Received: 26 January 2024 | Revised: 21 April 2024 | Accepted: 23 April 2024

DOI: 10.1111/aogs.14874

AOGS Acta Obstetricia et Gynecologica Scandinavica

ORIGINAL RESEARCH

Effect of Mediterranean diet or mindfulness-based stress reduction during pregnancy on placental volume and perfusion: A subanalysis of the IMPACT BCN randomized clinical trial

Ayako Nakaki[1,2] | Eugenio Denaro[1] | Maddalena Crimella[1] | Roberta Castellani[1] | Kilian Vellvé[1] | Nora Izquierdo[1] | Annachiara Basso[1,3] | Cristina Paules[1,4] | Rosa Casas[5,6,7] | Leticia Benitez[1,2] | Irene Casas[1,2] | Marta Larroya[1,2] | Mariona Genero[1,8] | Sara Castro-Barquero[1,5,6,7] | Alex Gomez-Gomez[9] | Óscar J. Pozo[9] | Eduard Vieta[2,10] | Ramon Estruch[2,5,6,7] | Alfons Nadal[2,11] | Eduard Gratacós[1,2,8,12] | Francesca Crovetto[1,8,13] | Fàtima Crispi[1,2,12] | Lina Youssef[1,2,8,14]

[1]BCNatal – Barcelona Center for Maternal-Fetal and Neonatal Medicine (Hospital Clínic and Hospital Sant Joan de Deu), University of Barcelona, Barcelona, Spain

[2]Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain

[3]Department of Obstetrics and Pediatrics ASST Lecco, A. Manzoni Hospital, Lecco, Italy

[4]Instituto de Investigación Sanitaria Aragón (IISAragon), Red de Salud Materno Infantil y del Desarrollo (SAMID), RETICS, Instituto de Salud Carlos III (ISCIII), Subdirección General de Evaluación y Fomento de la Investigación y Fondo Europeo de Desarrollo Regional (FEDER), Zaragoza, Spain

[5]Department of Internal Medicine Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Spain

[6]Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Institute de Salud Carlos III, Madrid, Spain

[7]Institut de Recerca en Nutrició i Seguretat Alimentaria (INSA-UB), University of Barcelona, Barcelona, Spain

[8]Institut de Recerca Sant Joan de Déu, Esplugues de Llobregat, Spain

[9]Integrative Pharmacology and Systems Neuroscience Group, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

[10]Department of Psychiatry and Psychology, Hospital Clinic, Neuroscience Institute, University of Barcelona, CIBERSAM, Barcelona, Spain

[11]Department of Pathology, Hospital Clinic, University of Barcelona, Barcelona, Spain

[12]Center for Biomedical Research on Rare Diseases (CIBER-ER), Madrid, Spain

[13]Primary Care Interventions to Prevent Maternal and Child Chronic Diseases of Perinatal and Developmental Origin RD21/0012/0003, Instituto de Salud Carlos III, Madrid, Spain

[14]Josep Carreras Leukemia Research Institute, Hospital Clinic/University of Barcelona Campus, Barcelona, Spain

Correspondence
Francesca Crovetto, BCNatal (Hospital Sant Joan de Déu and Hospital Clínic), Pg. de Sant Joan de Déu, 2, 08950 Esplugues de Llobregat, Barcelona, Spain.
Email: francesca.crovetto@sjd.es

Abstract

Introduction: The *IMPACT BCN* trial—a parallel-group randomized clinical trial where 1221 pregnant women at high risk for small-for-gestational age (SGA) newborns were randomly allocated at 19- to 23-week gestation into three groups: Mediterranean

Abbreviations: FOV, field of view; IMPACT BCN, Improving Mothers for a Better Prenatal Care Trial Barcelona; IVIM, intra voxel incoherent motion; MR, magnetic resonance; ROI, region of interest; SGA, small for gestational age; TE, echo time; TR, repetition time.

Fàtima Crispi and Lina Youssef contributed equally to this study.

Funding information
Ministerio de Ciencia e Innovación, Grant/Award Number: FJC2021-048123-I; Instituto de Salud Carlos III, Grant/Award Number: AC19/00100, CM19/00140, INT21/00027, PI17/00675, PI18/00073, PI20/00246 and PI22/00684; Fundación Mutua Madrileña, Grant/Award Number: CEX2021-001234-M; Cerebra; 'la Caixa' Foundation, Grant/Award Number: LCF/BQ/DR19/11740018 and LCF/PR/GN18/10310003; Departament d'Innovació, Universitats i Empresa, Generalitat de Catalunya, Grant/Award Number: 2021-SGR-01422

diet, Mindfulness-based Stress reduction or non-intervention—has demonstrated a positive effect of Mediterranean diet and Stress reduction in the prevention of SGA. However, the mechanism of action of these interventions remains still unclear. The aim of this study is to investigate the effect of Mediterranean diet and Stress reduction on placental volume and perfusion.

Material and Methods: Participants in the Mediterranean diet group received monthly individual and group educational sessions, and free provision of extra-virgin olive oil and walnuts. Women in the Stress reduction group underwent an 8-week Stress reduction program adapted for pregnancy, consisting of weekly 2.5-h and one full-day sessions. Non-intervention group was based on usual care. Placental volume and perfusion were assessed in a subgroup of randomly selected women ($n=165$) using magnetic resonance (MR) at 36-week gestation. Small placental volume was defined as MR estimated volume <10th centile. Perfusion was assessed by intravoxel incoherent motion.

Results: While mean MR placental volume was similar among the study groups, both interventions were associated with a lower prevalence of small placental volume (3.9% Mediterranean diet and 5% stress reduction vs. 17% non-intervention; $p=0.03$ and $p=0.04$, respectively). Logistic regression showed that small placental volume was significantly associated with higher risk of SGA in both study groups (OR 7.48 [1.99–28.09] in Mediterranean diet and 20.44 [5.13–81.4] in Stress reduction). Mediation analysis showed that the effect of Mediterranean diet on SGA can be decomposed by a direct effect and an indirect effect (56.6%) mediated by a small placental volume. Similarly, the effect of Stress reduction on SGA is partially mediated (45.3%) by a small placental volume. Results on placental intravoxel incoherent motion perfusion fraction and diffusion coefficient were similar among the study groups.

Conclusions: Structured interventions during pregnancy based on Mediterranean diet or Stress reduction are associated with a lower proportion of small placentas, which is consistent with the previously observed beneficial effects of these interventions on fetal growth.

KEYWORDS
fetal growth restriction, intrauterine growth restriction, magnetic resonance, Mediterranean diet, Mindfulness, placenta, placental insufficiency, placental MR, prenatal, stress reduction

1 | INTRODUCTION

Infants born small for gestational age (SGA) represent 7%–10% of all newborns[1] representing a leading cause of stillbirth, neonatal mortality, and both short- and long-term cardiovascular, metabolic and neurodevelopmental *sequelae*.[2,3] Most SGA cases are related to placental dysfunction.[4,5] As oxygen and nutrient availability is crucial for fetal development, abnormal placentation and altered uteroplacental circulation may impair fetal growth and lead to SGA.[6] Given the lack of treatment to reverse its course, preventive strategies and timely diagnosis represent vital aspects of SGA management. *IMPACT BCN*, a recent randomized clinical trial by Crovetto et al.[7,8] involving 1221 high-risk pregnancies, demonstrated that the proportion of SGA newborns is significantly reduced by structured maternal Mediterranean diet and Mindfulness-based Stress reduction interventions during pregnancy, when compared to usual care.

> **Key message**
>
> This study shows a positive effect of Mediterranean diet and Stress reduction during pregnancy on placental volume which could be partially mediating these interventions' effect on reduced proportion of small for gestational age newborns observed in the IMPACT BCN trial.

These findings are of remarkable clinical significance even though the mechanism of action of these interventions is still to be elucidated. Given the utmost importance of placenta in fetal growth, we hypothesized that placental size could mediate the observed effect of these interventions on the incidence of SGA.

Over the last years, magnetic resonance (MR) imaging has emerged as an adjuvant technique for precise assessment of placental volume since it is characterized by low operator dependence, large field of view (FOV), and high tissue resolution.[9,10] Apart from an accurate estimation of placental volume, novel MR sequences could determine placental perfusion and diffusion mapping[2,6,11] providing advantageous tools for the early detection of placental dysfunction. Indeed, placental MR allows for objective quantification of placental function and elucidation of the complex mechanisms underlying the development of fetal growth restriction, preeclampsia, and other placenta-related pathologies such as placental confined mosaicism.[12–14]

The aim of this study was to investigate the effect of maternal Mediterranean diet and stress reduction interventions during pregnancy on placental volume and perfusion assessed by MR.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This study is a secondary analysis of the *IMPACT BCN* trial (Improving Mothers for a better PrenAtal Care Trial BarCeloNa).[7,8] *IMPACT BCN* was a parallel, randomized clinical trial conducted at BCNatal (Hospital Clínic and Hospital Sant Joan de Déu), a large referral center for maternal-fetal and neonatal medicine in Barcelona, Spain. The study was conducted from 2017 to 2020, including 1221 pregnant women at high risk for SGA (defined as birthweight below the 10th centile) randomly allocated at 19- to 23-week gestation into three groups (1:1:1 ratio): a nutritional intervention based on Mediterranean diet, a Stress reduction intervention based on Mindfulness, or a usual care group without any intervention (Figure 1). The study design and interventions are described elsewhere.[7,8] In brief, participants in the Mediterranean diet group received monthly individual and group educational sessions, and free supplementation of extra-virgin olive oil and walnuts. Women in the Stress reduction group underwent an 8-week Mindfulness-based program adapted for pregnancy, consisting of weekly 2.5-h and one full-day sessions. Participants who were randomized to the usual care group received usual pregnancy care following institutional protocols. At baseline (19- to 23-week gestation) and the final (34–36 weeks) evaluation, maternal adherence to interventions was assessed by a 17-item dietary score (Mediterranean diet score[7]) and cortisone/cortisol ratio[15,16] measured in maternal 24-h urine.[7] The study protocol and the main outcomes (prevalence of SGA and adverse perinatal outcome) of this trial have been previously published elsewhere.[7,8]

For the purpose of the present study, a subgroup of randomly selected participants from the three study groups ($n = 196$) underwent an MR during the third trimester of pregnancy to assess placental volume and function. Small placental volume was defined as MR estimated volume below the 10th centile. Placental perfusion was assessed using intravoxel incoherent motion (IVIM). Placental volume is known to be an important determinant of birthweight and fetal growth,[17] and IVIM has been assessed in several studies demonstrating low placental perfusion in fetal growth restriction.[18–20] Thus, considering the significant reduction of the SGA prevalence in the intervention groups of *IMPACT BCN* trial, we expected that these interventions may have improved placental volume and perfusion.

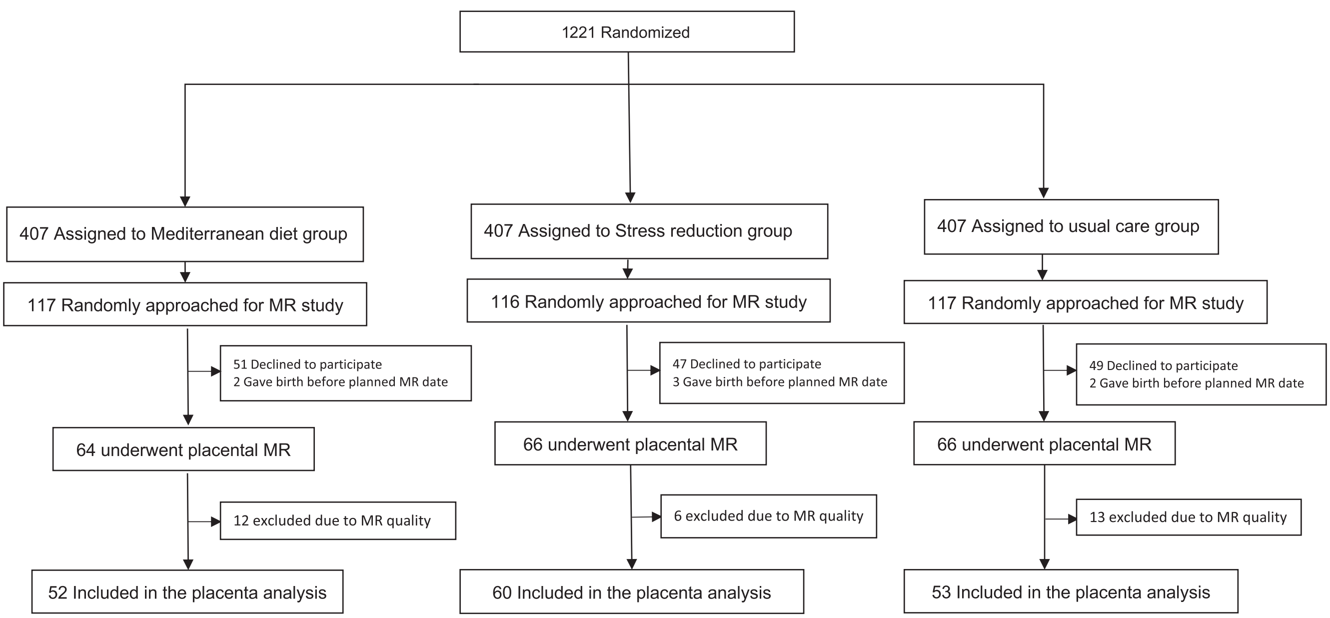

FIGURE 1 Flowchart of the study population undergoing placental magnetic resonance (MR).

The inclusion criteria for MR recruitment were those individuals who participated in the *IMPACT BCN* trial and did not have any MR contraindications, such as claustrophobia and metallic implants and devices.

The Institutional Review Board of the Hospital Clínic of Barcelona approved the study (HCB-2016-0830) on December 16, 2016. All participants provided written informed consent on the day of MR procedure.

2.2 | Placental MR acquisition

Between 33- and 39-week gestation, participants randomly selected underwent a 3.0 T MR scanner using an eight-channel body array radiofrequency coil without fetal sedation following the American College of Radiology guidelines for pregnancy.[21] Participants were allowed to choose their positions, either a supine, a slightly tilted left decubital position, or a sided position. Single-shot fast spin-echo T2-weighted sequences and diffusion-weighted echo-planner imaging sequence were achieved in one of two hospitals (Hospital San Joan de Déu and Hospital Clínic) with Philips Ingenia or Siemens MR MAGNETOM Vida scanner. MR examiners were blinded to the *IMPACT BCN* trial group and to SGA status. The T2-weighted sequence was performed from the fundus to the cervix of the uterus to assure the whole placenta was included. For the diffusion-weighted images, the umbilical cord insertion area was detected by a trained researcher, then the diffusion-weighted echo-planner imaging sequence was performed close to the cord insertion slice. The parameters used in the T2-weighted sequence for each machine were as follows: (1) Philips: repetition time (TR) 1330 ms, echo time (TE) 150 ms, FOV 400 × 400 mm, slice thickness 3 mm, voxel spacing 0.78 × 0.78 mm, no interslice-slice gap; (2) Siemens: TR 1220 ms, TE 150 ms, FOV 420 × 420 mm, slice thickness 3 mm, voxel spacing 0.7 × 0.7 mm, no interslice-slice gap. The parameters used in the IVIM for each machine were as follows: (1) Philips: TR 5500 ms, TE 76 ms, FOV 343 × 343 mm, slice thickness 4 mm, voxel spacing 0.98 × 0.98 mm, with 4 *b*-values (0, 300, 450, 600 s/mm^2); Siemens: TR 4500 ms, TE 84 ms, FOV 350 × 350 mm, slice thickness 3.4 mm, voxel spacing 3.4 × 3.4 mm, with 12 *b*-values (0, 10, 20, 30, 40, 50, 80, 100, 200, 400, 800, and 1000 s/mm^2).

2.3 | Placental MR image processing

The placental volume was assessed with the software ImageJ Fiji®, by delineating the whole placenta on each T2-weighted image slices including the basal plate. The region of interest (ROI) was delineated on all the slices where placenta was present, ranging from 39 to 74 slices per participant (57 slices on average) and summed to calculate the total volume in pixels (Figure 2A). The volume was converted into cube centimeters with the formula: total pixels × pixel spacing × thickness (3 mm).

The IVIM analysis was assessed with *ivim.sav* software for Philips images and a prototype software Siemens MR Body Diffusion Toolbox for Siemens images. Low-quality images due to fetal/maternal movements or artifacts were excluded from the analysis. The whole placenta including the basal plate was delineated on the seven slices closest to the cord insertion slice (Figure 2B). The IVIM parameters, perfusion fraction (*f*, %), diffusion coefficient (*D*, 10^{-3} mm^2/s), and pseudo diffusion coefficient (Dp, 10^{-3} mm^2/s), were automatically generated for each ROI with the equation:

$$S(b) = S0((1 - f)\exp(-b \cdot D) + f\exp(-b \cdot \mathrm{Dp}))$$

where $S(b)$ is the measured mean signal intensity, $S0$ is the signal measured at $b = 0$. The f represents the microcirculation volume compared to the total tissue volume, D is the diffusion parameter representing slow component of diffusion and reflects the extravascular tissue cellularity, and Dp is the diffusion parameter representing fast component of diffusion which reflects the microcirculation of regional capillary.[4,6,9,20,22] The average values of the seven slices were used for statistical analysis. All the ROIs were delineated by trained researchers blinded to the intervention arms and to SGA status. A single researcher delineated all ROIs obtained by each machine (AK and ED delineated ROIs obtained by Philips and Siemens, respectively).

2.4 | Statistical analyses

Data are presented as mean (±standard deviation) or number (percentage), as appropriate. Normal distributions of variables were tested using the Shapiro-Wilk test and histograms. To determine the rate of small placentas, the 10th centile of placental volume was defined from the whole study population (estimated as 649.9 cm^3 in this population).

Comparisons of maternal baseline and perinatal characteristics were performed using Student's *t*-test for continuous variables and Pearson's chi-squared test for categorical variables, to compare each intervention group vs the usual care group. Placental parameters (volume and IVIM) were compared by linear or logistic regression adjusted by gestational age at MR, MR machine, and maternal thyroid disorder. Additional analyses were conducted to assess the association between small placental volume and SGA, Mediterranean diet score, or urinary cortisone/cortisol ratio results by logistic regression. Moreover, parametric mediation analysis was performed to investigate whether placental volume might be mediating the effect of Mediterranean diet and stress reduction interventions on the proportion of SGA fetuses previously reported in the *IMPACT BCN* trial.[7] The estimation of average causal mediation effects, average direct effects, the total effects, and the proportion-mediated effects were computed for each of 1000 bootstrapped resamples, and the 95% confidence interval was computed by determining 2.5th and 97.5th centiles for the resamples.[23]

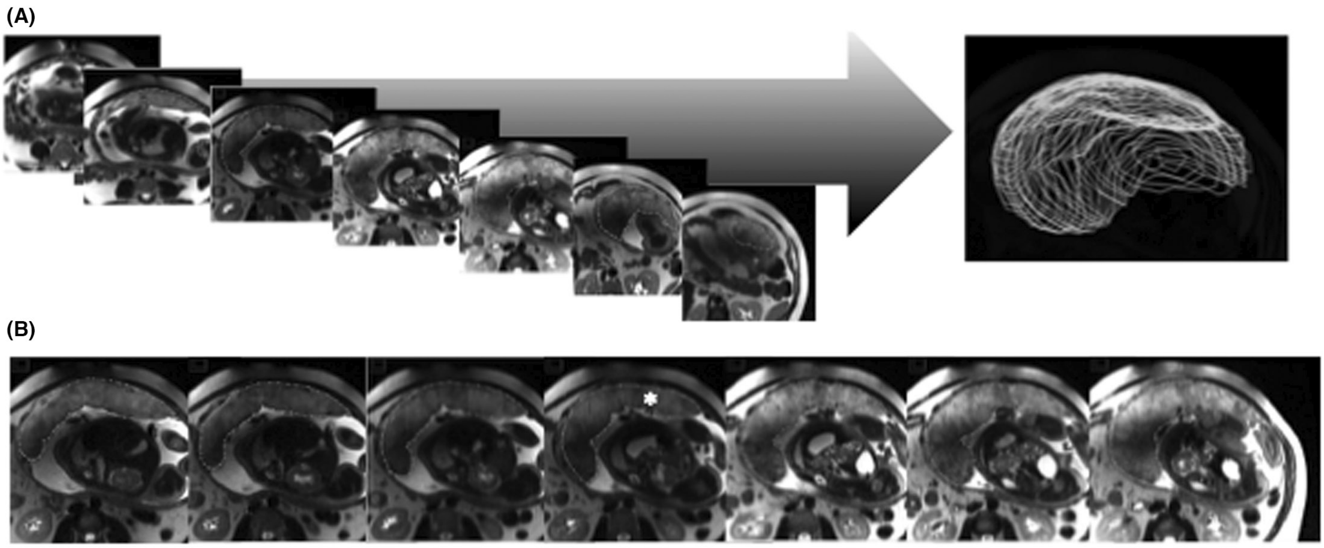

FIGURE 2 Delineation of the placenta using magnetic resonance imaging. (A) Delineation of the whole placenta on all the slices where placenta is present, and the combined image of the region of interest. (B) Illustrative sample of delineation of the whole placenta, seven slices closest to the cord insertion slice (Current image done on a T2-weighted image on Fiji software). *Cord insertion point.

For all comparisons, $p<0.05$ was considered statistically significant. All statistical analyses were performed with software R (version 4.0.5, R Foundation) and R Studio (version 1.4.1106, R Studio) including mediation package version 4.5.0.[24]

3 | RESULTS

3.1 | Characteristics of the study population

Among 350 participants initially approached, 196 mothers underwent a placental MR. No differences in baseline characteristics or perinatal outcome were observed between accepting and declining participants. The main reason to decline participation was uncertainty and fear since MR is not commonly performed during pregnancy. After quality image control, data from 165 participants were included in the current study, including 52 Mediterranean diet group, 60 Stress reduction group, and 53 usual care group mothers. The flowchart of individuals included in the examinations and analyses here reported are shown in Figure 1.

This subpopulation of 165 participants was representative of the *IMPACT BCN* trial population.[7,8] No differences were observed in maternal baseline characteristics among the study groups, except for higher prevalence of pre-pregnancy thyroid disorders in the Stress reduction group (Table 1). Mediterranean diet score at the final visit was significantly higher in the Mediterranean diet group participants compared to the usual care, and significantly improved compared to the initial assessment within the Mediterranean diet group. Maternal urinary cortisone/cortisol ratio at the final visit did not differ between groups. However, it has significantly improved compared to the initial assessment within the Stress reduction group and also in the Mediterranean diet group (Table S1).

In line with the main results from the *IMPACT BCN* trial, a tendency to lower SGA incidence was observed in the intervention groups. Other pregnancy complications and neonatal results were similar among the study groups, with all pregnancies delivering at term (Table 1).

3.2 | Placental MR

Table 2 displays the results of MR placental volume and IVIM according to the study groups. The mean gestational age at the time of MR was 36.6 ± 1 weeks of gestation in all study groups with similar percentage of MR machine use (Siemens machine was used in 52% of the participants of the Mediterranean diet, 62% in Stress reduction, and 62% in usual care, $p=0.28$ and 0.95, respectively). The mean placental volume and IVIM parameters were similar among the study groups. Both Mediterranean diet and Stress reduction showed a significant reduction of the proportion of small placental volume (3.9% in the Mediterranean diet group and 5% in the Stress reduction vs. 17% in usual care). Table S2 displays maternal baseline characteristics and perinatal outcome of pregnancies with small placental volume. The small placental volume participants were found more in the usual care group, they were younger (maternal age mean [SD] 34.6 [4.7] years in small placenta vs. 37.9 [4.4] years in normal placenta) and had earlier gestational age at delivery (39.8 [1] weeks of gestation in small placenta vs. 38.9 [1.2] weeks of gestation in normal placenta) and smaller newborns (birthweight centile 12.9 [18.1] in small placenta vs. 47.3 [29.1] in normal placenta) compared to normal placental volume participants. Small placental volume was inversely associated with Mediterranean diet score (odds ratio [OR] 0.78 [95% confidence interval 0.64–0.93, $p=0.009$]) (Figure S1) and maternal urinary cortisone/cortisol ratio (OR 0.19 [0.01–0.96], $p=0.10$).

TABLE 1 Maternal baseline and perinatal characteristics according to intervention groups.

	Mediterranean diet n = 52	Stress reduction n = 60	Usual care n = 53	Mediterranean diet vs. usual care p value	Stress reduction vs. usual care p value
Maternal baseline characteristics					
Age (years)	38 (4.3)	37.9 (4.5)	36.9 (4.8)	0.19	0.24
Ethnicity				0.12	0.25
Afro-American	1 (1.9)	1 (1.7)	0 (0)		
Asian	2 (3.8)	0 (0)	1 (1.9)		
Latin	8 (15.4)	7 (11.7)	2 (3.8)		
White	41 (78.8)	51 (85)	50 (94.3)		
Study class				0.96	0.52
No education/Primary grade	2 (3.8)	1 (1.7)	2 (3.8)		
Secondary/Technology grade	15 (28.8)	21 (35)	14 (26.4)		
University	35 (67.3)	38 (63.3)	37 (69.8)		
Socioeconomic status[a]				0.88	0.35
Low	2 (3.8)	1 (1.7)	2 (3.8)		
Medium	16 (30.8)	23 (38.3)	14 (26.4)		
High	34 (65.4)	36 (60)	37 (69.8)		
BMI before pregnancy (kg/m^2)	23.7 (4.4)	23.4 (4.4)	23.1 (3.7)	0.47	0.77
Medical condition					
Thyroid disorders	6 (11.5)	10 (16.7)[+]	1 (1.9)	0.05	<0.01
Autoimmune disease	7 (13.5)	6 (10)	9 (17)	0.62	0.28
Obesity[b]	5 (9.6)	6 (10)	4 (7.5)	0.71	0.65
Diabetes mellitus	4 (7.7)	2 (3.3)	1 (1.9)	0.16	0.63
Chronic hypertension	3 (5.8)	1 (1.7)	3 (5.7)	0.98	0.25
Psychiatric disorders	1 (1.9)	1 (1.7)	4 (7.6)	0.18	0.13
Nulliparous	29 (55.8)	41 (68.3)	34 (64.2)	0.38	0.64
Assisted reproductive technologies	17 (32.7)	17 (28.3)	13 (24.5)	0.35	0.65
During pregnancy					
Cigarette smoking	9 (17.3)	8 (13.3)	10 (18.9)	0.84	0.42
Alcohol intake	11 (21.1)	13 (21.7)	8 (15.1)	0.42	0.37
Drugs consumption	1 (1.9)	0 (0)	0 (0)	0.53	0.90
Gestational age at recruitment (weeks)	20.9 (0.6)	20.9 (0.7)	20.8 (0.7)	0.42	0.22
High adherence to the intervention[c]	43 (82.7)	47 (78.3)	NA	NA	NA
Perinatal data					
Gestational diabetes mellitus	9 (17.3)	5 (8.3)	5 (9.4)	0.24	0.84
Pre-eclampsia[d]	1 (1.9)	2 (3.3)	4 (7.6)	0.18	0.32
Gestational age at delivery (weeks)	39.9 (1)	39.8 (1)	39.6 (1)	0.08	0.34
Cesarean section	16 (30.8)	15 (25)	15 (28.3)	0.88	0.92
Female sex	26 (50)	28 (46.7)	22 (41.5)	0.38	0.58
Birthweight (g)	3342 (427)	3322 (419)	3198 (493)	0.11	0.15
Birthweight centile	46.5 (31.1)	46.2 (28)	40.3 (31.2)	0.31	0.29
Small for gestational age[e]	7 (13.5)	5 (8.3)	12 (22.6)	0.22	0.03

(Continues)

TABLE 1 (Continued)

	Mediterranean diet	Stress reduction	Usual care	Mediterranean diet vs. usual care	Stress reduction vs. usual care
	n = 52	*n* = 60	*n* = 53	*p* value	*p* value
Neonatal Apgar 5 min <7	0 (0)	0 (0)	0 (0)	0.99	0.93
Umbilical artery pH	7.19 (0.09)	7.20 (0.07)	7.19 (0.09)	1.00	0.53
Admission to NICU	0 (0)	4 (6.7)	4 (7.5)	0.04	0.86

Note: Data are given as mean (SD) or *n* (%).

Abbreviations: BMI, body mass index; NA, non-applicable; NICU, neonatal intensive care unit; PI, pulsatility index.

[a]Socioeconomic status is defined as follows: low (never worked or unemployed >2 years), medium (secondary studies and work), and high (university studies and work).

[b]Obesity defined as BMI above 30.

[c]A high adherence to the Mediterranean diet intervention was defined by an improvement of ≥3 points in the final score of the 17-item dietary screener compared with the baseline score. Adherence to the Mindfulness-based stress reduction intervention was considered high if at least six out of nine Mindfulness sessions were attended.

[d]Pre-eclampsia defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg at least 4 h apart after 20 weeks of gestation and proteinuria of ≥300 mg in 24 h or protein/creatinine ratio >0.3.

[e]Small-for-gestational age defined as birthweight below 10th centile according to local standards.

TABLE 2 Placental volume and intravoxel incoherent motion (IVIM) results using magnetic resonance (MR) according to the intervention groups.

	Mediterranean diet	Stress reduction	Usual care	Mediterranean diet vs. usual care *p* value[a]	Stress reduction vs. usual care *p* value[a]
Gestational age at MR (weeks)	36.5 (1)	36.6 (0.9)	36.7 (0.9)	0.43	0.73
Placental volume	*n* = 52	*n* = 60	*n* = 53		
Placental volume (cm^3)	922 (226.6)	935 (196.2)	899.2 (219)	0.70	0.19
Placental volume/birthweight (g/cm^3)	27.6 (5.7)	28.1 (4.9)	28.1 (4.9)	0.61	0.72
Small Placental volume[b]	2 (3.9%)	3 (5%)	9 (17%)	0.03	0.04
Placental IVIM	*n* = 50	*n* = 51	*n* = 50		
Perfusion fraction (%)	38.3 (10.3)	38.7 (9.2)	37.1 (9.4)	0.50	0.35
Diffusion coefficient (10^{-3} mm^2/s)	1.43 (0.23)	1.46 (0.21)	1.45 (0.28)	0.74	0.80
Pseudo-diffusion coefficient (10^{-3} mm^2/s)[c]	35.9 (8.3)	34.9 (7.3)	36.2 (9.2)	0.93	0.62

Note: Data are given as mean (SD) or *n* (%).

[a]Placental MR volume and IVIM variables were compared using a linear or logistic regression adjusted for gestational age at MR scan, MR machine, and maternal thyroid disorder.

[b]Small placental volume is defined as placental volume below the 10th centile.

[c]Pseudo-diffusion coefficient data were available for 23 Mediterranean diet, 24 Stress reduction, and 22 usual care.

3.3 | Association of placental MR with SGA

Small placental volume was significantly associated with the proportion of SGA (Figure 3). Mediation analysis showed that the effect of Mediterranean diet intervention on SGA can be decomposed by a direct effect and also an indirect effect (56.6%) mediated by a small placental volume. Similarly, the effect of Stress reduction intervention on SGA is partially mediated (45.3%) by a small placental volume as shown in Figure 4.

4 | DISCUSSION

To our knowledge, this is the first trial evaluating the effect of structured maternal lifestyle interventions during pregnancy on placental volume and perfusion. Given the significantly reduced percentage of SGA within the *IMPACT BCN* trial, we hypothesized that these interventions could have positive effects on placental size and function. Our results show that both Mediterranean diet and Stress reduction interventions during pregnancy are associated with a lower

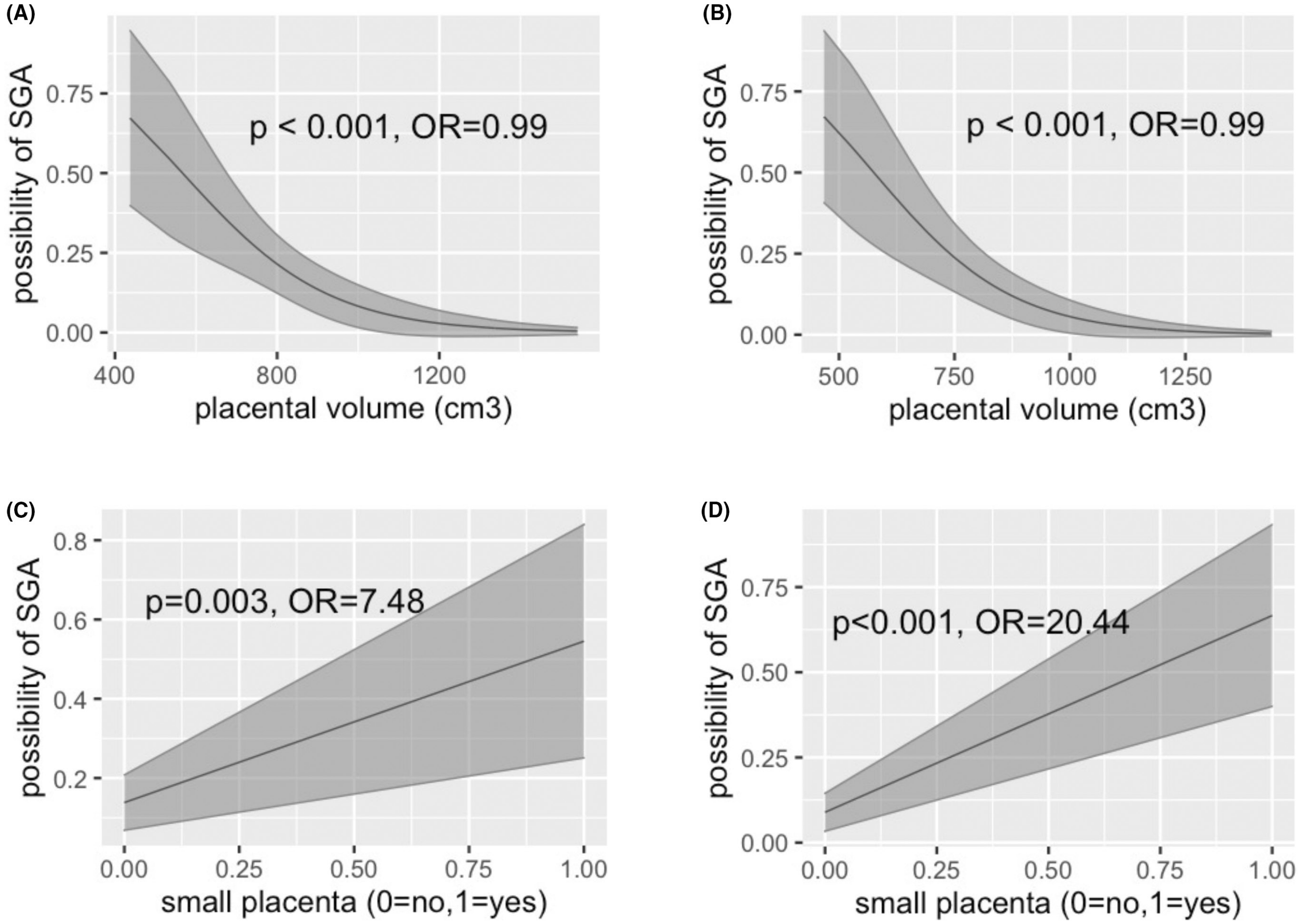

FIGURE 3 Association between placental volume and the proportion of small-for-gestational age (SGA) newborns in the Mediterranean diet vs the usual care group (A, C) and in the Stress reduction vs the usual care group (B, D). Graphs A and B are generated from logistic regression including SGA as outcome and placental volume (in continuous) as predictive variable. Graphs C and D are generated from logistic regression including SGA as outcome and small placental volume (in dichotomic, defining small placenta as placental volume below the 10th centile estimated using magnetic resonance) as predictive variable. Lines represent the mean predicted possibility and 95% confidence interval. OR, odds ratio.

proportion of small placentas, partially mediating the influence of these interventions on SGA.

In this study, we demonstrate that the promotion of Mediterranean diet during pregnancy is associated with lower rates of small placentas, being consistent with the previously reported lower rates of SGA in this population.[7] Indeed, we demonstrated a significant correlation between maternal Mediterranean diet score and placental volume. This represents the first evidence of an association between placental volume and maternal diet from a randomized trial. These findings are in line with previous observational studies suggesting an association between maternal healthy dietary pattern and biomarkers of placental function.[25] Interestingly, previous observations described a higher adherence to Mediterranean diet prior to conception in relation with lower uteroplacental vascular resistance.[26] However, in our study, no differences in placental perfusion were observed between the study groups using MR IVIM. This inconsistency might be explained by the limited standardization and sensitivity of the IVIM technique or differences in the study population and the timing of lifestyle intervention. Nevertheless, our results support the concept that an adequate maternal diet is crucial for an optimal placental development.[27,28] One of the possible mechanisms that could be mediating the effect of Mediterranean diet on placental and fetal size is its anti-inflammatory effect. Mediterranean diet is known for its high antioxidant properties and its anti-inflammatory effect through decreasing proinflammatory molecules such as interleukins and chemokines.[29] In fact, our group has recently portrayed that a high intake of (poly) phenols—bioactive compounds with strong anti-inflammatory and antioxidant properties—seems to mediate the effect of Mediterranean diet on fetal growth (Castro-Berraquero et al., unpublished data). In addition, supplementation of omega-3-polyunsaturated fatty acids, which is rich in Mediterranean diet, could also reduce maternal and placental inflammatory markers in obese pregnant women.[30] Future studies are warranted to determine the dietary pattern or specific nutrients that influence placental development.

Mediation results

(A) Mediterranean diet

	Estimate	95% lower CI	95% upper CI	p-value
ACME	-0.0524	-0.1416	0.00	0.04
ADE	-0.0402	-0.1775	0.10	0.59
Total Effect	-0.0926	-0.2454	0.05	0.22
Proportion Mediated	0.5661	-2.7848	4.44	0.23

(B) Stress reduction

	Estimate	95% lower CI	95% upper CI	p-value
ACME	-0.0637	-0.158	0.01	0.06
ADE	-0.0768	-0.1993	0.04	0.20
Total Effect	-0.1404	-0.2855	0.00	0.04
Proportion Mediated	0.4533	-0.1771	-1.80	0.09

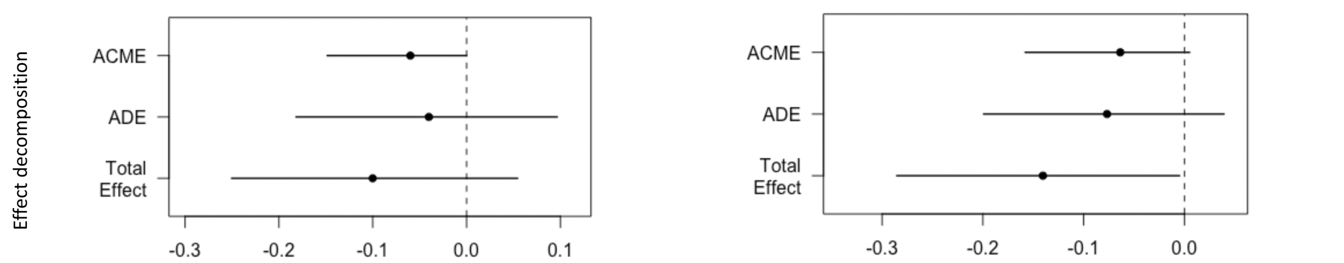

FIGURE 4 Parametric mediation analysis to assess the potential mediation of small placental volume on the interventions' effect (A, Mediterranean diet; B, Stress reduction) on small-for-gestational newborns. The upper panel shows the causal model of the hypothesized mechanisms of each intervention. The lines represent the effect of the Mediterranean diet or Stress reduction interventions. The middle panel displays the results for estimated effect and its 95% confidence intervals (CI) of the average causal mediation effects (ACME), average direct effects (ADE), total effect and proportion of mediated Effect. The lower panel graphics show that the average total effect of the intervention on SGA is decomposed into direct effect (ADE) and indirect (mediated by small placenta) effect (ACME). The point represents the estimated effect and the lines represent the 95% confidence intervals.

Our results suggest that Stress reduction during pregnancy has a beneficial effect on placental size, in line with its positive effect on fetal growth. We have also observed a tendency to lower maternal cortisone/cortisol ratio—a marker of maternal stress—in association with small placental volume. These results are consistent with previous observational studies describing an association between maternal stress, reduced placental expression of 11β-hydroxysteroid dehydrogenase type-2 the enzyme that inactivates cortisol conversion to cortisone,[15,31] restricted umbilical artery blood flow,[32] and reduced fetal growth. Excess of placental glucocorticoids not only leads to consequences on fetal development[33] but also negatively affects placental growth, vascularization, and nutrient transport.[32,34,35] Similar to the Mediterranean diet group, our study does not demonstrate significant changes in placental perfusion in Stress reduction, possibly due to the relatively low sensitivity of the technique. Leastwise, our data suggest a beneficial effect of maternal Stress reduction on placental development and fetal growth, highlighting the importance of programs designed to improve maternal well-being during pregnancy.

Placental size is known to be a significant determinant of both birthweight and fetal growth.[17] Indeed, it could modify the effect of maternal determinants of fetal growth especially maternal anthropometry and weight gain during pregnancy.[17,36] Subsequently, reduced placental size has been demonstrated to be associated with higher risk of SGA.[37] On the other hand, maternal nutritional and metabolic factors that influence fetal growth, birthweight, and neonatal body composition are also independent determinants of placental size.[38] Interestingly, the *IMPACT BCN* trial has demonstrated a positive effect in the prevention of SGA with lifestyle-structured interventions like Mediterranean diet and Stress reduction.[21] However, the mechanism of action of these interventions on fetal growth remains still unknown. In the current study, we demonstrate the beneficial effect of both Mediterranean diet and Stress reduction during pregnancy in the reduction of small placentas. The effect on placental size seems to mediate partially the effect of these interventions on the reduction of SGA. Thus, these findings are relevant to understand the mechanism(s) of action of lifestyle interventions on SGA.

Our study has some strengths that merit a comment. Firstly, it is based on data from a randomized trial with well-controlled and comparable study groups. Secondly, placental volume was accurately estimated using MR. Thirdly, we followed a prespecified and strict methodology in collecting and analyzing the data included in this study. On the other hand, we acknowledge some limitations. Firstly, MR could only be performed in a relatively small subset of participants of the *IMPACT BCN* trial due to logistic and budgetary issues. Secondly, two different machines and protocols were employed for the MR. For this reason, MR machine was included as a covariate in the statistical analysis to reduce the impact of this variance. Thirdly, the study participants had mainly high socioeconomic status and relatively low rates of obesity and gestational diabetes, limiting its replicability in other settings. Finally, since placental assessment was not the main outcome of the *IMPACT BCN* trial, these results should be taken with caution.

5 | CONCLUSION

This study suggests that improving maternal diet and well-being improves placental volume. These findings open opportunities for lifestyle programs in pregnancy to boost pregnancy outcomes since placental volume mediates the effect of these programs on fetal growth. Future studies are warranted to determine the exact mechanisms of this association and identify the best maternal lifestyle strategies to optimize placental development and size.

AUTHOR CONTRIBUTIONS

Francesca Crovetto, Fàtima Crispi, and Eduard Gratacós conceived and designed the study. Francesca Crovetto, Ayako Nakaki, Eugenio Denaro, Maddalena Crimella, Roberta Castellani, Kilian Vellvé, Nora Izquierdo, Annachiara Basso, Cristina Paules, Leticia Benitez, Irene Casas, Marta Larroya, Mariona Genero, and Lina Youssef had responsibility for day-to-day running of the trial including participant recruitment, data and sample collection, data management and data curation. Francesca Crovetto and Fàtima Crispi: guarantying the correct execution of the trial. Sara Castro-Barquero was the dietitian involved in the Mediterranean diet program, and Roberta Castellani and Ramon Estruch were responsible for the program. Óscar J. Pozo and Alex Gomez-Gomez were responsible for the analysis of 24-h urinary cortisone/cortisol ratio. Alfons Nadal was responsible for placental sample management. Eduard Vieta was responsible for the Mindfulness-Based Stress Reduction program. Ayako Nakaki, Eugenio Denaro, and LN performed the data processing and the statistical analysis. Ayako Nakaki, Eugenio Denaro, Maddalena Crimella, Lina Youssef, and Fàtima Crispi drafted the first version of the manuscript. All authors critically reviewed and approved the final version of the manuscript.

FUNDING INFORMATION

The project was partially funded by a grant from "La Caixa" Foundation (LCF/PR/GN18/10310003); Cerebra Foundation for the Brain Injured Child (Carmarthen, Wales, UK); Departament d'Innovació, Universitats i Empresa, Generalitat de Catalunya (2021-SGR-01422); Instituto de Salud Carlos III and co-funded by the European Union (INT21/00027, PI17/00675, PI18/00073, PI20/00246, CM19/00140, PI22/00684); Fundación Mutua Madrileña (AP180722022); MCIN/AEI/10.13039/501100011033 (CEX2021-001234-M). Francesca Crovetto has received support from Centro de Investigaciones Biomédicas en Red sobre Enfermedades Raras (CIBERER). Ayako Nakaki has received support from a fellowship from "La Caixa" Foundation, Doctoral INPhINIT Retaining fellowship (LCF/BQ/DR19/11740018). Ramon Estruch has received support from the Instituto de Salud Carlos III (AC19/00100), as part of the FoodPhyt project, under the umbrella of the European Joint Programming Initiative "A Healthy Diet for a Healthy Life" (JPI HDHL) (2019–02201). Lina Youssef was supported from Ministerio de Ciencia e Innovación (FJC2021-048123-I), and by the European Union "NextGenerationEU"/PRT. Additionally, we would like to thank the Fundació Jesús Serra of the Grup Catalana Occident for the Fundació Jesús Serra Research Prize in the Clinical category awarded to the Researcher Fatima Crispi in its 4th edition for the project titled "Cardiovascular prevention from fetal life: benefits of Mediterranean diet during gestation."

CONFLICT OF INTEREST STATEMENT

Ramon Estruch reports grants from Fundación Dieta Mediterránea, Spain and Cerveza y Salud, Spain. Eduard Vieta has received grants and served as consultant, advisor or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbott, Abbvie, Aimentia, Angelini, Biogen, Biohaven, Boehringer Ingelheim, Casen-Recordati, Celon, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo Smith-Kline, Idorsia, Janssen, Lundbeck, Novartis, Organon, Otsuka, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris. The remaining authors report no conflict of interest.

ETHICS STATEMENT

The Institutional Review Board of the Hospital Clínic of Barcelona approved the study (HCB-2016-0830) on December 16, 2016.

ORCID

Kilian Vellvé https://orcid.org/0000-0002-2376-7664
Leticia Benitez https://orcid.org/0000-0002-4950-036X
Lina Youssef https://orcid.org/0000-0002-0554-5507

REFERENCES

1. Gómez O, Figueras F, Fernández S, et al. Reference ranges for uterine artery mean pulsatility index at 11–41 weeks of gestation. *Ultrasound Obstet Gynecol*. 2008;32:128-132.
2. Crispi F, Miranda J, Gratacós E. Long-term cardiovascular consequences of fetal growth restriction: biology, clinical implications, and opportunities for prevention of adult disease. *Am J Obstet Gynecol*. 2018;218:S869-S879.
3. Arcangeli T, Thilaganathan B, Hooper R, Khan KS, Bhide A. Neurodevelopmental delay in small babies at term: a systematic review. *Ultrasound Obstet Gynecol*. 2012;40:267-275.
4. Antonelli A, Capuani S, Ercolani G, et al. Human placental microperfusion and microstructural assessment by intra-voxel incoherent motion MRI for discriminating intrauterine growth restriction: a pilot study. *J Matern Fetal Neonatal Med*. 2022;35:9667-9674.
5. Andescavage N, You W, Jacobs M, et al. Exploring in vivo placental microstructure in healthy and growth-restricted pregnancies through diffusion-weighted magnetic resonance imaging. *Placenta*. 2020;93:113-118.

6. Siauve N, Chalouhi GE, Deloison B, et al. Functional imaging of the human placenta with magnetic resonance. *Am J Obstet Gynecol*. 2015;213:S103-S114.
7. Crovetto F, Crispi F, Casas R, et al. Effects of Mediterranean diet or mindfulness-based stress reduction on prevention of small-for-gestational age birth weights in newborns born to at-risk pregnant individuals: the IMPACT BCN randomized clinical trial. *JAMA*. 2021;326:2150-2160.
8. Crovetto F, Crispi F, Borras R, et al. Mediterranean diet, Mindfulness-Based Stress Reduction and usual care during pregnancy for reducing fetal growth restriction and adverse perinatal outcomes: IMPACT BCN (Improving Mothers for a better PrenAtal Care Trial BarCeloNa): a study protocol for a randomized controlled trial. *Trials*. 2021;22:362.
9. Andescavage NN, Du Plessis A, Limperopoulos C. Advanced MR imaging of the placenta: exploring the in utero placenta–brain connection. *Semin Perinatol*. 2015;39:113-123.
10. Bulas D, Egloff A. Benefits and risks of MRI in pregnancy. *Semin Perinatol*. 2013;37:301-304.
11. Liu XL, Feng J, Huang CT, Mei YJ, Xu YK. Use of intravoxel incoherent motion MRI to assess placental perfusion in normal and Fetal Growth Restricted pregnancies on their third trimester. *Placenta*. 2022;118:10-15.
12. Sinding M, Peters DA, Frøkjaer JB, et al. Placental magnetic resonance imaging T2* measurements in normal pregnancies and in those complicated by fetal growth restriction. *Ultrasound Obstet Gynecol*. 2016;47:748-754.
13. Ho AEP, Hutter J, Jackson LH, et al. T2* placental magnetic resonance imaging in preterm preeclampsia: an observational cohort study. *Hypertension*. 2020;75:1523-1531.
14. Dyhr JJ, Linderoth IR, Hansen DN, et al. Confined placental mosaicism: placental size and function evaluated on magnetic resonance imaging. *Ultrasound Obstet Gynecol*. 2023;62:130-136.
15. Glover V, Bergman K, Sarkar P, O'Connor TG. Association between maternal and amniotic fluid cortisol is moderated by maternal anxiety. *Psychoneuroendocrinology*. 2009;34:430-435.
16. Mairesse J, Lesage J, Breton C, et al. Maternal stress alters endocrine function of the feto-placental unit in rats. *Am J Physiol Endocrinol Metab*. 2007;292:E1526-E1533.
17. Roland MCP, Friis CM, Voldner N, et al. Fetal growth versus birthweight: the role of placenta versus other determinants. *PLoS One*. 2012;7:e39324.
18. Anderson KB, Hansen DN, Haals C, et al. Placental diffusion-weighted MRI in normal pregnancies and those complicated by placental dysfunction due to vascular malperfusion. *Placenta*. 2020;91:52-58.
19. Derwig I, Lythgoe DJ, Barker GJ, et al. Association of placental perfusion, as assessed by magnetic resonance imaging and uterine artery Doppler ultrasound, and its relationship to pregnancy outcome. *Placenta*. 2013;34:885-891.
20. Moore RJ, Strachan BK, Tyler DJ, et al. In utero perfusing fraction maps in normal and growth restricted pregnancy measured using IVIM Echo-planar MRI. *Placenta*. 2000;21:726-732.
21. Tremblay E, Thérasse E, Thomassin-Naggara I, Trop I. Quality initiatives: guidelines for use of medical imaging during pregnancy and lactation. *Radiographics*. 2012;32:897-911.
22. Sigmund EE, Cho GY, Kim S, et al. Intravoxel incoherent motion imaging of tumor microenvironment in locally advanced breast cancer. *Magn Reson Med*. 2011;65:1437-1447.
23. Lee H, Cashin AG, Lamb SE, et al. A guideline for reporting mediation analyses of randomized trials and observational studies: the AGReMA Statement. *JAMA*. 2021;326:1045-1056.
24. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. Mediation: *R* package for causal mediation analysis. *J Stat Softw*. 2014;59(5):1-38.
25. Parisi F, Savasi VM, Di Bartolo I, Mandia L, Cetin I. Associations between first trimester maternal nutritional score, early markers of placental function, and pregnancy outcome. *Nutrients*. 2020;12:1799.
26. Timmermans S, Steegers-Teunissen R, Vujkovic M, et al. The Mediterranean diet and fetal size parameters: the generation R study. *Br J Nutr*. 2012;108:1399-1409.
27. Baker BC, Hayes DJ, Jones RL. Effects of micronutrients on placental function: evidence from clinical studies to animal models. *Reproduction*. 2018;156:R69-R82.
28. Mousa A, Naqash A, Lim S. Macronutrient and micronutrient intake during pregnancy: an overview of recent evidence. *Nutrients*. 2019;11:443.
29. Casas R, Sacanella E, Urpí-Sardà M, et al. Long-term immunomodulatory effects of a Mediterranean diet in adults at high risk of cardiovascular disease in the PREvención con DIeta MEDiterránea (PREDIMED) randomized controlled Trial1-3. *J Nutr*. 2016;146:1684-1693.
30. Haghiac M, Hua YX, Presley L, et al. Dietary omega-3 fatty acid supplementation reduces inflammation in obese pregnant women: a randomized double-blind controlled clinical trial. *PLoS One*. 2015;10:e0137309.
31. Hölzel BK, Carmody J, Vangel M, et al. Mindfulness practice leads to increases in regional brain gray matter density. *Psychiatry Res*. 2011;191:36-43.
32. Bronson SL, Bale TL. The placenta as a mediator of stress effects on neurodevelopmental reprogramming. *Neuropsychopharmacology*. 2016;41:207-218.
33. Waffarn F, Davis EP. Effects of antenatal corticosteroids on the hypothalamic-pituitary-adrenocortical axis of the fetus and newborn: experimental findings and clinical considerations. *Am J Obstet Gynecol*. 2012;207:446-454.
34. Hewitt DP, Mark PJ, Waddell BJ. Glucocorticoids prevent the normal increase in placental vascular endothelial growth factor expression and placental vascularity during late pregnancy in the rat. *Endocrinology*. 2006;147:5568-5574.
35. Wyrwoll CS, Seckl JR, Holmes MC. Altered placental function of 11β-hydroxysteroid dehydrogenase 2 knockout mice. *Endocrinology*. 2009;150:1287-1293.
36. Thame M, Osmond C, Bennett F, Wilks R, Forrester T. Fetal growth is directly related to maternal anthropometry and placental volume. *Eur J Clin Nutr*. 2004;58:894-900.
37. Liu HJ, Liu PC, Hua J, Zhao Y, Cao J. Placental weight and size in relation to fetal growth restriction: a case-control study. *J Matern Fetal Neonatal Med*. 2021;34:1356-1360.
38. Roland MCP, Friis CM, Godang K, Bollerslev J, Haugen G, Henriksen T. Maternal factors associated with fetal growth and birthweight are independent determinants of placental weight and exhibit differential effects by fetal sex. *PLoS One*. 2014;9:e87303.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Nakaki A, Denaro E, Crimella M, et al. Effect of Mediterranean diet or mindfulness-based stress reduction during pregnancy on placental volume and perfusion: A subanalysis of the IMPACT BCN randomized clinical trial. *Acta Obstet Gynecol Scand*. 2024;103:2042-2052. doi:10.1111/aogs.14874