Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both (WOMB project): a protocol of the follow-up of a multicentre randomised controlled trial

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ABSTRACT

Introduction Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both (WOMB) project is the follow-up of the LIFEstyle study, a randomised controlled trial in obese infertile women, and investigates the effects of a preconception lifestyle intervention on later health of women (WOMB women) and their children (WOMB kids).

Methods and analysis Obese infertile women, aged between 18 and 39 years, were recruited in 23 Dutch fertility clinics between June 2009 and June 2012. The 284 women allocated to the intervention group received a 6-month structured lifestyle programme. The 280 women in the control group received infertility care as usual. 4 to 7 years after inclusion in the trial, all women (n=564) and children (n=305 singletons and age 3–5 years) will be approached to participate in this follow-up study (starting in 2015). The main focus of outcome will be cardiovascular health, but the dataset comprises a wide range of physical and mental health measures, diet and physical activity measures, child growth and development measures, biological samples and genetic and epigenetic information. The follow-up assessment consists of three stages that take place between 2016 and 2018, and includes (online) questionnaires, accelerometry and physical and behavioural measurements in a mobile research vehicle. A subsample of 100 women and 100 children are planned for cardiac ultrasound measurements.

Ethics and dissemination The protocol of this follow-up study is approved by the local medical ethics committee (University Medical Centre Groningen). Study findings of the WOMB project will be widely disseminated to the scientific community, healthcare professionals, policy makers, future parents and general public.

Trial registration number The original LIFEstyle study is registered at The Netherlands Trial Registry (number 1530).

INTRODUCTION

The overall aim of the Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both (WOMB) project is to examine the effects of a preconception lifestyle intervention on health in obese women (WOMB women) and their children (WOMB kids). It concerns a follow-up of the LIFEstyle study, a multicentre randomised controlled trial (RCT) (Netherlands Trial Registry number 1530), that was originally set up to investigate the effects and costs of a structured lifestyle programme in overweight and obese infertile couples to prevent unnecessary infertility treatment and improve reproductive outcome.1 Compared with prompt infertility treatment, the LIFEstyle intervention did not increase the healthy singleton live birth rate, although it did raise the chance of spontaneous conception.2 Furthermore, live birth rate was higher

Strengths and limitations of this study

- The main strength of the Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both project is the fact that it concerns the follow-up of a randomised controlled trial in which a structured lifestyle intervention was given preconceptionally.
- This study provides the opportunity to study the long-term health effects of the intervention on the mother and the prenatal programming effects on her child.
- Reasons to be cautious: attrition will lead to a reduction in power, and there may be selective attrition reducing the representativeness of the study sample.
- The LIFEstyle study women were included as patients with infertility problems which inevitably leads to limitations with respect to the generalisability of the findings to the obese female population in general.
in women who succeeded in losing weight. Currently, 4–7 years after the LIFEstyle study, we will investigate the effects of the intervention on women’s and offspring’s lifestyle and health, with specific focus on cardiovascular health.

Overweight and obese women have a higher risk of developing cardiovascular diseases (CVD) compared with normal weight women. They also have a higher chance of medical and obstetric complications during pregnancy, such as gestational hypertension, pre-eclampsia and gestational diabetes. The cardiovascular and metabolic health of women before and during pregnancy may influence the development of cardiovascular structure and function, and metabolic balance in the offspring, either mediated by increased risk of obstetric complications or by affecting placental and foetal growth and physiology. Through these pathways, obese women may transfer the obesity risk to their children by non-Mendelian, for example, epigenetic, mechanisms.

This intergenerational cycle of obesity and consequent susceptibility for non-communicable diseases (NCDs), including CVD, may be broken by improving the health of obese women before and during pregnancy, making a preconceptional lifestyle intervention the ideal window to improve the health of the current and subsequent generations. In general, women are especially receptive to advice about lifestyle before and during pregnancy and optimising their lifestyle for the benefit of their offspring’s health will be a powerful motivator. Therefore, lifestyle interventions before and during pregnancy may be more effective than lifestyle interventions at any other time during the lifespan. Optimising lifestyle of women before and during pregnancy may be an innovative way of improving cardiovascular health and preventing CVD both in women and in their offspring. The design of the LIFEstyle study creates a unique opportunity to investigate the long-term effects of preconception lifestyle advice to overweight and obese women.
The LIFEstyle study was performed within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology. The WOMB project will be carried out in a collaboration between the Academic Medical Centre (coordinating centre), the VU University Medical Centre, the University Medical Centre Groningen and Wageningen University and Research.

**METHODS AND ANALYSIS**

In the following section, we will adhere to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to the extent to which it is possible in a cohort profile. More details on handling of (quantitative) variables and statistical analyses will be provided in the papers describing the findings; the STROBE guidelines will be followed in papers resulting from this study.11

The WOMB cohort consists of women who participated in the LIFEstyle study (WOMB women) and their offspring (WOMB kids).

**Participants WOMB women**

Between June 2009 and June 2012, women were recruited for the LIFEstyle study at fertility clinics of six university medical centres and 17 general hospitals, spread over

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**Table 1** Baseline characteristics of eligible participants and participants lost to attrition for WOMB women, according to trial group*

| Characteristics† | Intervention group | Control group |
|-----------------|--------------------|---------------|
|                 | Eligible n=280     | Lost to attrition n=10 | Eligible n=284 | Lost to attrition n=3 |
| Characteristics of woman |                     |               |               |               |
| Age (years): mean±SD | 28.8±4.5           | 25.8±3.4      | 29.8±4.6      | 30.4±4.8      |
| Caucasian‡ | 249 (88.9) | 8 | 246 (86.6) | 1 |
| Education |                     |               |               |               |
| Primary school (4–12 years) | 16 (5.7) | 1 | 9 (3.2) | 1 |
| Secondary education | 67 (23.9) | 1 | 63 (22.2) | 1 |
| Intermediate vocational education | 129 (46.1) | 7 | 131 (46.1) | 0 |
| Higher vocational education and university | 55 (19.6) | 1 | 69 (24.3) | 1 |
| Unknown | 13 (4.6) | 0 | 12 (4.2) | 0 |
| Smoker | 72 (25.7) | 5 | 60 (21.1) | 0 |
| Nulliparous | 218 (77.9) | 9 | 215 (75.7) | 2 |
| Duration of time attempting to conceive (months): median (IQR) | 22.0 (14.0–36.0) | 26.5 | 19.0 (13.0–32.5) | 22.0 |
| BMI, median (IQR) | 36.0 (33.4–38.5) | 34.7 | 36.0 (33.5–38.2) | 39.8 |
| Characteristics of male partner |                     |               |               |               |
| Age (years), mean±SD | 33.6±6.1           | 31.1±4.7      | 33.6±6.2      | 36.7±9.8      |
| BMI, median (IQR) | 27.7 (24.5–31.0) | 26.4 | 27.2 (24.2–31.0) | 26.0 |
| Infertility diagnosis§ |                     |               |               |               |
| Female factor: anovulation | 123 (43.9) | 5 | 140 (49.3) | 1 |
| Female factor: other | 19 (6.8) | 10 | 22 (7.7) | 0 |
| Male factor | 65 (23.2) | 2 | 64 (22.5) | 0 |
| Unexplained | 84 (30.0) | 3 | 77 (27.1) | 2 |
| PCOS |                     |               |               |               |
| PCOS (Rotterdam criteria): number/total number (%)¶ | 93/123 (75.6) | 4/5 | 104/140 (74.3) | 0/1 |

Differences between the eligible intervention group and the eligible control group were compared with the use of Student’s t-test for means, Mann-Whitney U test for medians and χ² test or Fisher's exact test for proportions. There were no significant differences between the groups.

*Baseline is at randomisation for the LIFEstyle study.
†Number (%) unless otherwise specified.
‡Ethnic background was self-reported.
§Couples could have more than one diagnosis.
¶The denominator is the number of women with anovulatory infertility.

BMI, body mass index; PCOS, polycystic ovary syndrome; WOMB, Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both.
The Netherlands. Women, aged between 18 and 39 years, who presented with infertility and a body mass index (BMI) ≥29 kg/m² could be included in the study. Women were diagnosed with infertility because of chronic anovulation, oligomenorrhoea or amenorrhoea or, in case of a functioning ovulatory cycle, unsuccessful conception for at least 12 months. Exclusion criteria were severe endometriosis, premature ovarian insufficiency, endocrinopathy (e.g., diabetes type I and Cushing’s syndrome), the use of donor semen because of azoospermia and untreated preconceptional hypertension or hypertension-related complications in a previous pregnancy.

Of the 822 eligible women, 577 agreed to participate and were randomly assigned to the intervention or the control group after providing written informed consent. Three women withdrew informed consent later on and 10 women were lost to follow-up, leaving 280 women in the control group and 284 women in the intervention group (figure 1).

The 284 women allocated to the intervention group received a 6 months structured lifestyle programme aiming at 5%–10% loss of their original body weight. During this weight loss period, they did not receive infertility treatment. The programme was developed according to National Institutes of Health recommendations during a single centre pilot study. The participants were guided by trained coaches with a degree in nursing or dietetics. Women were stimulated to reduce energy intake by 600 kcal/day (with a minimum total intake of 1200 kcal/day), supported by an online diet diary. They were also encouraged to increase physical activity, aiming at 10 000 steps per day, monitored by a step counter, and at least 30 min of exercise of moderate intensity two or three times a week. Furthermore, the coaches provided individualised motivational counselling, directed at awareness of healthy lifestyle and formulating goals. The intervention was terminated earlier if women became pregnant. In case of a miscarriage, women could resume the intervention. To enhance compliance with the intervention, the infertility treatment was offered as soon as women had reached minimal 5% wt loss or a BMI <29 kg/m².

The 280 women in the control group received infertility treatment according to the Dutch infertility guidelines, irrespective of their BMI.

In total, 564 women will be eligible for the follow-up measurements of WOMB women.

**Participants WOMB kids**

The study population comprises all children of the 564 women eligible for follow-up who were conceived within 24 months after inclusion in the study. In total, 341 children were born of whom 7 children died antepartum, during or short after labour. After exclusion of the children from multiple pregnancies (n=29), 305 singletons will be eligible for WOMB kids (figure 2).
What has been measured in the LIFEstyle study?
In the LIFEstyle study, information was obtained about demographics, medical, gynaecological and obstetric history, anthropometry, blood pressure, preconception lifestyle, eating behaviour, infertility treatment, pregnancy outcome, quality of life and medical costs of the intervention. Blood samples were taken and weight was measured at 0, 3 and 6 months after entering the study. In the intervention group, step counters and dietary assessments were used during the 6 months of the intervention. The majority of these data was collected during the 6 months after inclusion in the study. Key measures are summarised in table 2.

WOMB project: planned follow-up assessments
In the WOMB project, data will be collected about present lifestyle, and mental and physical health, with a specific focus on cardiovascular health. An overview of all key measures is given in table 3 (WOMB women) and table 4 (WOMB kids).

The follow-up assessment consists of three stages (flowchart in figure 3) and comprises of (online) questionnaires (focusing on physical and mental health, diet, sleep of woman and child and growth and development of the child), accelerometry, physical measurements and collection of biospecimens (blood, faeces and buccal swab samples) as well as child behavioural observations. A subsample of 100 women and 100 children are planned for in depth cardiovascular measurements, including intima–media thickness and ultrasound assessment of cardiac function.

The physical measurements and observations are done in a mobile research vehicle in the vicinity of the participants’ homes to optimise participation and collect the data in a standardised situation.

Statistical methods and power analyses
Following the RCT design, we will examine the effect of the preconception lifestyle intervention on later lifestyle and health of the women and their offspring by means of intention-to-treat analyses. In addition, we will perform per-protocol analyses in which women who did not complete the intervention will be excluded. Finally, the registered variations in adherence to the prescribed lifestyle intervention will allow us to also perform exploratory dose–response analyses in which associations between measures of variation in diet (eg, fruit/vegetable intake, soft drink intake and snack intake) or physical activity (eg, weekly moderate to vigorous physical activity) will be linked to outcomes (blood pressure, glucose/lipid levels, weight, child development and health) in both short and long term for women and their children. Furthermore, we will investigate whether physical, psychological, socioeconomic or genetic characteristics contribute to the effectiveness of

Table 2 Measurements of LIFEstyle study

| Measures | Timing of assessment | Data type |
|----------|---------------------|-----------|
| Demographic variables (also of partner) | Age, ethnicity, education level and smoking status | 0 | Self-reported |
| General health | Medical history | 0 | Medical record |
| | Quality of life | 0 + 12 + 24 + 52 | Self-reported |
| Anthropometrics | Hip and waist circumference and weight | 0 + 12 + 24 | Physical examination |
| Cardiometabolic health | Blood pressure, glucose and insulin levels, lipid profile, inflammatory markers and hormone profile | 0 + 12 + 24 | Physical examination |
| Lifestyle | Eating behaviour | 0 | Self-reported |
| | Diet (frequency and portion sizes, kcal†) | 0 + 12 + 24 + 52 | Self-reported |
| | Physical activity | 0 + 12 + 24 + 52 | Self-reported and measured by pedometer† |
| Reproductive health | Previous pregnancies, anovulation, PCOS, infertility and gynaecological history | 0 | Self-reported and medical record |
| | Method of conception, infertility treatments and complications | 0-104 | Medical record |
| Pregnancy outcomes | Complications (gestational and postpartum maternal), foetal or neonatal outcomes and complications | 0–6 weeks after birth | Medical record |
| | Gestational weight gain | 0 through birth | Self-reported |
| Economic evaluation | Medical costs | 0–104 (or 6 weeks after birth in case of pregnancy) | Medical record |

*Number of weeks after inclusion, 0=baseline.
†Till 24 weeks in intervention group only.
PCOS, polycystic ovary syndrome.
the intervention, giving insight into potential gene–environment interactions, personality factors or susceptible socioeconomic groups and ultimately allowing us to refine and personalise future lifestyle intervention programmes to maximally target specific groups.

The main strength of the WOMB project is the fact that it concerns the follow-up of a RCT in which a structured lifestyle intervention was given preconceptionally. We will capitalise on the randomised design in which interference by other factors, like genetic variability and environmental characteristics, will be balanced between the intervention and the control arm. Inevitably, there will be loss to follow-up, since it is 4–7 years ago that the women were included in the LIFEstyle study. In general, attrition will lead to a reduction in power, and there may be selective attrition reducing the representativeness of the study sample.\textsuperscript{16} To control for selection bias, we will always report on the baseline characteristics of those who did and did not participate in

| Phase | Measures | Data type |
|-------|----------|-----------|
| 4–7 years after lifestyle intervention | Demographic variables | Information about current civil status, work and partner | Self-reported |
| | General health | Diseases/health problems, medication hospital admissions and quality of life | Self-reported |
| | Anthropometrics | Hip, waist and upper arm circumference, height and weight | Physical examination |
| | Body composition | Lean body mass, fat mass and total body water | Physical examination |
| | Cardio metabolic health | Blood pressure, heart rate, arterial stiffness, ECG, physical condition, glucose and insulin levels, lipid profile and inflammatory markers | Physical examination |
| | Reproductive health | Reproductive history, symptoms PCOS and sexual health | Self-reported |
| | Mental health | Anxiety and depression, personality, stress, sleep, traumatic life events and social support | Self-reported |
| | Lifestyle | Information about weight lost attempts last 4–7 years | Self-reported |

Table 3 Planned measurements of WOMB women

| Phase | Measures | Data type |
|-------|----------|-----------|
| Between birth and age 3–5 years | Growth | Height, weight and head circumference | Registration municipal youth healthcare visits |
| | General health | Diseases/health problems, medication and hospital admissions | Parent reported |

Age 3–5 years

| Phase | Measures | Data type |
|-------|----------|-----------|
| | Demographic variables | | Parent reported |
| | Anthropometrics | Hip, waist and upper arm circumference, height and weight. | Physical examination |
| | Body composition | Lean body mass, fat mass and total body water | Physical examination |
| | Cardiometabolic health | Blood pressure, heart rate, arterial stiffness, glucose and insulin levels, lipid profile and inflammatory markers | Physical examination |
| | General development | | Parent reported |
| | Cognitive and behavioural development | Executive functioning, psychosocial skills and problems, sleep pattern and eating behaviour | Parent reported |
| | Lifestyle | Diet | Observed in laboratory setting |
| | | Physical activity | Parent reported |

Table 4 Planned measurements of WOMB kids

PCOS, polycystic ovary syndrome; WOMB, Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both.
follow-up. The original study was not powered on long-term outcome of the women in advance, let alone the follow-up of their offspring, neither was it powered on cardiovascular outcomes. Therefore, we conducted power analyses with respect to the main outcome BMI, which can be considered a risk factor for later CVD. With respect to BMI, we need 90 women in each arm (31.9% of the total population) to detect a $0.5\, \text{kg/m}^2$ difference ($27.5\, \text{kg/m}^2$ vs $28\, \text{kg/m}^2$) with a power of 80% (alpha level of 5% and an SD of 1.2). For the children, the participation rate needs to be higher: 70.1% (214 children), to detect a comparable difference ($15.3\, \text{kg/m}^2$ vs $15.8\, \text{kg/m}^2$) with the same power (alpha level of 5% and an SD of 1.3). All in all, power to detect meaningful differences between the groups, especially with respect to secondary outcomes, will depend on the attrition levels. To increase power and generalisability, we are planning to pool data with other studies that use a comparable conceptual framework and an equivalent design and implementation (of which the Finnish RADIEL study is one).

**Ethics and dissemination**

**Ethics and safety considerations**

The study will be conducted according to the principles of the Declaration of Helsinki (revised version of October 2013) and in accordance with the Dutch Medical Research Involving Human Subjects Act.

For WOMB women and WOMB kids separate written informed consents will be obtained, as well as for each follow-up stage. The participants and/or parents will be asked to sign a separate consent form to store biological material in the biobank for up to 50 years. The data will be handled confidentially and analysed coded, in compliance with the Dutch Personal Data Protection Act.

The study imposes no risks on the participants. Taking a venous blood sample (women 40 mL and children 15 mL) can be a small discomfort for the participants, but is considered safe. In the informed consent, the participants/parents have the ability to choose to participate in the study without blood sampling.

**Dissemination**

The study findings of the WOMB project will be widely announced and reported to the scientific community, healthcare professionals, policy makers, future parents and general public. Dissemination is crucial in actually achieving the ultimate goal of WOMB project to prevent CVD in two generations by optimising lifestyle of women before and during pregnancy.

The project has a Dutch website mainly focused on participants and a scientifically orientated international website (http://womb-project.eu/). In 2015, we started a social media community on Facebook (http://www.facebook/hetwombproject), primarily directed to Dutch women in the reproductive age group, with the goal to maximally reach our target population at the time that results of the study will be known (2018/2019). This community is regularly fed by interesting news facts, short films about our project, blogs of our researchers and guest blogs of other stakeholders. We will also specifically focus on the dissemination of the study results among nutritionists, general practitioners, midwives and gynaecologists, who are in

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**Figure 3** Flowchart follow-up assessment of WOMB project. WOMB, Women, their Offspring and Improving lifestyle for Better cardiovascular health of both.
the position to advice (future) pregnant women about (pre)conceptional lifestyle.

CONCLUSION

The results of the present ongoing WOMB project, the follow-up of the LIFeStyle study, will show us if a preconception lifestyle intervention can have long-term health benefits for obese women and their children. The project will also provide more detailed information about the relationship between preconceptional diet and physical activity and later health: for the women, but also with respect to the prenatal programming effect on the conceived children. In general, this project will bring forth new knowledge on the prevention of obesity and our opportunities of breaking the intergenerational cycle of obesity and consequent susceptibility for NCDs, including CVD.

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Contributors

All authors have contributed to the design and development of the protocol. TJR is the chief investigator of this study. The coordination and drafting of the manuscript was done by OvdB. Critical revision of the manuscript was done by all authors, who also approved the final version.

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Competing interests

None declared.

Patient consent

Obtained.

Ethics approval

The study was approved by the Local Medical Ethics Committee (UMCG, Groningen, The Netherlands).

Provenance and peer review

Not commissioned; internally peer reviewed.

Data sharing statement

The WOMB project group is open to collaboration: in case of data requests, additional analyses or collaborative studies, please contact the WOMB project coordinator (TJR, roseboom@amc.uva.nl).

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