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ARTICLE

Preconception lifestyle intervention in women with obesity and echocardiographic indices of cardiovascular health in their children

Tamara den Harink[1,2]✉, Nico A. Blom[3], Reinoud J. B. J. Gemke[4], Henk Groen[5], Annemieke Hoek[6], Ben W. J. Mol[7], Rebecca C. Painter[8], Irene M. Kuipers[3], Tessa J. Roseboom[1,2,8] and Arend W. van Deutekom[1,9]

BACKGROUND: Improving maternal lifestyle before conception may prevent the adverse effects of maternal obesity on their children's future cardiovascular disease (CVD) risk. In the current study, we examined whether a preconception lifestyle intervention in women with obesity could alter echocardiographic indices of cardiovascular health in their children.
METHODS: Six years after a randomized controlled trial comparing the effects of a 6-month preconception lifestyle intervention in women with obesity and infertility prior to fertility care to prompt fertility care, 315 of the 341 children conceived within 24 months after randomization were eligible for this study. The intervention was aimed at weight loss (≥5% or until BMI < 29 kg/m^2). Children underwent echocardiographic assessment of cardiac structure and function, conducted by a single pediatric cardiologist, blinded to group allocation. Results were adjusted for multiple variables including body surface area, age, and sex in linear regression analyses.
RESULTS: Sixty children (32 girls, 53%) were included, mean age 6.5 years (SD 1.09). Twenty-four children (40%) were born to mothers in the intervention group. Children of mothers from the intervention group had a lower end-diastolic interventricular septum thickness (−0.88 Z-score, 95%CI −1.18 to −0.58), a lower left ventricle mass index (−8.56 g/m^2, 95%CI −13.09 to −4.03), and higher peak systolic and early diastolic annular velocity of the left ventricle (1.43 cm/s 95%CI 0.65 to 2.20 and 2.39 cm/s 95%CI 0.68 to 4.11, respectively) compared to children of mothers from the control group.
CONCLUSIONS: Children of women with obesity, who underwent a preconception lifestyle intervention, had improved cardiac structure and function; a thinner interventricular septum, lower left ventricle mass, and improved systolic and diastolic tissue Doppler velocities. Despite its high attrition rates, our study provides the first experimental human evidence suggesting that preconception lifestyle interventions may present a method of reducing CVD risk in the next generation.
CLINICAL TRIAL REGISTRATION: LIFEstyle study: Netherlands Trial Register: NTR1530 (https://www.trialregister.nl/trial/1461). This follow-up study was approved by the medical ethics committee of the University Medical Centre Groningen (METC code: 2008/284).

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INTRODUCTION

The prevalence of maternal obesity is rapidly rising worldwide, with some countries reporting half of all women entering pregnancy with overweight or obesity [1, 2]. Maternal obesity is associated with adverse perinatal outcomes and poorer health in children, including increased rates of obesity, stroke, type 2 diabetes, and cardiovascular disease (CVD) leading to premature cardiovascular mortality [3–5]. Therefore, maternal obesity is now considered an important risk factor for CVD in the offspring.

Detrimental changes to both structure and function of the developing fetal heart have been suggested to directly underpin the association between maternal obesity and offspring CVD in later life. In animal models, maternal obesity leads to left ventricular and septal hypertrophy, myocardial fibrosis and impaired left ventricular function in the offspring [6–8]. In humans, similar changes in cardiac structure and function have been described from as early as in utero: fetuses of mothers with obesity exhibited impaired diastolic function and myocardial dysfunction with reduced strain in utero [9, 10]. Neonates exposed to maternal obesity demonstrate impaired cardiac function, with increased interventricular septal thickness [11]. Several possible pathways through which maternal obesity could affect cardiac outcomes in offspring have been proposed, including impaired maternal glucose metabolism

[1]Department Epidemiology and Data Science, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands. [2]Amsterdam UMC, University of Amsterdam, Department(s), Amsterdam Reproduction & Development Research Institute, Amsterdam, the Netherlands. [3]Department of Pediatric Cardiology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands. [4]Department of Pediatrics, Emma Children's Hospital Amsterdam UMC, Amsterdam, Amsterdam, the Netherlands. [5]Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands. [6]Department of Obstetrics and Gynecology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands. [7]Department of Obstetrics and Gynecology, Monash University, Clayton, Victoria, Australia. [8]Department of Obstetrics and Gynecology, Amsterdam UMC, Amsterdam Reproduction and Development, University of Amsterdam, Amsterdam, the Netherlands. [9]Department of Pediatrics, Division of Paediatric Cardiology, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands. ✉email: t.denharink@amsterdamumc.nl

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[12, 13] and hypertensive disorders of pregnancy, which are more common in women with obesity [14].

Animal models have suggested that the effects of maternal obesity on offspring cardiac structure and function can be amended by lifestyle improvements during pregnancy [15]. Yet, in humans, none of the interventions aimed at weight loss, improving maternal diet or increasing exercise among pregnant women with obesity have been able to achieve beneficial effects on perinatal outcome, let alone on the long-term health of the offspring [11, 16]. It is conceivable that, given the gestational age at which these interventions were offered, many of the deleterious effects of maternal obesity had already been established. Therefore, the period before conception may present a better time frame to attempt weight loss and improve lifestyle [17]. In the current study we examined the effects of a preconception lifestyle intervention in women with obesity on cardiac structure and function in their 6 year old children as measured by echocardiography. We hypothesize that a preconception lifestyle intervention in women with obesity will enhance the cardiac structure and function in their children. In addition, we explore potential underlying mechanisms that might explain this association, including maternal characteristics before or during pregnancy such as nutritional intake, physical activity, biochemical markers such as glucose and insulin, and offspring characteristics including blood pressure and insulin resistance.

METHODS

Study population

This study is a follow-up of the LIFEstyle study: an open label randomized controlled trial including infertile women with obesity, allocating them in a 1:1 ratio to a preconception lifestyle intervention preceding fertility care as usual (intervention group) or prompt fertility care (control group), as described in detail in the published protocol [18]. The original LIFEstyle study included 577 women who conceived 341 children within 24 months after randomization. The study was set up to determine the effect of weight loss on conception rates and the primary outcome was a vaginal birth of a healthy singleton at term within 24 months after randomization. Briefly, the 6-month lifestyle intervention was aimed at achieving ≥5% weight loss or reducing BMI to <29 kg/m^2. The lifestyle intervention consisted of six outpatient visits and four telephone consultations during a 24-week period. Women with pregestational diabetes were excluded from participation. Despite improved lifestyle during the intervention, no effect was found on obstetric or perinatal outcomes, including pregnancy complications, gestational age at birth or birth weight were found [19]. However, there was a higher incidence of spontaneous pregnancies in the intervention group as compared with the control group (rate ratio 1.61, 95% CI 1.16–2.24) [19]. The 5 year follow-up outcomes in the women demonstrated that women who successfully lost weight in the intervention group had better cardiometabolic outcomes in terms smaller waist circumferences, lower weight, BMI, glucose and HbA1c, as well as higher HDL cholesterol concentrations [20].

After receiving written informed consent by the parents or legal guardians, we enrolled children born to participating women from the LIFEstyle study for pediatric echocardiography at one of the two participating academic hospitals in the Netherlands. Children were eligible if they had been conceived within 24 months after randomization in the LIFEstyle study, were known to be alive and had contact information available. In case of twins or triplets, only the first born was used in the analysis. Children born with congenital heart defects were excluded. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the medical ethics committee of the UMCG (METc code: 2008/284). This study was reported according to the CONSORT guidelines for reporting randomized trials.

Echocardiography and carotid intima-media thickness

Before echocardiography, weight (in kg) and length (in cm) were measured to the nearest decimal. Complete pediatric transthoracic echocardiograms were obtained in accordance with the prevailing medical professional protocols laid down by the American Society of Echocardiography and the European Society of Cardiology [21]. This protocol contains M-mode, 2D, tissue Doppler imaging and continuous- and pulse-wave Doppler echocardiography using subxiphoid, parasternal long and short axis, apical four chamber views and speckle tracking of the cardiac chambers. We used the Vivid E95 Ultrasound System (GE Healthcare, Australia). Three heart-cycle image loops were recorded. All examinations were performed by one pediatric cardiologist (AvD) blinded to group allocation. After the echocardiogram we assessed carotid intima media thickness (CIMT) using the Panasonic CardioHealth Station (Panasonic Healthcare Co., Ltd.). This is an ultrasonography device that allows automated measurement of the CIMT and was only available in one of the study centers. The child was in recumbent position and both right and left CIMT were assessed. Echocardiographic images were analyzed offline by the same pediatric cardiologist that performed the echocardiography's using commercial analysis software (EchoPAC, GE Vingmed).

Primary and secondary outcome variables

The primary echocardiographic outcome measures for this study are IVS at end-diastole thickness (IVSd) Z-scores [22] and LV mass index (LVMI) for the assessment of cardiac structure, longitudinal strain and ejection fraction (EF) for the assessment of systolic function, and Tissue Doppler E/E′ and mitral valve early diastole (e)/late diastole (a) ratio for diastolic function. To explore other potential effects we also assessed the effect of the intervention on other echocardiographic variables as secondary outcome variables. Each variable was measured three times, and the mean was calculated. For a total overview of the included echocardiographic variables, their method of assessment and their derived formulas, see Supplemental Table 1.

Covariates

CIMT Z-scores were calculated adjusted for age using reference values for children [23]. Body surface area (BSA) was calculated using the Mosteller formula [24]. Mode of conception was dichotomized in assisted reproductive techniques (ART) (consisting of in vitro fertilization and intracytoplasmic sperm injection including cryopreserved embryo–transfer cycles) and not-ART (including spontaneous conception, intra-uterine insemination and ovulation induction). Hypertensive disorders of pregnancy were defined by the classifications of the *International Society for the Study of Hypertension in Pregnancy* [25]. Maternal fasting glucose and 2-h after ingestion values during pregnancy were retrieved from oral glucose tolerance tests (OGTT). If no OGTT was performed, fasting glucose measurements were used. Only glucose measures between 16 and 32 weeks of gestation were included. Gestational diabetes was defined as a fasting glucose of ≥7.0 mmol/l or ≥7.8 mmol/l 2 h after ingestion of 75-g glucose during pregnancy, according the Dutch guidelines at the time the study was conducted and according to the WHO 1999 guidelines [26].

Maternal self-reported food frequency questionnaires were collected during the intervention. Last measured nutritional intake before conception was included for analyses since this measurement was significantly different between the control and intervention group in previous research from our group [27]. The nutritional variables included were: Sugary drinks (fruit juice and soda; glasses/day), intake of savory snacks (crisps, pretzels, nuts and peanuts; handful/week) and sweet snacks (biscuits, pieces of chocolate, candies or liquorices; portion/week). One portion of sweet snacks included two biscuits, two pieces of chocolate, five pieces of candy, or five pieces of liquorice. Maternal physical activity before pregnancy was also reported using the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) four times within the first year after randomization. The SQUASH is a validated questionnaire to rank subjects according to their level of physical activity [28].

Statistical analyses

To assess possible selection bias due to attrition, we compared maternal and neonatal baseline characteristics of our participants and non-participants to the original LIFEstyle study for women who conceived a child within 24 months after randomization. To assess the effect of the intervention on echocardiographic outcomes in children, we performed intention-to-treat analyses to compare echocardiographic outcomes between intervention and control group using independent sample *t*-tests, Mann-Whitney *U* test and Pearson Chi-Square for normally distributed continuous, non-normal continuous and binary variables, respectively. Variance between groups will be assessed using Levene's test. Primary echocardiographic outcomes that were significantly different between groups were analyzed in multivariable linear regression analyses. Model 1 corrected for BSA and model 2 additionally corrected for age and

sex. ART has been associated with several adverse cardiac outcomes in offspring [29], therefore model 3 additionally corrected for ART. Variables already indexed to BSA (such as left ventricle mass (LVM) index (LVMI) and IVSd Z-score) are displayed as univariable analyses in model 1. Results of the regression analyses are expressed with the coefficient and associated 95% confidence interval (CI). Measurements of all variables with a significance level of $p < 0.2$ in between-group comparisons were reassessed offline by a second blinded reviewer (TdH) using intraclass correlation coefficients (ICC) were calculated to examine the inter-individual variability of the measurements. ICC estimates and their 95% confident intervals were calculated based on a single-rater, absolute-agreement, 2-way mixed-effects model. ICC values less than 0.5 are indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.90 indicate excellent reliability [30]. Variables with an ICC < 0.5 were reassessed by a third independent blinded reviewer (IK). The analyses were performed using IBM SPS Statistics 26 (SPSS, Chicago, IL). A p value of <0.05 was statistically significant.

Explorative analyses

To assess potential underlying mechanisms of a beneficial effect of the preconception lifestyle intervention on the echocardiographic outcomes in the children, we performed several explorative analyses on those echocardiographic variables that differed significantly between intervention and control groups. First, we assessed whether there was a dose–response relationship between the amount of maternal weight loss and the effects on the offspring, by stratifying the outcome for maternal weight loss during the 6-month lifestyle intervention. If a women became pregnant within the first 6 months after randomization the last known weight before conception was taken. Preconception weight loss defined as weight loss between randomization and 6 months later and was categorized into three groups: (1) no weight loss, (2) 0–5 kg weight loss and (3) ≥5 kg weight loss. Both women in the control and intervention group lost weight, therefore we evaluated this dose–response relationship in both groups. Second, we conducted mediation analyses guided by Preacher and Hayes' bootstrapping method to explore potential underlying mechanisms [31]. We assessed the following potential mediators: i. Maternal glycaemia during pregnancy, ii. Maternal nutritional intake during the intervention, iii. Maternal physical activity before pregnancy, iv. Offspring's systolic blood pressure, v. Offspring's HOMA-IR levels. All mediation analyses were corrected for offspring´s sex, age and BSA.

RESULTS

Study population

315 children were eligible for our follow-up study (Fig. 1). Of these, 60 (19%) gave written informed consent. Their children were included for echocardiography, 24 children (40%) of whom were born to mothers in the intervention group. Mean age was 6.5 years, 32 (53%) of them were girls. The characteristics of children and their mothers participating in the present follow-up study were similar to eligible children and mothers who did not participate (Supplementary Table 2). Table 1 shows maternal, pregnancy and child characteristics in control and intervention group of the participants in the follow-up study. Unlike in the original sample, in this selection, PIH had occurred more frequently in the intervention group (33% vs 6%, $P = 0.005$). None of the other maternal, pregnancy of neonatal characteristics differed according to allocation to intervention or control strategy.

Primary and secondary outcomes

Table 2 demonstrates that IVSd thickness Z-score, LVMI, left ventricular tissue Doppler systolic (LV S') and early-diastolic (LV E') met our criteria of primary outcome and $p < 0.05$ for entry in multivariable linear regression analyses. 36% of ICCs for the echocardiographic variables demonstrated poor agreement and were assessed by a third reviewer. 43% indicated moderate agreement and 21% indicated good correlation between the reviewers. Supplementary Table 3 demonstrates the ICCs and 95% CI. Our final regression model -correcting for BSA, age, sex, and ART- demonstrated that children born in the intervention group had a lower IVSd Z-score ($B = -0.88$ 95% −1.18 to −0.58) and a lower LVMI ($B = -8.56$ g/m^2 95%CI −13.09 to −4.03). In addition, children born to mothers in the intervention group had a higher LV S' ($B = 1.43$ cm/s 95% CI 0.65 to 2.20) and LV E' ($B = 2.39$ cm/s 95%CI 0.68 to 4.11) (Table 3).

Explorative analyses

Figure 2 demonstrates the dose–response relationship between the maternal preconception weight loss and randomization group for each echocardiographic outcome that differed significantly between intervention and control group. LVMI, IVSd Z-scores and LWLV S' demonstrated a significant positive effect of the intervention, independent of weight loss. Our mediation analyses demonstrated that maternal preconception nutritional intake, physical activity, glycemic status during pregnancy, offspring blood pressure and HOMA-IR did not mediate the effect of the maternal lifestyle intervention on the echocardiographic outcomes in the offspring (Supplementary Table 4).

DISCUSSION

We demonstrated that a 6-month preconception lifestyle intervention in women with obesity leads to changes cardiac structure and function in their 6-year-old children as compared to children born to mothers with obesity in the control group. These changes include a thinner interventricular septum, a lower LVMI, and increased systolic and diastolic myocardial velocities in children of women who underwent the lifestyle intervention. Although the outcomes of all children in our study are within the normal range for healthy children [32], a lower myocardial mass and increased myocardial performance is considered indicative of better cardiac health. This suggests that a preconception lifestyle intervention in women with obesity has the potential to improve cardiovascular health in their children.

Better maternal cardiovascular health during pregnancy has been associated with better offspring cardiovascular health at ages 10–14 years [33]. In addition, cardiovascular risk factors emerging in childhood, such as markers of obesity and biochemical measurements, have previously been identified as predictors of CVD risk in adulthood [34]. In regard to cardiac geometry, both LVM and IVS are known to track from childhood into adulthood [35, 36]. LVM and IVS have also been identified as risk factors for CVD in adult life, as demonstrated in large cohort studies [37, 38]. A possibly underlying mechanism could be that increased LVM and IVS increase myocardial oxygen consumption while reducing coronary blood-flow reserve [37]. The Framingham study demonstrated that in women a 50 g/m increase in LVM gave a relative risk of 2.21 for death attributable to CVD, after correcting for multiple confounders [37]. A more recent cohort study in non-hypertensive adults demonstrated that individuals within the highest IVS quintile in the cohort were 1.8 times as likely to develop hypertension after 5 years as compared to individuals with the lowest IVS in the cohort [38]. Both studies included participants free from CVD and the majority of the cardiac outcome values varied within the normal ranges. This suggests that echocardiographic values that are considered normal, could still indicate an increased CVD risk in later life relative to other normal values. In our study, all echocardiographic markers in our participants were within the normal range for healthy children. However, in line with the results of the adult cohort studies [37, 38] we believe that the lower LVM and higher myocardial performance in children caused by the preconception lifestyle intervention could lower the long-term CVD risk.

While our study is the first to assess effects of a preconception intervention, two other studies have reported on cardiac outcomes in children after a lifestyle intervention during obese pregnancy or women at increased risk of gestational diabetes.

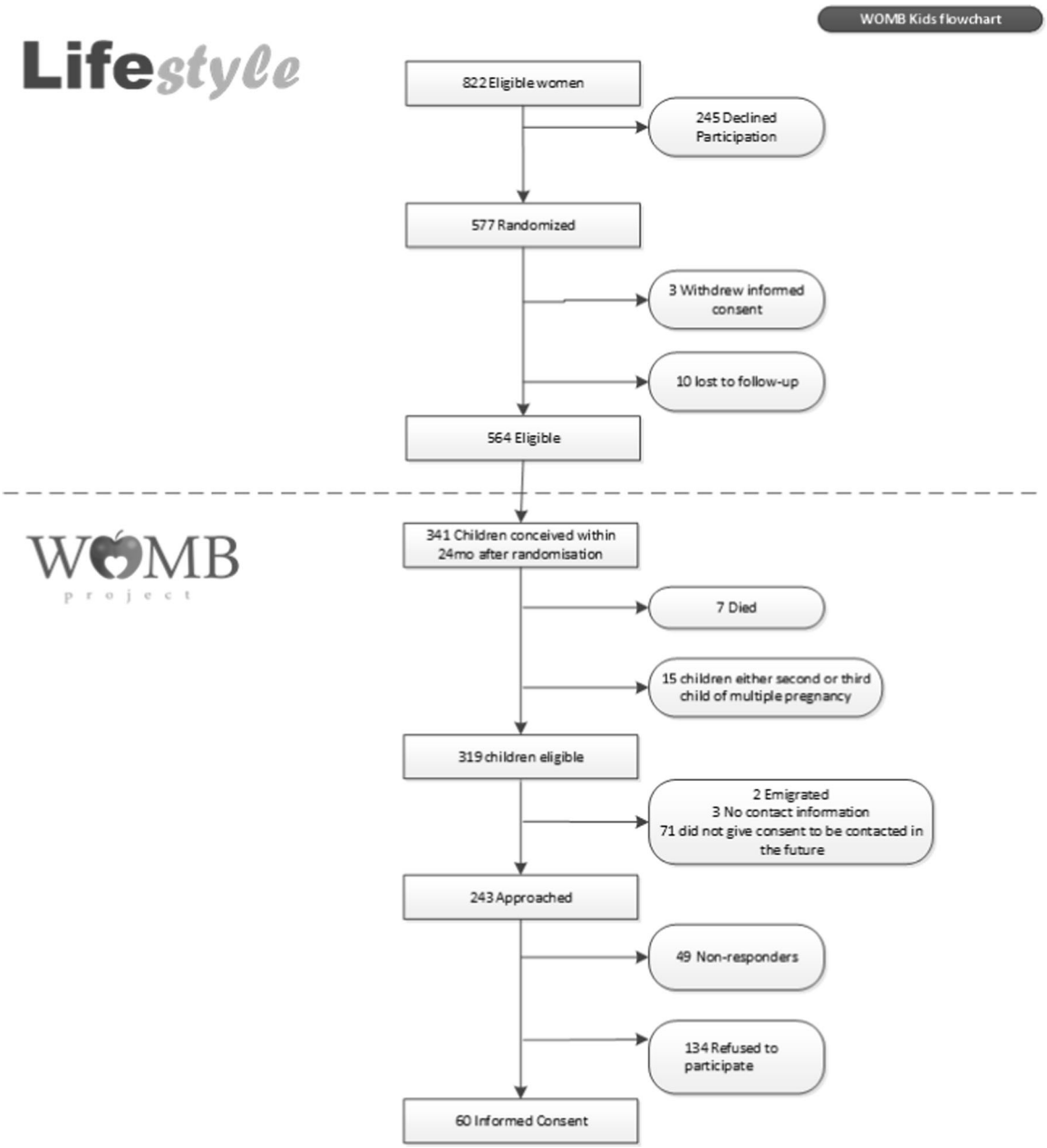

Fig. 1 Flowchart of the LIFEstyle follow-up.

Nyrnes et al. [11]. conducted the follow-up of the ETIP trial [39], a randomized controlled trial assessing a 60-min workout given three times a week, starting at circa 24 weeks of gestation in women with overweight or obesity. They did not find a beneficial effect of the exercise intervention during pregnancy on the cardiac outcomes in their infants at 6–8 weeks of age [11]. The second study is the follow-up of the RADIEL trial, including pregnant women with an increased risk of gestational diabetes (previous gestational diabetes or preconception BMI ≥ 30 kg/m^2) [40]. The RADIEL intervention consisted of four sessions of lifestyle counseling, started around 13 weeks of gestation [40]. The follow-up did not find an effect of the intervention on LVM and cardiac geometry in their children of 6 years of age [41]. This might be because these interventions are implemented after the first trimester, which is an important period for fetal cardiac development [42], and therefore are unable to achieve beneficial effects in the cardiac outcomes of the children.

The dose-response analyses stratified for maternal preconception weight loss demonstrated that the preconception lifestyle intervention still had beneficial effects on the cardiac outcomes in the children, even when there was no maternal weight loss. This indicates that other factors are accountable for the positive effects of the intervention on offspring's health. Maternal diet before and during pregnancy has previously been associated with cardiometabolic health in the offspring [43–45], but not all research is able to demonstrate such an association [46]. Exercise during pregnancy has been associated with increased heart rate variability during fetal life and in the first month of life, indicating that it may positively influence neonatal cardiac health [47]. However, most exposures have been studied during pregnancy as opposed to the preconception period, which makes it difficult to translate the results directly to our study. In our mediation analyses, maternal diet, physical activity, glucose and insulin resistance before or during pregnancy did not mediate the association between the intervention and the echocardiographic

Table 1. Child and maternal characteristics at follow-up data are presented as mean (SD), median [range] or number {%}.

Child characteristics					
At time of follow-up	***N***	**Intervention**	***N***	**Control**	***P* value**
Age (years)	24	6.6 (1.2)	36	6.5 (1.0)	0.9
BMI (kg/m^2)	23	16.8 (2.6)	35	16.8 (2.1)	0.8
BSA (m^2)	23	0.9 (0.1)	35	0.9 (0.1)	0.7
Female - no {%}	24	13 {54}	36	18 {50}	0.8
Available from earlier examinations					
SBP (mmHg)	9	100.1 (6.1)	20	101.0 (7.76)	0.77
DBP (mmHg)	9	65.19 (8.70)	20	65.13 (6.06)	0.98
Mean age at BP (years)	9	4.89 (0.91)	20	4.65 (0.96)	0.54
HOMA-IR	5	0.88 (0.46)	9	0.85 (0.66)	0.93
Mean age at blood withdrawal (years)	5	5.57 (0.99)	9	4.66 (0.90)	0.11
At/after birth					
Birthweight (kg)	24	3.3 (0.5)	35	3.5 (0.8)	0.1
GA (weeks)	24	38.7 (1.6)	36	38.6 (2.9)	0.9
Breastfeeding - no {%}	23	9 {39}	32	9 {28}	0.4
From multiple pregnancy	24	1 (4.17)	36	1	0.77
Maternal characteristics					
At time of randomization					
BMI (kg/m^2)	24	35.4 (3.2)	36	36.1 (2.7)	0.4
Age (years)	24	29.3 (4.2)	36	29.1 (4.2)	0.9
Smoker - no {%}	24	4 {17}	36	6 {17}	1
Alcohol use – (units/week)	19	0 (0–14.7)	31	0 (0–3.67)	0.78[b]
Social economic status[a] (SD)	21	−0.69	30	−0.52	0.65
Cause of infertility - no {%}	24		36		
Anovulation		14 (58)		18 (50)	0.53
Unexplained		6 (25)		11 (31)	0.64
Male factor		4 (17)		5 (14)	0.77
Tubal factor		1 (4)		2 (6)	0.81
Other		1 (4)		1 (3)	0.77
Physical activity[c] - min/week	20	385 [0–2820]	32	370 [0–3504]	0.71[b]
Paternal BMI	21	28.7 [21.3–49]	33	26.3 [20.6–55.60]	0.74[b]
Intervention outcomes					
Weight loss 6 months after randomization (kg)	24	3.35 (4.86)	36	1.87 (2.75)	0.19
Pregnancy related outcomes					
Assisted reproductive techniques[d] - no {%}	24	3 {12}	36	8 {22}	0.3
Fasting glucose (mmol/L)	21	5.0 (0.4)	26	5.0 (0.5)	0.63
GA at time of fasting glucose measurement (weeks)	21	26.5 (2.43)	26	26.49 (3.24)	0.97
2-h glucose (mmol/L)	18	6.9 (5.3 – 10.1)	25	6.5 (4.8 – 10.9)	0.64[b]
GA at time of 2-h glucose measurement (weeks)	18	26.56 (2.56)	25	26.73 (3.15)	0.85
Diabetes gravidarum - no {%}	24	7 {29.2}	35	8 {22.9}	0.58
Pregnancy induced hypertension - no {%}	24	8 {33}	35	2 {6}	0.005
Preeclampsia - no {%}	24	1 {4}	35	0 {0}	0.2
HELLP syndrome - no {%}	24	1 {4}	35	1 {4}	0.8

BMI body mass index, *BSA* body surface area ,*SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance, *GA* gestational age, *HELLP* Hemolysis Elevated Liver enzymes Low Platelets.

[a]Statusscore in 2010 Sociaal Cultureel Planbureau as measure for Socioeconomic status on behalf of zip area code.

[b]Mann-Whitney *U* test.

[c]Total minutes per week moderate to vigorous active.

[d]Assisted reproductive techniques = in vitro fertilization/intracytoplasmic sperm injection (including cryopreserved embryo–transfer cycles).

Table 2. Between groups comparisons Data is presented as mean (SD) or median [range].

Offspring					
	N	**Intervention group**	***N***	**Control group**	***P* value**
HR mean	24	89.3 (7.3)	36	88.6 (12.1)	0.8
Cardiac structure					
IVSd (mm)	24	5.12 (0.70)	36	6.11 (0.79)	<0.001
IVSd – Z- score	23	−0.60 (0.65)	35	0.27 (0.51)	<0.001
IVSs (mm)	24	7.71 (1.13)	36	8.7 (1.31)	0.004
LVM (g)	24	50.09 (10.51)	36	58.28 (13.4)	0.015
LVMI (g/m^2)	23	53.55 (8.52)	35	62.22 (8.84)	<0.001
Systolic function					
Longitudinal strain (%)	24	−23.82 (3.44)	35	−24.25 (2.55)	0.61
EF (%)	24	54.44 (4.78)	34	55.43 (3.52)	0.37
SV (ml)	24	62.52 (14.55)	36	58.13 (16.84)	0.30
CO (l/min)	24	5.56 (1.24)	36	5.06 (1.28)	0.14
E/E′	24	0.05 (0.01)	36	0.06 (0.02)	0.09
E′/A′	24	2.83 (0.85)	36	2.9 (1.14)	0.80
E/A	24	2.03 (1.41–4.97)	36	2.29 (1.34–4.56)	0.63[a]
Tissue Doppler Imaging					
IVS S′ (cm/s)	24	6.79 (1.09)	36	6.41 (0.99)	0.17
IVS E′ (cm/s)	24	13.82 (1.99)	36	12.87 (1.99)	0.08
IVS A′ (cm/s)	24	5.68 (1.21)	36	5.59 (1.76)	0.84
LV S′ (cm/s)	24	7.27 (1.74)	36	5.87 (1.3)	0.001
LV E′ (cm/s)	24	17.78 (2.99)	36	15.59 (3.34)	0.012
LV A′ (cm/s)	24	6.91 [3.72–10.29]	36	5.92 [3.05–16.92]	0.09[a]
RV S′(cm/s)	24	10.39 (1.91)	36	10.02 (2.26)	0.52
RV E′(cm/s)	24	14.26 (3.34)	36	13.57 (2.55)	0.37
RV A′(cm/s)	24	9.74 (2.81)	36	8.65 (1.92)	0.08
Carotid intima media thickness					
Left (mm)	17	0.49 (0.04)	26	0.47 (0.07)	0.36
Z-score left	17	2.19 (0.55)	26	1.90 (1.03)	0.23
Right (mm)	17	0.46 (0.04)	26	0.47 (0.05)	0.29
Z-score right	17	1.79 (0.64)	26	1.98 (0.69)	0.38

[a]Mann-whitney *U* test
IVSd interventricular septum at end diastole, *IVSs* interventricular septum at end systole, *LVM* left ventricular mass , *LVMI* left ventricular mass index, *EF* ejection fraction, SV stroke volume, *CO* cardiac output, *IVS* interventricular septum, *LV* left ventricle, *RV* right ventricle.

Table 3. Effect of intervention group on cardiac parameters B (95% CI).

	Model 1	**Model 2**	**Model 3**
IVSd (Z-score)	−0.87 (−1.17 to −0.57)[a]	−0.88 (−1.18 to −0.59)	−0.88 (−1.18 to −0.58)
LVMI (g/m^2)	−8.67 (−13.30 to −4.05)[a]	−8.71 (−13.20 to −4.22)	−8.56 (−13.09 to −4.03)
LV S′ (cm/s)	1.42 (0.63 to 2.20)	1.45 (0.69 to 2.21)	1.43 (0.65 to 2.20)
LV E′ (cm/s)	2.26 (0.56 to 3.96)	2.29 (0.57 to 4.00)	2.39 (0.68 to 4.11)

Model 1= Corrected for BSA
Model 2= Model 1 + Age + Sex
Model 3= Model 2 + Assisted reproductive techniques
IVSd Interventricular septum at end diastole, *LVMI* Left ventricular mass index, *LV* Left ventricle.
[a]Not corrected for BSA.

outcomes (Supplementary Table 4). However, maternal diet and physical activity were both based on self-reported data prone to bias and are therefore difficult to measure precisely. In addition, our sample size was small and our study was not powered for these explorative analyses, so mediating effects may have gone undetected. Other mechanisms have been proposed as pathways from maternal preconception lifestyle to cardiac outcomes in the children, including reduced fetal hyperinsulinemia in response to lower maternal glucose levels, and decreased activation of inflammatory pathways linked to maternal obesity leading to improved placentation [48, 49]. However,

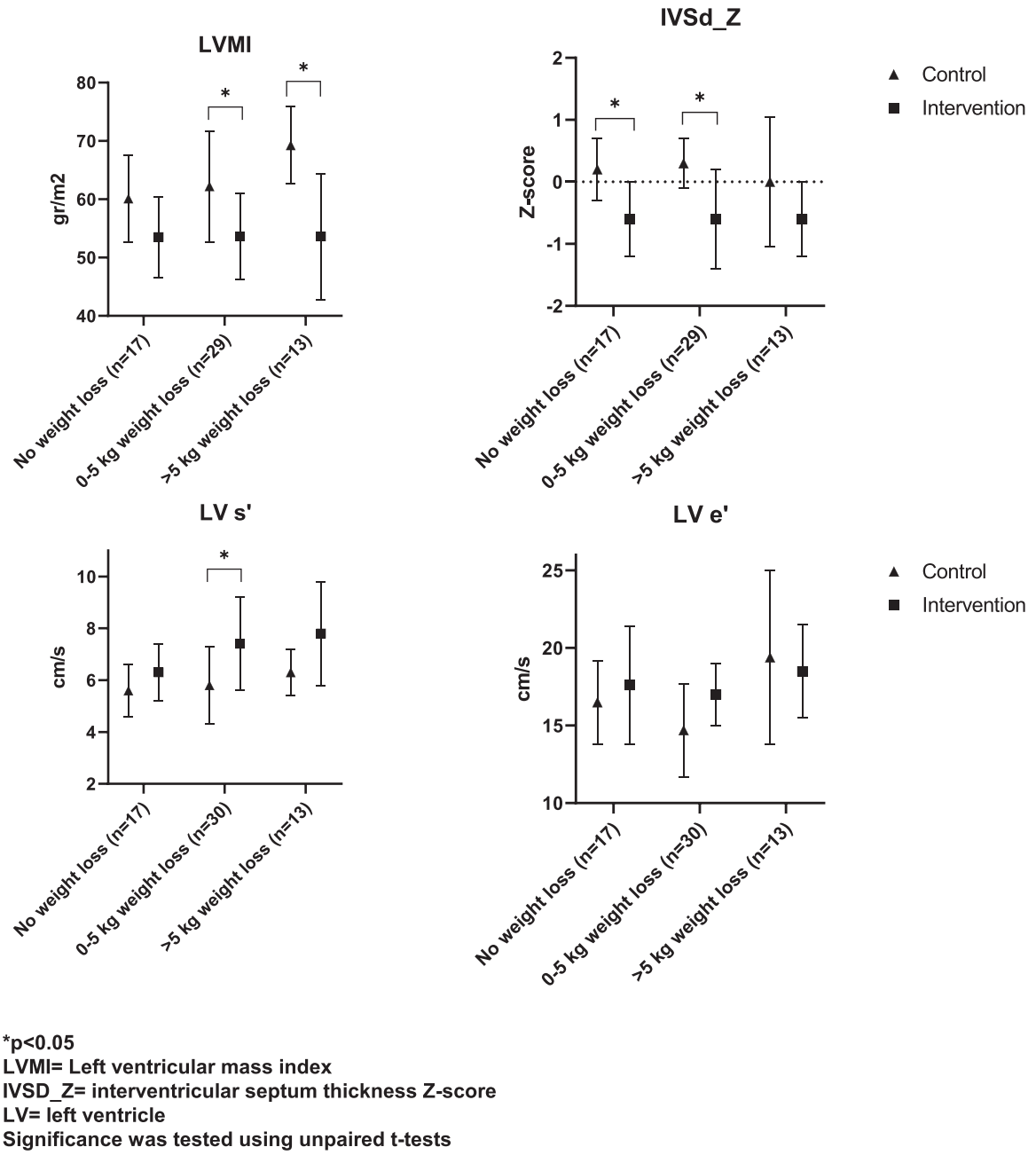

Fig. 2 Dose–response relationships between maternal weight loss 6 months after randomization and cardiac outcomes in offspring. Stratified for control and intervention group. Mean and standard deviation are displayed.

we would argue that an adverse preconception and in-utero environment has important consequences that are not only directly targeted at the developing fetal heart, but also work through other pathways in the postnatal period. For example through increase of blood pressure or increase of BMI [44, 50, 51], which may than in turn alter left ventricular geometry [52]. Recent research suggested that single adverse maternal risk factors such as obesity during pregnancy do not drive the associations with offspring cardiovascular health, but that a composite indicator of fetal cardiometabolic exposures including increased maternal BMI, blood pressure, total cholesterol level and glucose level were responsible for this association [33]. So, the positive effect of the preconception lifestyle intervention could also be the result of a combination of underlying maternal and/or fetal effects. This complex matter should be the subject of future research. However, the fact that an improvement in maternal lifestyle positively influences cardiac health in their children without relying on weight loss might be an important, motivating message for women with obesity planning on pregnancy.

Strengths and limitations

An important strength of this study is that, to our knowledge, it is the first experimental human trial analyzing the effect of a preconception lifestyle intervention in women with obesity on offspring's cardiac health. Previous research investigating offspring's cardiac structure after a diabetic pregnancy demonstrate transient alterations within the first 6 months after birth, probably due to normalization of the high glycemic environment in-utero [53]. Therefore, with a mean follow-up of 6.5 years we hypothesize that possible transient cardiac

alterations might have already occurred and that our results indicate sustained alterations in cardiac structure and function.

There are some limitations to this study. First, there was a high attrition rate (81%) which makes the results prone to selection bias. The characteristics of the cohort in this follow-up study were comparable to those of eligible non-participants regarding pregnancy complications including hypertension during pregnancy and (gestational) diabetes, and gestational age at birth- all of which can affect cardiac structure and function [54–56]. While this indicates that selection bias based on these characteristics is unlikely, selection bias may still have occurred on other undefined variables and our results should therefore be interpreted within the framework of these limitations. Second, another related limitation is the small sample size and we cannot rule out that our findings could be due to chance (type 1 error). Nonetheless, our findings show remarkable internal consistency, with all cardiac parameters showing beneficial effects of the preconceptional lifestyle intervention. Third, several echocardiographic outcomes had low ICC's between the two assessors. Echocardiography has previously been demonstrated to be an operator-dependent technique that is prone to variable reproducibility and interpretation [57]. Therefore, we included a third independent blinded reviewer in case of poor ICCs. This strategy improved the ICCs to at least moderate agreement. Last, due to the number of variables included as primary outcomes, there is a potential risk of multiple testing. However, most statistically significant differences in outcome variables between the two groups reach a high significance level ($p < 0.001$), making a false-positive result due to multiple testing less likely. Therefore, due to these limitations our results should be perceived as preliminary. Longer follow-up and external validation are necessary to determine the consistency and clinical relevance of these findings.

CONCLUSION

We demonstrated that a preconception lifestyle intervention in women with obesity improves echocardiographic parameters of cardiac structure and function associated with increased future CVD risk in their children at six years of age. This provides the first experimental evidence in humans suggesting that a preconception lifestyle intervention is a novel strategy to reduce CVD risk in the next generation.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author, TdH, upon reasonable request.

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AUTHOR CONTRIBUTIONS

AWvD designed the research protocol, assessed all children by means of echocardiography, and extracted offline data. TdH was responsible for planning the echocardiography's, safely storing all data, extracting and analyzing the data, and writing the article. IMK was responsible for part of the data extraction. RCP, AWvD, AH, HG, BWM, NAB, TJR, RJBJG, and IMK all carefully reviewed the articleAH, HG, BWM, RJBJG, TJR, and AWvD were involved in the set-up of the original intervention study and follow-up study. All authors provided intellectual input and were involved in the writing of the article.

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COMPETING INTERESTS

Annemieke Hoek: received a modest fee from Ferring Pharmaceutical company for participation in an expert board, unrelated to the current study.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Tamaraden Harink.

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