self-monitoring techniques utilized in previous trials include exercise logs, diaries, heart rate monitors and pedometers (94). In addition, self-weighing can be used (184). In an effectiveness trial aimed to prevent weight gain among women with young children, regular self-weighing was associated with weight loss (185). Also, self-weighing has been reported to prevent weight regain. Wing et al found that, among 314 U.S adults who had lost a mean of 19.3 kg in the past two years, daily self-weighing was associated with decreased risk of regaining ≥2.3kg over a period of 18 months (186). In the LEVA in Real Life trial, women randomized to the diet group were instructed to self-weigh at least three times per week in order to monitor weight loss and adjust energy intake according to their progress. Between the 1- and 2-year follow-up, a tendency towards a decreased self-weighing frequency was observed among women who regained weight as compared to women who did not. Although there is a risk of reverse causality, where decreased self-weighing could be a cause or a consequence of weight regain, these results suggest that self-weighting could be an important technique to promote weight loss maintenance following initial weight loss in postpartum women.

6.2 Methodological considerations

6.2.1 Study design and analysis

Papers I and II
In papers I and II, cross-sectional as well as longitudinal secondary analyses of the LEVA trial were performed. As cross-sectional analyses do not allow causal interference, only associations could be described between baseline variables in paper I. As for the longitudinal analyses, these are exploratory analyses from a trial powered to detect differences in anthropometric outcomes and should be interpreted thereafter. Consequently, the findings on dietary change from the LEVA trial need to be reviewed in the light of the dietary advice given.

In paper I, the observed association between change in eating frequency and change in energy intake during the intervention might have several explanations. Firstly, the association could be a result of a conscious decision among women to limit eating frequency in an attempt to reduce energy intake. As each additional intake occasion comprises a risk of overconsumption, restricting the daily number of intake occasions could have been applied as weight loss strategy by some women. Second, the association could be a result of women cutting back on energy-dense, nutrient-poor foods, which are often consumed in-between main meals (i.e. intakes that contribute to higher eating frequency). With this interpretation, changes in eating frequency would be a result of, or occurred concurrent with, changes in food choice and energy intake. In fact, both scenarios are plausible as dietary advice was given by the dietitian both to review the number of daily snacks consumed and to limit intake of sweets, caloric drinks etc. Thus, the direction of the association is difficult to extract. Nevertheless, in an attempt to interpret the associations found in paper I, the results were discussed from the perspective that changes in eating frequency occur prior to changes in energy intake and body weight as this stand point has been suggested by others (13, 147).

In paper II, the resemblance between the reported changes in food choice and the four key dietary principles suggest that the observed changes in intake of sweets, salty snacks, caloric drinks and vegetables in D-groups were most likely a consequence of the diet treatment. Still, these secondary analyses do not provide evidence of a cause-effect or dose-response relation between specific food groups and weight change. Also, they may lack power to detect all changes in food choice achieved. Furthermore, only descriptive data are presented for changes in energy intake and quantity in order to reduce the risk

of multiple statistical testing. Instead, statistical tests were performed on E%, which captures the overall energy contribution from each food group. Still, results on changes in energy intake and quantity are important complements to the results on E% to acquire the overall picture of the changes in food choice achieved.

Papers III and IV

Randomized controlled trials are considered the ideal study design to examine causal interference between treatment and outcome. Likewise, they provide strongest empirical evidence for assessing efficacy and effectiveness (187). However, there are some important differences in the setup of efficacy vs effectiveness trials. As for efficacy trials, they aim to evaluate treatments under ideal conditions in strict research settings. These trials strive for high internal validity, narrow inclusion criteria, high adherence, and optimal interventions (188). In contrast, effectiveness trials aim to evaluate treatments under usual circumstances in real world settings. These trials strive for high external validity and generalizability, broad inclusion criteria, variable adherence, and feasible interventions (188). As a consequence, the LEVA in Real Life trial was conducted at primary health care clinics, had limited exclusion criteria (e.g. no restriction on lactation, smoking, medicine use, upper BMI etc.), and replaced the home visit after six weeks of intervention from the LEVA trial with a telephone call in order not to interfere too much with the participants' daily life. Still, the progression from efficacy to effectiveness is often described as a continuum rather than a dichotomy as it is impossible to conduct a "pure" efficacy or effectiveness trial, irrespective of the aim and research design (188).

Despite the advantages of randomized controlled trials, they still comprise several limitations. For example, they are costly and time-consuming to conduct and can suffer from problems with non-compliance, ethical aspects and feasibility. In addition, attrition is a major concern, i.e. participants who drop out during the trial duration, causing incomplete data at one or several measurement points (187). Attrition often introduces several problems, including reduced statistical power and precision, potential loss of internal validity and challenges in analyzing the resulting incomplete dataset (189). In the LEVA in Real Life trial, the attrition rate was 9% at 12 week and 15% at 1 year. This is considerably lower than that reported in previous weight loss trials among the postpartum (91, 94), and the general (45, 190), population. Also, it is well below the 30% estimated at 1 year in our power calculations for the trial. This high estimate was used due to the nature of effectiveness studies, where broad inclusion criteria and varying adherence are expected to cause sample heterogeneity, broad confidence intervals and high rates of drop

out. However, despite the low attrition rate at 12 week and 1 year, women who did drop out were younger, had higher baseline BMI and were less educated than women who remained in the trial. Consequently, women remaining in the trial might not be representative of women who chose to discontinue. By the 2-year follow-up, so far, 21 women have dropped out and an additional 18 women have reported a new pregnancy during the trial duration. Hence, as drop outs reduce sample size, and the inclusion of women with new pregnancies produce greater variability in outcome data, the statistical power to detect a difference in weight between the two groups at 2 year was limited.

As attrition may undermine the scientific credibility of randomized controlled trials, careful handling of participants who drop out in statistical analyses is crucial to attain reliable results (187, 191). The preferred approach to handle missing data is to follow the intention to treat principle (192, 193). In such procedures, all randomized participants are analysed according to their assigned study group, regardless of subsequent withdrawal or deviation from the treatment protocol. Intention to treat analyses can be performed using various strategies for replacement of missing data. For example, baseline or last observation carried forward can be used. In such analyses, the baseline value or the last available measurement for each individual at the time point prior to withdrawal is retained in the analysis. However, as postpartum women have natural fluctuations in body weight, and weight regain is expected following initial weight loss, this method was not used for the LEVA in Real Life trial. Instead, missing values were replaced with the group-specific first (i.e., good outcome for that group) and third (i.e., poor outcome for that group) quartile values, respectively, to evaluate two different scenarios. Still, single-imputation methods have been criticized for not reflecting the true uncertainty and variability of the imputed value (193, 194). Also, the treatment effect derived from intention to treat analysis is generally considered conservative. Nevertheless, if the results from the completer only analysis are confirmed by the intention to treat approach, the conclusions of the trial are considered reinforced (193).

One of the core features of clinical trials is that all study groups are treated equally throughout the trial, except for the experimental treatment. In that way, potential differences in outcome between study groups can be related to the treatment. However, as drop out is a major concern, participants in control groups are often offered some form of “minimal care”, e.g. leaflets, access to websites, self-help materials or few sessions of advice to increase participant motivation to complete the trial (94). As a consequence, weight loss is often observed also among participants randomized to the control

group. In addition, repeated study visits and multiple weigh-ins throughout the trial duration might further motivate weight loss among both the intervention and control group. In a recent report, weight change among control groups receiving various level of minimal care was evaluated (195). The authors found weight losses of 1.0 kg after 3 months, 0.72 kg after 6 months, and 0.76 kg after 12 months, with a tendency for increased weight loss with each additional weight-in, and with increased care intensity. In the LEVA in Real Life trial, women in the control group only received a brochure on health eating at the baseline visit and thereafter attended three additional study visits. Still, questionnaires at 12 week and 1 year show that 49% and 40% of women in the control group, respectively, considered the trial participation to have changed their lifestyle habits. In addition, the questionnaires demonstrate that 25% and 27% of control women had made dietary changes on their own at 12 week and 1 year, respectively. Thus, this indicates that a substantial proportion of women in the control group did perceive the LEVA in Real Life trial as more than a usual care condition and that one in four women induced dietary changes on their own during the first year postpartum.

6.2.2 Study population

The LEVA and the LEVA in Real Life trials were designed to examine the effect of lifestyle intervention among 1) exclusively lactating women with pre-pregnancy overweight and obesity, and 2) women with overweight and obesity in early postpartum. As a consequence, the study populations observed through these two trials might not be fully representative of the general population of postpartum women in Sweden. Firstly, 74% and 60% of women in the two trials were highly educated (i.e. ≥3 years beyond high school), respectively. This is higher than the 36-37% highly educated women aged 25-44 years in the general population (196). This could have affected the results throughout the four papers as educational level has been positively associated with diet quality (166, 197), physical activity (7), prevalence and duration of lactation (70), and negatively associated with the risk of pre-pregnancy obesity and excessive gestational weight gain (59, 135). Still, high educational level is often observed among women in health research (198, 199). Second, 93% in the LEVA trial and 57% in the LEVA in Real Life trial reported exclusive breastfeeding at 6-15 weeks postpartum. In the general Swedish population, 66% and 53% of women report exclusive breastfeeding at two and four months postpartum, respectively (138). In the LEVA trial, breastfeeding was an inclusion criterion while in the LEVA in Real Life trial, no such criterion was applied, resulting in a more representative sample. Finally, the results observed in the two trials may only apply to women who

are motivated to lose weight and who have contemplated the lifestyle changes required to achieve weight loss after pregnancy.

In 2010, the prevalence of pre-pregnancy overweight and obesity in Västra Götaland was 31.5% (32.4% nationally), while the prevalence of pre-pregnancy obesity alone was 9.9% (10.2% nationally) (136). In the LEVA trial, pre-pregnancy BMI of 25-35 kg/m^2 was applied as an inclusion criterion and as a result, approximately 70% had overweight and 30% had obesity prior to pregnancy. In the LEVA in Real Life trial, no such criterion was applied; still, 52% and 36% reported pre-pregnancy overweight and obesity, respectively. Thus, women in both trials had substantially higher pre-pregnancy BMI compared to the general population. Only speculations can be made as to how this affected the results. In the LEVA in Real Life trial, a trend emerged in the control group for greater percent weight loss among women with pre-pregnancy normal weight compared with obesity (6.1% vs 1.2% after 12 weeks, and 13.3% vs 4.6% after 1 year). This could indicate that women who enter pregnancy with normal weight achieve greater, and/or faster, postpartum weight loss. This speculation is supported by results from Gunderson et al who examined differences in pattern of weight change after pregnancy across pre-pregnancy BMI groups. They found that early weight losses up to six weeks postpartum were similar for all BMI groups, but that late postpartum weight losses, defined as pre-pregnancy weight at next pregnancy minus weight at six weeks postpartum, were 4 kg higher in women with pre-pregnancy normal weight compared with obesity (116). However, considering that women with pre-pregnancy normal weight likely experienced substantial gestational weight gain prior to study entry, this amount of weight loss might not be enough for these women to return to pre-pregnancy weight. For the same reason, late postpartum weight retention might not differ by pre-pregnancy BMI group as heavier women usually gain less pregnancy weight (116). Nevertheless, as only four women in the control group entered pregnancy with normal weight, these results must be interpreted with caution.

6.2.3 Anthropometric data

In the LEVA and the LEVA in Real life trials, anthropometric outcomes were measured using standard procedures at the research clinic or at the primary health care clinics. However, pre-pregnancy weight was self-reported in both trials and is thus likely subject to reporting error (27). In the general population, body weight is usually underreported while height is overreported, resulting in an underestimation of the true BMI (200). Studies have shown that self-report underestimate true BMI by 0.2–0.3 units on

average (corresponding to 0.56-0.84 kg for a woman with a height of 168 cm) (27). Similarly, in a validation of 5033 women participating in the Danish National Birth Cohort, self-reported pre-pregnancy weight was on average 0.66 kg lower than that observed at the first antenatal care visit (201). Furthermore, Phelan et al used measured weights from clinical records from the year before pregnancy to validate self-reported pre-pregnancy weight among 401 U.S women participating in a pregnancy trial and found high correlation between the two variables (r=0.95) (202). Nevertheless, underreporting of body weight has been observed to increase with increasing pre-pregnancy BMI (201). In fact, underreporting of up to 5 kg has been observed among high BMI groups, as compared to 1 kg among lower BMI groups (26). This could have substantial impact on study results as underestimation of pre-pregnancy weight by 5 kg could overestimate gestational weight gain by 50%. Likewise, underestimation of 1 kilo could overestimate postpartum weight retention by 100% given the commonly observed mean weight retention of 0.5-3.0 kg at 6-18 months postpartum (26). Consequently, the prevalence of pre-pregnancy overweight and obesity in the LEVA and the LEVA in Real Life trials might be underestimated. Moreover, as pre-pregnancy weight is included in the calculations of postpartum weight retention, the true weight retention might be lower, and the proportion of women reaching pre-pregnancy weight higher, than reported, especially among high BMI groups.

In addition to the risk of systematic bias induced by the use of self-reported pre-pregnancy weight, small natural fluctuations in body weight (due to menstrual cycle, time of day, food and water intake, voiding, breastfeeding etc.) might have introduced random error in measurements as no strict protocol was applied for these factors (203). Nevertheless, comparisons of group means of weight loss should still be valid. Furthermore, in paper IV, weight loss maintenance was assessed. However, there is no consensus in the literature on the definition of weight maintenance to be used (203). In paper IV, a weight increase of >1 kg was used to define weight regainers between 1-2 year while the criterion of ±1 kg was used to defined return to pre-pregnancy weight. This criterion has previously been used in a weight loss trial among lactating women (126) and a similar cut-off (±0.9 kg) was recently applied in the Fit for Delivery trial, examining whether a behavioural intervention during pregnancy can prevent excessive gestational weight gain and reduce postpartum weight retention (202). Return to pre-pregnancy weight has also been defined as a postpartum weight retention of ≤0 kg (204), while others have not described the criteria used (173, 177). In the general population, Stevens et al have suggested that long-term weight maintenance of adults should be defined as a weight change of <3% to allow heavier

individuals to have greater fluctuations in weight (203). However, considering that most women retain 0.5-3.0 kg with each pregnancy (94), large cut-offs from pre-pregnancy weight could mask a true weight retention following pregnancy.

In the LEVA in Real Life trial, women less than 12 weeks pregnant at a follow-up visit were included in the analysis to preserve sample size. According to IOM, pregnancy-related weight gain during the first trimester is estimated to 0.5-2.0 kg (69). Walter et al recently estimated the rate of gestational weight gain across several maternal characteristics and found the overall weekly weight gain rate in the first trimester to be 0.22 kg (74). Interestingly, while sociodemographic variables were not associated with first-trimester weight gain, maternal behaviours such as smoking, pre-pregnancy diet and physical activity were (74). Thus, inclusion of first-trimester pregnant women in the analysis might have underestimated weight loss and overestimated postpartum weight retention depending on gestational week. Still, some women experience heavy nausea during the first trimester, which could cause initial weight loss. Also, as women became pregnant in both study groups and comparisons of outcome were mainly performed at the group level, the influence of this error is likely to be random and relatively small. In support of this notion, results from paper III were not altered in sensitivity analyses excluding all pregnant women at a follow-up visit.

6.2.4 Dietary assessment

In the LEVA trial, dietary intake was assessed prospectively using weighed diet records. In the absence of better techniques, and despite severe critic of all self-reported dietary data (205, 206), weighed diet record is considered the most precise dietary assessment method available for estimating usual food and nutrient intakes of individuals (207). The advantages of the method include provision of exact portion sizes, detailed information on foods and drinks consumed, and estimates for intake of energy, nutrients, foods and food groups. In addition, diet records can provide contextual information, including timing and location of meals and snacks, and sources of food and drinks (208). The limitations of the method include high respondent burden, expensive and time-consuming administration and difficulty in capturing foods eaten seldom due to large day-to-day variation in intake. In addition, individuals may change their diet and eating pattern during recording because of awareness that food intake is being measured, increased self-reflection, desire to simplify the reporting process and/or to comply with socially desirable norms (207, 208). Consequently, such data may not be reflective of usual dietary intake.

In the LEVA in Real Life trial, 24-h recalls were performed to assess dietary intake retrospectively. The recall interview can be performed in person, by telephone or via the internet. In a comparison of telephoned vs face-to-face interviews, no difference in dietary intake was found except for a higher E% of protein in the face-to-face group (209). The advantages of the method include a low cost and participant burden, and provision of detailed information on time of day, type, and portion size of each food and beverage consumed (207). Nevertheless, the quality of data depends on the respondent's memory, motivation, perception and conceptualization of portion sizes. To enhance memory and increase accuracy, trained personnel, check lists with commonly forgotten foods and drinks, a structured interview technique and photographs, household measures or food models may be used (207). Moreover, as with diet records, subjects may change their eating habits in pre-scheduled 24-h recalls. Finally, a single 24-h recall is not considered representative of usual diet of individuals due to day-to-day variation in dietary intake. However, multiple single-day recalls on different individuals can provide measures of intake at the group-level (207).

A final limitation applicable to all self-reported dietary assessment methods concerns the fact that self-reported dietary data are subject to misreporting of the types and amounts of food and drink consumed which can induce substantial systematic error (210, 211). Although some misreporting in prospective methods relates to undereating (as described above), most of the difference between self-reported energy intake and measured energy expenditure is related to underreporting (212, 213). In general, underreporting of dietary intake varies with the type of food consumed (214, 215) and is associated with female sex, lower education, lower income, smoking, irregular meal habits, dietary restraint and overweight and obesity (216-218). Below, the potential consequences of misreporting of dietary intake on the results in papers I-III are discussed.

Papers I and II

Considerable degree of energy underreporting has been reported using diet records, especially in populations with overweight and obesity (216). In a recent comparison between energy intake derived from diet records and total energy expenditure measured by the doubly labelled water method, 37% of women were found to be underreporters, with the mean magnitude of energy underreporting being 31% (218). Underreporting of energy intake has also been observed among women during reproduction. In a study among 260 pregnant Irish women, dietary intake was measured at 14 weeks gestation using 3-day diet records. The authors found that up to 45% of women may be

underreporters, with the main predictor of energy underreporting being BMI above 25 kg/m^2 (219).

Previous reports from the LEVA trial have shown that energy intake was underreported by approximately 20% at baseline (139). As eating frequency, and especially intake occasions consumed in-between-meals, is commonly underreported together with energy intake (220, 221), the actual number of intake occasions at baseline might be higher than reported in paper I. Furthermore, as energy underreporting is positively associated with BMI (216), this might have affected the association between eating frequency and body weight at baseline if women with high BMI underreported eating frequency to a higher degree than did women with lower BMI. In support of this notion, McCrory et al reported that, although many cross-sectional studies show an inverse relationship between eating frequency and adiposity, the association becomes positive when misreporting of energy intake is taken into account (222). As for the association between eating frequency and energy intake at baseline, misreporting could have 1) affected both variables if energy intake consumed in-between-meals was left out, or 2) affected energy intake only if underreporting was related to inaccurate reporting of portion size, without a concurrent effect on eating frequency. However, likely a combination of the two occurred. Furthermore, as energy underreporting at 12 week was smaller in D-groups than in ND-groups (139), the between-group-difference in change in eating frequency might be larger than reported. Also, the greater underreporting among ND-groups at 12 week may have attenuated the association between change in eating frequency and change in body weight if women who did not achieve weight loss underreported eating frequency to a greater extent than did women who lost weight (i.e. D-groups).

In paper II, diet records from the LEVA trial were used to examine food choice. Research has suggested that a dual bias may be present in self-reported dietary data, including both general underreporting of energy intake as well as food-specific, or selective, underreporting (214, 215, 223). For example, underreporters have been found to report less frequent consumption, and smaller quantities, of butter, French fries, sweets, desserts, snacks, sugary drinks, and higher intakes of vitamin C and fiber than do non-underreporters (215, 223, 224). Furthermore, Poppitt et al observed that intakes of total carbohydrates, added sugar and alcohol were especially prone to underreporting among women (220), and overreporting of protein has been associated with obesity (217). Thus, although an attempt was made to adjust for energy underreporting in paper II, selective misreporting of specific foods and drinks most likely remained. Furthermore, as energy underreporting was greater in ND-groups than in D-groups at 12 week, this likely reduced the

possibility to detect between-group-differences in change in food choice at 12 week. Likewise, as energy reduction was reported among ND-groups at 1 year without a concurrent reduction in weight (i.e. an indication of energy underreporting), the same problem may have biased the results at 1 year. Finally, as women in D-groups were instructed to change specific foods through the diet plan, there is a risk that such changes were reported, but not implemented, due to fear of negative evaluation. Still, concurrent measures of body weight and physical activity confirm that energy intake reduction was achieved, supporting the notion that changes in energy-dense food groups most likely did occur.

Paper III

As with diet records, 24-h recalls are also prone to misreporting, especially in populations with overweight and obesity. A recent evaluation of 24-h recalls among approximately 19 600 U.S. adults found the proportion of underreporters to be 25% based on the agreement between the ratio of energy intake to basal metabolic rate and a physical activity level of 1.55 (a sedentary lifestyle) (216). Furthermore, in a comparison between self-reported energy intake using 24-recalls and measured total energy expenditure using the doubly labelled water method, the proportion of underreporters was found to be 29%, with the mean magnitude of female energy underreporting being 40% (72% of participants had BMI of ≥25 kg/m^2) (218).

The reason for not choosing multiple 24-h recalls or 4-day diet records in the LEVA in Real Life trial, which would provide data also at the individual level, relates to the overarching aim of the trial, i.e. to evaluate effectiveness of the diet treatment under real life conditions where women are minimally disturbed and study measurements are kept limited and non-invasive. Thus, simple methods that yield accurate information on group-level were chosen (207). Further, the reason for only conducting weekday interviews relates to the expected logistical difficulties of performing interviews on a pre-specified weekday or weekend day throughout all three study visits. In order not to introduce more severe methodological problems, all 24-h recalls were performed during Tuesday-Friday, with the recognition that the results would be limited to weekday dietary changes only.

As for the energy underreporting in paper III, no solid method to estimate this, based on the available data, was identified due to several methodological limitations. Firstly, lactation increases energy requirements among postpartum women; therefore, energy cost of lactation should be included in the calculations. Using the Goldberg method (225), underreporters are

classified based on the agreement between the ratio of energy intake to basal metabolic rate and physical activity level. To include energy cost of lactation, this needs to be added to the basal metabolic rate, i.e., the denominator of the equation. However, such ratios would be difficult to interpret and compare with physical activity level. Second, to estimate energy cost of partial lactation, information on infants' energy intake from complementary feeding is needed. Unfortunately, such information was not collected with sufficient precision to be used for this purpose. If energy cost of lactation would be omitted, the calculations would have low sensitivity as exclusively and partially lactating women would be incorrectly classified as valid reporters. Third, comparison of FAO-table-derived estimated mean energy requirements (kcal/kg/day) and self-reported energy intake was considered. However, no detailed information on degree of lactation was collected to correct the calculations for energy cost of lactation. Also, as only weekday dietary intake was captured, such comparisons would be misleading. Finally, because only single-day recalls were performed, calculation of misreporting at the individual level was not possible.

Nevertheless, underreporting of energy intake most likely did occur as lactating women with overweight and obesity should have higher energy intake than the reported 2250 kcal per day if weight stable at approximately 87 kg. Still, the reported energy intake reduction in the two groups during the intervention (667 vs 180 kcal per day) corresponds fairly well to the weight loss achieved at 12 week (6.1 vs 1.6 kg), under the assumption that a daily energy reduction of 500 kcal from the daily energy needs results in a weekly weight loss of approximately 0.5 kg (226). In addition, the dietary changes observed in the diet group during the intervention, e.g. decreased E% of fat and increased fiber density, correspond to the message communicated through the four key dietary principles.

6.2.5 Physical activity assessment

In general, self-report of physical activity is overreported and the degree of overreporting has been positively associated with BMI and weight loss (227). However, in contrast to dietary assessment, assessment of physical activity has moved from use of subjective to objective methods through technological advancements in portable sensing devices such as pedometers and accelerometers (205).

In paper I, estimates of total energy expenditure and resting metabolic rate, measured by gold standard methods from the LEVA trial, were used to calculate PAL and adjust for physical activity in the regression models.

However, as doubly-labelled-water derived total energy expenditure includes the extra maternal energy cost of breast milk production, corresponding to approximately 150 kcal per day (70), calculations of PAL were likely somewhat overestimated. However, as the majority of women were lactating at both baseline and 12 week, differences in physical activity between women should still appear.

In paper III, step counts were used as measure of physical activity. The advantages of pedometers include provision of a low-cost measure of physical activity with low participant and researcher burden (141). Nevertheless, a limitation of pedometers is the inability to capture non-steps-producing physical activity such as weight lifting, swimming, horse riding etc. A further limitation is that they may induce behaviour change in response to readings if step counts are visible. As step counts were observable for the pedometers used in the LEVA in Real Life trial, women received feedback on their activity which might have led to non-representative measures of step counts during the data collection period. Finally, as general advice on physical activity was provided to women in the diet group in relation to their step counts at baseline, fear of negative evaluation could have led women in the diet group to increase physical activity in relation to usual activity during the data collection period.

7 CONCLUSIONS

In papers I and II, dietary changes associated with successful weight loss in the LEVA trial were examined. The results from paper I demonstrate a positive association between eating frequency and energy intake at baseline and that women who received diet treatment in the LEVA trial reduced their eating frequency more than did women not receiving it. During the intervention, a positive association was observed between change in eating frequency and change in energy intake. Although this finding did not translate into an association between eating frequency and body weight, the results from paper I suggest that lower, rather than higher, eating frequency might assist reduction of energy intake among postpartum women with overweight and obesity.

The results from paper II show that women in the LEVA trial had poor diet quality at baseline. This was mainly related to high intake of energy-dense, nutrient-poor foods and low intake of fruit and vegetables. During the intervention, women receiving diet treatment reduced their E% of sweets, salty snacks and caloric drinks, and increased their E% of vegetables, more than did women not receiving it. At the 1-year follow-up, only the difference in E% of vegetables remained. The findings from paper II suggest that changes in food choice in line with the current dietary recommendations can help postpartum women with overweight and obesity to achieve weight loss following pregnancy.

In papers III and IV, effectiveness of the diet treatment to produce postpartum weight loss in a primary health care setting was examined though the LEVA in Real Life trial. The results from paper III show that women randomized to the diet group achieved greater weight loss at 12 week and 1 year compared to women in the control group. In paper IV, the 2-year outcome of the LEVA in Real Life trial was examined. The preliminary results show that the diet group has had a greater weight regain between the 1- and 2-year follow-up compared with the control group such that the observed difference in weight loss between the two groups at 1 year is not maintained at 2 years. The combined results from papers III and IV provide evidence that a low-intensity diet treatment delivered by a dietitian within a primary health care setting can produce clinically relevant weight loss in postpartum women with overweight and obesity. However, the results also highlight the difficulty of maintaining weight lost during the first year postpartum.

8 FUTURE PERSPECTIVES

In Sweden, pregnant women are offered 7-10 antenatal visits to the midwife during pregnancy, with one follow-up visit approximately 6-8 weeks postpartum. By that time, the majority of women still weigh more than they did prior to conception. Thereafter, child health care services are responsible for providing follow-up and parental support regarding the health of the child. As a consequence, focus on the health and lifestyle of the postpartum woman is currently limited within the Swedish health care system.

The LEVA and the LEVA in Real Life trials now provide high-quality translational evidence of the efficacy and effectiveness of a diet treatment program to produce postpartum weight loss among women with overweight and obesity. Given the growing body of evidence demonstrating the clinical importance of interpregnancy weight change, increased focus on the lifestyle habits of postpartum women could have significant implication for subsequent pregnancies. Firstly, considering the difficulty in reaching women of reproductive age prior to conception, the postpartum period could be a unique opportunity for health care to impact on the pre-conceptional BMI of future pregnancies. Second, postpartum lifestyle interventions have the potential to provide spill-over effects on gestational weight gain in subsequent pregnancy and thereby increase the proportion of women gaining within the recommendations. Finally, the importance of postpartum women as a target group is further underlined by their influence on the lifestyle habits of the offspring; thus, targeting this group could increase the reach of health-promoting efforts. However, to attain these benefits, policy makers need to take action, mobilise resources, reform management of postpartum women and give priority to maternal lifestyle in the health care system.

In the long term, postpartum weight retention has been associated with development of overweight and obesity. Although no ideal time to return to pre-pregnancy weight has been established, current guidelines recommend women to attain this within the first year postpartum. The results from the LEVA and the LEVA in Real Life trials suggest that such weight loss can be achieved through diet treatment in line with current guidelines. However, as illustrated by the LEVA in Real Life trial, long-term maintenance of postpartum weight loss remains a challenge. Therefore, future studies should evaluate how maintenance of weight lost during the first year postpartum could be enhanced, and how weight gain among women (and men!) with young children could be prevented.

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