# Effects of Mediterranean diet or mindfulness-based stress reduction on fetal and neonatal brain development: a secondary analysis of a randomized clinical trial

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**BACKGROUND:** Maternal suboptimal nutrition and high stress levels are associated with adverse fetal and infant neurodevelopment.

**OBJECTIVE:** This study aimed to investigate if structured lifestyle interventions involving a Mediterranean diet or mindfulness-based stress reduction during pregnancy are associated with differences in fetal and neonatal brain development.

**STUDY DESIGN:** This was a secondary analysis of the randomized clinical trial Improving Mothers for a Better Prenatal Care Trial Barcelona that was conducted in Barcelona, Spain, from 2017 to 2020. Participants with singleton pregnancies were randomly allocated into 3 groups, namely Mediterranean diet intervention, stress reduction program, or usual care. Participants in the Mediterranean diet group received monthly individual sessions and free provision of extra-virgin olive oil and walnuts. Pregnant women in the stress reduction group underwent an 8-week mindfulness-based stress reduction program adapted for pregnancy. Magnetic resonance imaging of 90 fetal brains was performed at 36 to 39 weeks of gestation and the Neonatal Neurobehavioral Assessment Scale was completed for 692 newborns at 1 to 3 months. Fetal outcomes were the total brain volume and lobular or regional volumes obtained from a 3-dimensional reconstruction and semiautomatic segmentation of magnetic resonance images. Neonatal outcomes were the 6 clusters scores of the Neonatal Neurobehavioral Assessment Scale. Multiple regression analyses were conducted to assess the association between the interventions and the fetal and neonatal outcomes.

**RESULTS:** When compared with the usual care group, the offspring exposed to a maternal Mediterranean diet had a larger total fetal brain volume (mean, 284.11 $cm^3$; standard deviation, 23.92 $cm^3$ vs 294.01 $cm^3$; standard deviation, 26.29 $cm^3$; $P$=.04), corpus callosum (mean, 1.16 $cm^3$; standard deviation, 0.19 $cm^3$ vs 1.26 $cm^3$; standard deviation, 0.22 $cm^3$; $P$=.03), and right frontal lobe (44.20; standard deviation, 4.09 $cm^3$ vs 46.60; standard deviation, 4.69 $cm^3$; $P$=.02) volumes based on magnetic resonance imaging measures and higher scores in the Neonatal Neurobehavioral Assessment Scale clusters of autonomic stability (mean, 7.4; standard deviation, 0.9 vs 7.6; standard deviation, 0.7; $P$=.04), social interaction (mean, 7.5; standard deviation, 1.5 vs 7.8; standard deviation, 1.3; $P$=.03), and range of state (mean, 4.3; standard deviation, 1.3 vs 4.5; standard deviation, 1.0; $P$=.04). When compared with the usual care group, offspring from the stress reduction group had larger fetal left anterior cingulate gyri volume (1.63; standard deviation, 0.32 $m^3$ vs 1.79; standard deviation, 0.30 $cm^3$; $P$=.03) based on magnetic resonance imaging and higher scores in the Neonatal Neurobehavioral Assessment Scale for regulation of state (mean, 6.0; standard deviation, 1.8 vs 6.5; standard deviation, 1.5; $P$<.01).

**CONCLUSION:** Maternal structured lifestyle interventions involving the promotion of a Mediterranean diet or stress reduction during pregnancy were associated with changes in fetal and neonatal brain development.

**Key words:** MRI, Fetal brain, Maternal intervention, Mediterranean diet, Midfulness-Based Stress Reduction, Neurodevelopment

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## Introduction

Neurodevelopmental problems affect 1 in 10 children.[1] Adverse prenatal conditions are recognized as determinants of adverse neurodevelopment.[2–6] Particularly, maternal lifestyle habits, including suboptimal nutrition or high levels of stress, are associated with a higher prevalence of neurodevelopmental impairment in childhood.[3,7–12] Lifestyle modification has been proposed to be a potentially effective strategy to prevent maternal and fetal complications during pregnancy.[11,13–15] However, there are no randomized studies that evaluated if structured interventions aimed at improving diet or reducing stress during pregnancy affect fetal or neonatal neurodevelopment.

EDITOR'S CHOICE

## AJOG MFM at a Glance

### Why was this study conducted?

This study aimed to investigate if a Mediterranean diet or stress reduction during pregnancy influence the fetal and neonatal neurodevelopment.

### Key findings

In a randomized clinical trial sub analysis, the offspring of mothers who followed a Mediterranean diet had a larger total fetal brain volume, corpus callosum, and right frontal lobe and higher scores in neonatal autonomic stability, social interactive organization, and range of state. Those from mothers on a stress reduction program had a larger fetal left anterior cingulate gyri volume and higher scores in neonatal regulation of state.

### What does this add to what is known?

This was a clinical trial that demonstrated that structured maternal lifestyle interventions during pregnancy have the potential to modify offspring neurodevelopment.

The Improving Mothers for a Better Prenatal Care Trial Barcelona (IMPACT BCN) randomized clinical trial was designed to investigate the effects of structured lifestyle interventions specifically focussed on a Mediterranean diet or mindfulness-based stress reduction on the proportion of newborns born small-for-gestational age (SGA) and other adverse pregnancy outcomes.[16,17] In this study, we report the results of a secondary analysis of this trial, which aimed to test the hypothesis that structured lifestyle interventions during pregnancy improved fetal and neonatal neurodevelopment as assessed by fetal brain magnetic resonance imaging (MRI) and neonatal neurobehavior assessment.

## Materials and Methods

### Study design, population, and ethics

This study was part of a large randomized clinical trial, termed IMPACT BCN,[16,17] that was conducted at the Hospital Clínic and the Hospital Sant Joan de Déu, a referral center for maternal-fetal and neonatal medicine in Barcelona, Spain. The trial was registered at ClinicalTrials.gov under the identifier: NCT03166332 (https://clinicaltrials.gov/ct2/show/NCT03166332). Enrollment took place from February 2017 to October 2019 with follow-up until 2 years of newborns' postnatal age (final follow-up on May 1, 2022). The study population was pregnant individuals who were recruited at midgestation (19.0−23.6 weeks' gestation) for being at high risk of having an SGA newborn based on the criteria of the Royal College of Obstetrics and Gynaecologists.[18] Participants who agreed to join the trial provided written informed consent and were randomized in a 1:1:1 ratio into 3 groups, namely a nutritional intervention based on a Mediterranean diet with supplementation of extra-virgin olive oil and walnuts; a stress reduction intervention based on a mindfulness-based stress reduction (MBSR) program; or a control group without any intervention (usual care). All participants attended the baseline visit at enrollment and a final visit at the end of interventions when they completed several questionnaires and provided biologic samples and when perinatal data were collected. Details are provided in the Supplemental Materials and in the trial protocol.[17]

For the purposes of this study and according to the trial protocol,[17] a subgroup of participants (n=147), randomly selected from the 3 study groups, underwent an MRI of the fetal brain during pregnancy after 36 weeks of gestation. The inclusion criteria for MRI recruitment were those individuals who participated in the IMPACT BCN trial and who did not have any MRI contraindications, such as claustrophobia and metallic implants and devices. All individuals−−randomly selected−−who agreed to participate provided written informed consent on the day of the MRI procedure. Moreover, the whole population of IMPACT BCN was invited for a postnatal test to assess neonatal neurobehavior using the Neonatal Neurobehavior Assessment Scale (NBAS). The protocols were approved by the institutional review board (HCB-2016-0830 and HCB-2020-0267).

### Interventions during pregnancy

The dietary intervention was based on Mediterranean diet principles, adapted from the Prevención con Dieta Mediterránea (PREDIMED) trial,[19] with the aim of changing the general dietary pattern instead of focusing on changes in single foods or macronutrients. The intervention involved individual assessments every month and monthly group sessions, both provided by trained nutritionists, from recruitment (19−23 weeks' gestation) to the end of the intervention (34−36 weeks' gestation). In addition, participants in this group were provided with extra-virgin olive oil (2 L every month) and walnuts (450 g every month) at no cost and specific materials (recipes, a 1-week shopping list of food items according to the season of the year, a weekly plan of meals with detailed menus) were given at each visit. Additional details of the intervention are provided elsewhere.[16,17]

For the stress reduction group, an MBSR program, adapted for the pregnancy status of participants, was followed. The program included formal and informal techniques with the goal of enhancing nonjudgmental present-focused awareness and reducing rumination (dysregulated focus on the past) and anxiety. The program consisted of 8-weeks of weekly group classes (20−25 participants) of 2.5 hours, 1 full day, and daily home practice. The sessions included didactic presentations, formal 45-minute meditation practices with various mindfulness meditations, mindful yoga, body awareness, and group discussion. MP3s/CDs of formal meditations adapted to pregnancy were provided for home practice and a book and a notebook with relevant readings and the possibility to register their training. Additional details of the intervention are provided elsewhere.[16,17]

Participants who were randomized to the usual care group received usual pregnancy care following institutional protocols.

## Measures

*Fetal brain magnetic resonance. Data acquisition.* From 36 weeks 0 days to 39 weeks and 6 days of gestation, randomly selected participants underwent a 3.0 T MRI scan using a body array radio-frequency coil without sedation. Single-shot fast spin-echo T2-weighted sequences were done in 1 of 2 hospitals (Hospital San Joan de Déu or Hospital Clínic) with Philips Ingenia (Amsterdam, the Netherlands) or Siemens MRI MAGNETOM Vida (Munich, Germany) scanner. The parameters used for each machine were as follows: for Philips, repetition time 1570 ms, echo time 150 ms, slice thickness 3 mm, field of view 290 × 250 mm, voxel spacing 0.7 × 0.7 × 3.0 mm, no interslice-slice gap; and for Siemens, repetition time 1390 ms, echo time 160 ms, slice thickness 3 mm, field of view 230 × 230 mm, voxel spacing 1.2 × 1.2 × 3.0 mm, no interslice-slice gap. Three orthogonal planes, oriented along the axis of the fetal brainstem, obtaining 2-loops of axial, coronal, and sagittal single shoot slices were obtained for each subject. The participants could choose their position in supine, side, or oblique-left side. If the quality of the images was distorted because of fetal movements, consecutive repetitions were acquired until an acceptable quality image was obtained. MRI images were reviewed for the presence of anatomical abnormalities or acquired lesions by an experienced neuroradiologist (M.R. or M. G.).

*Image processing.* The obtained images were processed using the perinatal pipeline developed by Urru et al.[20] First, the fetal brain was reconstructed in 3 dimensions using a super-resolution reconstruction algorithm,[21,22] and taking into consideration the different voxel sizes of each MRI. Second, the brain was segmented in 2 phases; the first segmentation was performed using 9 labels for different tissue and structures[23] (Supplemental Figure 1), and the second segmentation was done using a multisubject atlas with 50 labels for regional brain segmentation[24] (Supplemental Figure 1). Third, using the computed segmentations, volumes of the total brain and the regional volumes were automatically generated (Supplemental Figure 1, A). Suboptimal reconstructions and segmentations were excluded from the final manual correction. The remaining computed segmentations were further corrected manually with the software ITK-SNAP (version 3.6.0)[25] by a single trained researcher (A.N.) who was blinded to the study groups, perinatal data, and automatically generated volumes. Total brain volume (TBV) was defined as the sum of all the intracranial structures except the cerebrospinal fluid and ventricular volumes, extracted from the tissue segmentation (Supplemental Figure 1, B in the Supplementary document). Intracranial volume was defined as the sum of TBV, cerebrospinal fluid, and ventricular volumes.

The volumes of the frontal, temporal, parietal, and occipital lobes, insula, anterior and posterior cingulate gyri, corpus callosum, cerebellum, and brain stem were also analyzed (Supplemental Figure 1, C). The volumes of each brain region were summed from the 50-label segmentation as in Supplemental Figure 1, D in Supplementary document.

*Neonatal neurobehavior assessment.* The NBAS was offered to all participants in the IMPACT BCN trial at 1 to 3 months of postnatal age. The tests were performed by 2 observers (A.C. and M.P.) who were accredited by the Brazelton Institute (Harvard Medical School, Boston, MA) and blinded to the study groups and perinatal results. The NBAS test is a standard method for evaluating the newborn's capacity to respond to the environment, as a surrogate of brain maturation,[26−28] and consists of 35 items of neurologic and behavioral assessments.[29] The items are scored to create 7 clusters. A cluster of reflexes, such as plantar grasp and Babinski, and 6 behavioral clusters, including habituation (the ability to respond to stimuli while asleep), motor system (the quality of movement and tone), autonomic stability (the signs of stress related to homeostatic adjustments of the central nervous system), social-interactive (the ability to attend animate and inanimate visual and auditory stimuli), range of state (the arousal and state lability), and regulation of state (the ability to regulate their state in increasing levels of stimulation).[29−32] The NBAS has been used extensively as an assessment tool for evaluating neonatal neurobehavior in complicated pregnancies,[33−35] and it is reported to predict the short- to mid-term cognitive development of the child.[27] In this study, NBAS assessments were performed in a small, quiet, semi-dark, warm room with at least 1 parent present. The 6 behavioral clusters were analyzed in this study (habituation, motor system, autonomic stability, social-interactive, range of state, and regulation of state). The cluster scores were transformed into z scores based on the normal curve references for our population and were defined as abnormal if the z score was below −1. An abnormal NBAS score was defined as 1 when there was at least 1 abnormal cluster and as 0 when all the clusters were normal.

### Questionnaires and biomarkers

Several questionnaires of food and maternal well-being and stress were collected, as well as maternal blood samples to assess biomarkers of diet and stress at baseline (19−23 weeks of gestation) and at the final study evaluation (34−36 weeks of gestation) (the Supplementary Methods contain details).

### Outcomes

The outcomes of the fetal brain MRI analysis were the TBV and the lobular and regional volumes, including the corpus callosum, cerebellum, brainstem, and intracranial volume. The outcomes for the NBAS were the scores obtained in each of the 6 clusters.

### Statistical analysis

Normal distributions of variables were evaluated using the Shapiro-Wilk test and histograms. Data are presented as mean (standard deviation [SD]), estimated marginal mean, median (interquartile range [IQR]), or number (percentage), as appropriate. Baseline characteristic comparisons among the study groups were assessed using analysis of variance with Tukey's post hoc test for continuous variables and Pearson[2] test for the categorical variables to compare each intervention group with the usual care group.

The sample size calculation is provided in the Supplementary document. In brief, the sample sizes for both fetal (n=17 per group, total n=51) and neonatal (n=95 per group, total n=285) outcomes were calculated, aiming for a power of 80% and assuming a type I error of 5% with 1:1:1 ratio randomization based on previous literature.[36,37]

Fetal brain volumes and NBAS cluster scores for each intervention group and the usual care group were compared using linear regressions. For fetal brain volume analysis, any malformations or anomalies of the central nervous system diagnosed based on MRI scan were excluded from the analysis. Data were adjusted by fetal sex, gestational age at MRI scan, MRI machine, and potential baseline differences among maternal characteristics. Furthermore, regional brain volumes were adjusted for total brain volume. NBAS scores were adjusted for the mother's socioeconomic status, potential baseline differences among maternal characteristics, gestational age at delivery, birth weight, fetal sex, neonatal age at examination, and breastfeeding. In additional analyses, the associations of the fetal brain volumes and NBAS scores with the questionnaires and biomarkers evaluated at the final study evaluation (34−36 weeks of gestation) were analyzed by linear regression analyses with adjustment for the same variables as above, and the association between the fetal brain volumes and abnormal NBAS scores was analyzed using logistic regression (the Supplementary document contains more details).

Statistical comparisons and adjusted means were computed using the emmeans library (v. 1.8.2). Considering the exploratory nature of this study and the use of novel image processing techniques, multiple comparison corrections were not performed, thus $P<.05$ was considered statistically significant. All statistical analyses were performed using software R (version 4.0.5; R Foundation, R Core Tema, Vienna, Austria) and RStudio (version 1.4.110; Rstudio).

## Results

### Study population

From February 2017 to October 2019, a total of 1221 pregnant individuals were included in the IMPACT BCN trial. The flowchart of individuals included in the secondary examinations and analyses reported here are shown in Figure 1. Briefly, for fetal brain MRI analysis, among the 350 participants initially approached, 147 mothers underwent an MRI after 36 weeks of gestation of which 90 were used for the study analysis (Figure 1) after 1 case was excluded owing to a diagnosis of mild ventriculomegaly. For the NBAS assessment, 692 neonates were evaluated. The maternal baseline characteristics among the study groups were similar except for a slight increase in previous thyroid disorders in the stress reduction group (Supplemental Table 1). Pregnancy and neonatal outcomes were similar among the study groups (Table 1).

### Fetal brain volumetric analysis

From each intervention group, 30 images with the best reconstruction and segmentation quality were selected. Fetal brain MRIs were performed at a mean (SD) gestational age of 36.91 (0.61) weeks. The TBV was significantly larger among fetuses from the Mediterranean diet group than among those in the usual care group (mean, 294.01 $cm^3$; SD, 26.29 $cm^3$ vs 284.11 $cm^3$; 23.92 $cm^3$; $P$=.04) (Table 2 and Supplemental Figure 2), whereas no differences were found between the stress reduction and the usual care group (mean, 286.83; SD, 18.75 $cm^3$ vs 284.11; 23.92 $cm^3$; $P$=.69). Intracranial volume did not differ among the study groups (Table 2). Regarding the regional brain volumes, fetuses in the Mediterranean diet group had a larger corpus callosum (mean, 1.26; SD, 0.22 $cm^3$ vs 1.16; 0.19 $cm^3$; $P$=.03) (Figure 2, A) and right frontal lobe (46.60; 4.69 $cm^3$ vs 44.20; 4.09 $cm^3$; $P$=.02) (Figure 2, B) than the usual care group. Fetuses in the stress reduction intervention group had larger volumes in the left anterior cingulate gyri (1.79; 0.30 $cm^3$ vs 1.63; 90.32 $cm^3$; $P$=.03) than the usual care group (Figure 2, C). The association of fetal brain volumes with maternal diet or stress questionnaires and biomarkers are shown in the Supplementary document. In summary, TBV was found to have positive associations with walnut intake and biomarkers of extra-virgin olive oil consumption, and the left anterior cingulate lobe volume had a positive association with one of the mother's mindfulness facets (Supplementary Results and Supplemental Tables 2, 3 and 4).

### Neonatal neurobehavior assessment

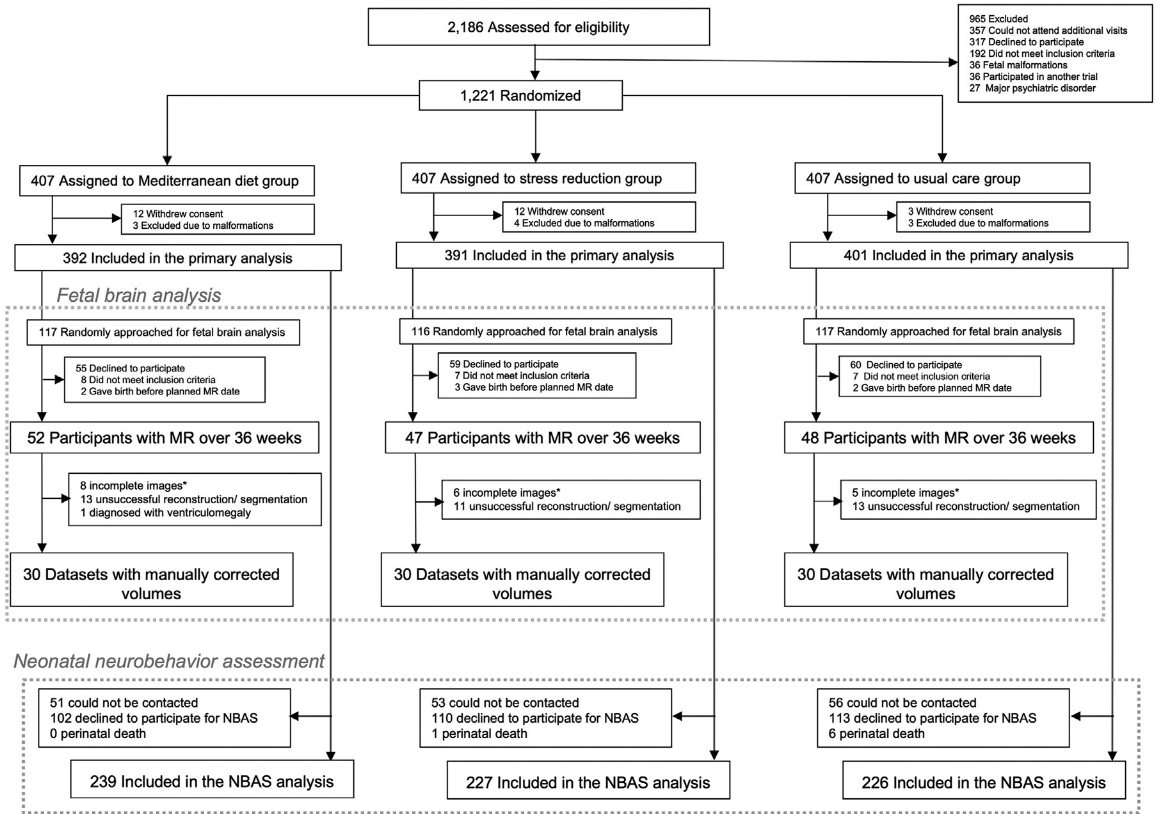
The NBAS assessment was done at a mean (SD) of 45.9 (3.0) days after birth. When compared with usual care, newborns from the Mediterranean diet group had significantly higher scores in the autonomic stability (mean, 7.6; SD, 0.7 vs 7.4; 0.9; $P$=.04), social-interactive (mean, 7.8; SD, 1.3 vs 7.5; 1.5; $P$=.03), and range of state (mean, 4.5; SD, 1.0 vs 4.3; 1.1; $P$=.04) clusters (Table 3). Newborns from the stress reduction group had significantly higher scores in the regulation of state cluster (mean, 6.5; SD, 1.5 vs 6.0; 1.8; $P<.01$) (Table 3). Associations of the NBAS analyses with maternal diet or stress questionnaires and biomarkers are shown in the Supplemental Results and Supplemental Tables 2, 3 and 4 in which several positive associations were found between the NBAS cluster results and nutritional analysis results. Associations between the fetal brain MRIs and NBAS are shown in the Supplemental Results and Supplemental Figure 3.

## Discussion

### Principal findings of the study

In this randomized clinical trial that involved pregnant individuals at high risk for delivering SGA newborns, an

FIGURE 1
**Flowchart for the study population**




*Asterisk* denotes segmentation errors are defined as images with excessive errors in the automatic segmentation, on which manual corrections were not performed.

*MR*, magnetic resonance; *NBAS*, Neonatal Behavioral Assessment Scale.

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intervention based on the Mediterranean diet in comparison with usual pregnancy care was associated with larger fetal brain volumes, larger corpus callosum and right frontal lobe volumes based on MRI measurements, and higher scores in several neonatal NBAS clusters. In addition, an intervention based on stress reduction was associated with larger left anterior cingulate gyri volumes obtained from fetal MRIs and higher scores in the NBAS regulation of state cluster.

## Maternal Mediterranean diet and offspring neurodevelopment

This randomized trial evaluated the association of a Mediterranean diet with fetal brain development and neonatal neurobehavior. Three randomized trials have evaluated the effects of docosahexaenoic acid (DHA) supplements during pregnancy on infant neurodevelopment. Two of these studies evaluated infant neurodevelopmental tests and reported either no improvements[38] or initial improvements that were not sustained over time.[39] A smaller trial evaluated MRIs of infants and reported larger TBVs, total gray matter, and corpus callosum volume.[40] The positive findings in our study may have been facilitated by the use of a dietary intervention instead of supplementation with specific nutrients, providing the synergistic effect of several dietary components, such as polyunsaturated fatty acids mainly from blue fish and walnuts, antioxidant vitamins and dietary fiber from vegetables, fruits and legumes, and (poly)phenols from walnuts and extra-virgin olive oil.[41] Good adherence to a Mediterranean diet has been reported to have positive effects on offspring neurodevelopment.[42,43] In adults, observational studies have reported associations between adherence to a Mediterranean diet and larger total and regional brain volumes[44,45] and with higher white and grey matter integrity.[46] Aside from its effects on oxidative stress and inflammatory mediators, a Mediterranean diet is rich in unsaturated fatty acids (such as DHA and eicosapentaenoic acid), which have relevant roles in neurogenesis[47,48] and neuroprotection.[49]

TABLE 1
**Perinatal outcome of the study population according to the intervention groups**

| Characteristics | Usual care n=226 | Mediterranean diet n=239 | Stress reduction n=227 | MedDiet vs usual care *P* value | Stress reduction vs usual care *P* value |
|---|---|---|---|---|---|
| Pregnancy outcomes | | | | | |
| Gestational diabetes mellitus | 24 (10.6%) | 29 (12.1%) | 21 (9.3%) | .61 | .63 |
| Gestational hypertension | 3 (1.3%) | 5 (2.1%) | 7 (3.1%) | .53 | .20 |
| Preeclampsia | 25 (11.1%) | 16 (6.7%) | 17 (7.5%) | .10 | .19 |
| Preterm birth | 10 (4.4%) | 9 (3.8%) | 17 (7.5%) | .72 | .17 |
| Delivery outcome | | | | | |
| Gestational age at delivery (wk) | 39.7 (38.6– 40.4) | 39.9 (39.1–40.4) | 39.7 (38.7–40.4) | .24 | .93 |
| Mode of delivery | | | | .16 | .78 |
| Vaginal delivery | 137 (60.6%) | 124 (51.89%) | 133 (58.6%) | | |
| Operative vaginal delivery | 22 (9.7%) | 28 (11.7%) | 20 (8.8%) | | |
| Cesarean delivery | 67 (29.7%) | 87 (36.4%) | 74 (32.6%) | | |
| Neonatal outcome | | | | | |
| Female sex | 103 (45.6%) | 118 (49.4%) | 100 (44.1%) | .41 | .74 |
| Birth weight (g) | 3167.0 (510.6) | 3226.2 (491.5) | 3193.6 (507.9) | .20 | .58 |
| Percentile birth weight | 41.2 (29.4) | 43.7 (29.0) | 43.6 (29.2) | .37 | .39 |
| SGA (<10th percentile) | 41 (18.1%) | 33 (13.8%) | 33 (14.5%) | .20 | .30 |
| Severe SGA (<3rd percentile) | 15 (6.6%) | 12 (5.0%) | 10 (4.4%) | .46 | .30 |
| LGA (>90th percentile) | 21 (9.3%) | 17 (7.1%) | 14 (6.2%) | .39 | .21 |
| Apgar 5 min <7 | 1 (0.4%) | 0 (0.0%) | 0 (0.0%) | .39 | .57 |
| pH umbilical artery | 7.20 (0.1) | 7.21 (0.1) | 7.20 (0.1) | .28 | .48 |
| NICU admission | 15 (6.6%) | 12 (5.0%) | 13 (5.7%) | .46 | .69 |
| Infant data (at 1 mo old) | | | | | |
| Kind of breastfeeding | 202 (89.4%) | 202 (84.5%) | 199 (87.7%) | | |
| Maternal breastfeeding | 154 (68.1%) | 153 (64.0%) | 146 (64.3%) | .35 | .39 |
| Mixed maternal and artificial breastfeeding | 52 (23.0%) | 61 (25.5%) | 63 (27.8%) | .53 | .25 |
| Artificial breastfeeding | 20 (8.9%) | 27 (11.3%) | 19 (8.4%) | .38 | .86 |
| Height (cm) | 53.3 (3.4) | 53.5 (3.4) | 53.5 (3.4) | .69 | .56 |
| Weight (g) | 4062.9 (832.9) | 4146.1 (791.6) | 4109.8 (835.3) | .29 | .57 |

The data for n=692 participants are presented. The data are expressed as median (IQR) or mean (standard deviation) or number (percentage).

*IQR*, interquartile range; *LGA*, large for gestational age; *NICU*, neonatal intensive care unit; *SGA*, small for gestational age.

*Nakaki. Mediterranean diet, stress reduction, and offspring neurodevelopment. Am J Obstet Gynecol MFM 2023.*

## Maternal stress reduction and offspring neurodevelopment

This randomized trial also evaluated the association of maternal stress reduction during pregnancy with fetal and neonatal neurodevelopment. Stress reduction is a plausible explanation for the findings of this study. Maternal stress and/or maternal anxiety consistently have been reported to be associated with impaired neurodevelopment[50–52] and with differences in fetal brain development and regional connectivity as assessed by MRI[11,53] in observational studies. The stress reduction program in this study was associated with improvements in well-being and stress scales and biomarkers when compared with the other study groups. Similar findings have been reported in pregnant[54] and nonpregnant individuals.[55] In adults, mindfulness has been associated with increased regional gray matter concentration in observational studies,[56] and 2 randomized controlled studies reported increased white matter integrity[57] and functional connectivity.[58]

TABLE 2
**Fetal brain magnetic resonance imaging results according to the intervention groups**

| Fetal brain assessment | Usual care n=30 | Mediterranean diet n=30 | Stress reduction n=30 | Mediterranean diet vs usual care | | Stress reduction vs usual care | |
|---|---|---|---|---|---|---|---|
| | | | | Estimate (95% CI) | *P* value | Estimate (95% CI) | *P* value |
| Gestational age at MRI (wk) | 36.8 (0.6) | 36.9 (0.7) | 37.0 (0.6) | | .71 | | .28 |
| Total brain volume ($cm^3$) | 284.11 (23.92) | 294.01(26.29)[a] | 286.83 (18.75) | −12.6 (−25.11 to −0.09) | .04 | −2.31 (−13.98 to 9.36) | .69 |
| Intracranial volume ($cm^3$) | 376.57 (32.35) | 393.36 (42.24) | 379.46 (31.33) | −5.65 (−16.98 to 5.69) | .32 | −2.42 (−10.97 to 6.13) | .57 |
| Corpus callosum ($cm^3$) | 1.16 (0.19) | 1.26 (0.22)[a] | 1.12 (0.14) | −0.1 (−0.2 to −0.01) | .03 | 0.07 (−0.01 to 0.14) | .08 |
| Brainstem ($cm^3$) | 5.56 (0.44) | 5.62 (0.31) | 5.64 (0.39) | 0.06 (−0.1 to 0.23) | .45 | −0.04 (−0.23 to 0.15) | .67 |
| Left cerebellum ($cm^3$) | 8.20 (0.86) | 8.26 (0.88) | 8.35 (0.73) | 0.11 (−0.28 to 0.5) | .58 | −0.08 (−0.44 to 0.28) | .67 |
| Right cerebellum ($cm^3$) | 7.95 (0.73) | 8.17 (0.82) | 8.22 (0.67) | −0.11 (−0.45 to 0.22) | .50 | −0.18 (−0.51 to 0.14) | .27 |
| Left frontal lobe ($cm^3$) | 44.62 (4.34) | 46.81 (4.74) | 45.00 (3.07) | −0.5 (−1.33 to 0.33) | .23 | 0.04 (−0.72 to 0.79) | .93 |
| Right frontal lobe ($cm^3$) | 44.20 (4.09) | 46.60 (4.69)[a] | 44.62 (2.98) | −0.84 (−1.6 to −0.09) | .02 | 0.13 (−0.56 to 0.83) | .70 |
| Left cingulate lobe ($cm^3$) | 3.52 (0.54) | 3.75 (0.47) | 3.70 (0.41) | −0.08 (−0.28 to 0.12) | .41 | −0.16 (−0.33 to 0.02) | .08 |
| Right cingulate lobe ($cm^3$) | 4.56 (0.59) | 4.66 (0.66) | 4.63 (0.46) | 0.07 (−0.17 to 0.31) | .56 | 0.01 (−0.2 to 0.22) | .95 |
| Left anterior cingulate lobe ($cm^3$) | 1.63 (0.32) | 1.73 (0.26) | 1.79 (0.30)[b] | −0.02 (−0.15 to 0.11) | .77 | −0.13 (−0.26 to −0.01) | .03 |
| Right anterior cingulate lobe ($cm^3$) | 2.25 (0.41) | 2.24 (0.44) | 2.29 (0.36) | 0.11 (−0.1 to 0.32) | .31 | 0.01 (−0.17 to 0.19) | .91 |
| Left posterior cingulate lobe ($cm^3$) | 1.88 (0.26) | 2.02 (0.30) | 1.91 (0.17) | −0.06 (−0.18 to 0.05) | .27 | −0.02 (−0.11 to 0.06) | .61 |
| Right posterior cingulate lobe ($cm^3$) | 2.32 (0.26) | 2.42 (0.34) | 2.35 (0.18) | −0.04 (−0.13 to 0.06) | .44 | −0.003 (−0.08 to 0.08) | .93 |
| Left insula lobe ($cm^3$) | 3.75 (0.37) | 3.75 (0.37) | 3.69 (0.30) | 0.06 (−0.11 to 0.23) | .47 | 0.002 (−0.14 to 0.15) | .98 |
| Right insula lobe ($cm^3$) | 4.34 (0.41) | 4.50 (0.44) | 4.37 (0.34) | −0.05 (−0.21 to 0.11) | .53 | −0.08 (−0.22 to 0.05) | .22 |
| Left parietal lobe ($cm^3$) | 29.05 (2.66) | 30.19 (3.28) | 29.46 (2.16) | −0.28 (−0.98 to 0.43) | .43 | −0.12 (−0.74 to 0.49) | .68 |
| Right parietal lobe ($cm^3$) | 26.95 (2.52) | 28.08 (3.08) | 27.56 (2.07) | −0.19 (−0.85 to 0.46) | .55 | −0.33 (−0.87 to 0.21) | .22 |
| Left occipital lobe ($cm^3$) | 14.09 (1.56) | 14.50 (1.60) | 14.39 (1.20) | 0.15 (−0.36 to 0.65) | .56 | −0.19 (−0.66 to 0.28) | .43 |
| Right occipital lobe ($cm^3$) | 14.73 (1.60) | 15.03 (1.60) | 14.78 (1.27) | 0.14 (−0.42 to 0.71) | .61 | 0.1 (−0.41 to 0.62) | .70 |
| Left temporal lobe ($cm^3$) | 23.67 (2.15) | 24.13 (2.23) | 23.91 (1.88) | 0.22 (−0.27 to 0.72) | .37 | 0.11 (−0.32 to 0.55) | .61 |
| Right temporal lobe ($cm^3$) | 23.36 (1.87) | 24.11 (2.42) | 23.83 (1.98) | −0.1 (−0.56 to 0.36) | .66 | −0.04 (−0.41 to 0.33) | .83 |

The data for n=90 participants are presented. Values are expressed as mean (standard deviation).

*P* values were generated using a linear model adjusted for gestational age at MR, fetal sex, thyroid disease, MR machine. and total brain volume (except for total brain volume).

*CI*, confidence interval; *MR*, Magnetic resonance.

[a] Statistical significance between Mediterranean diet and usual care groups; [b]Statistically significance between stress reduction and usual care groups.

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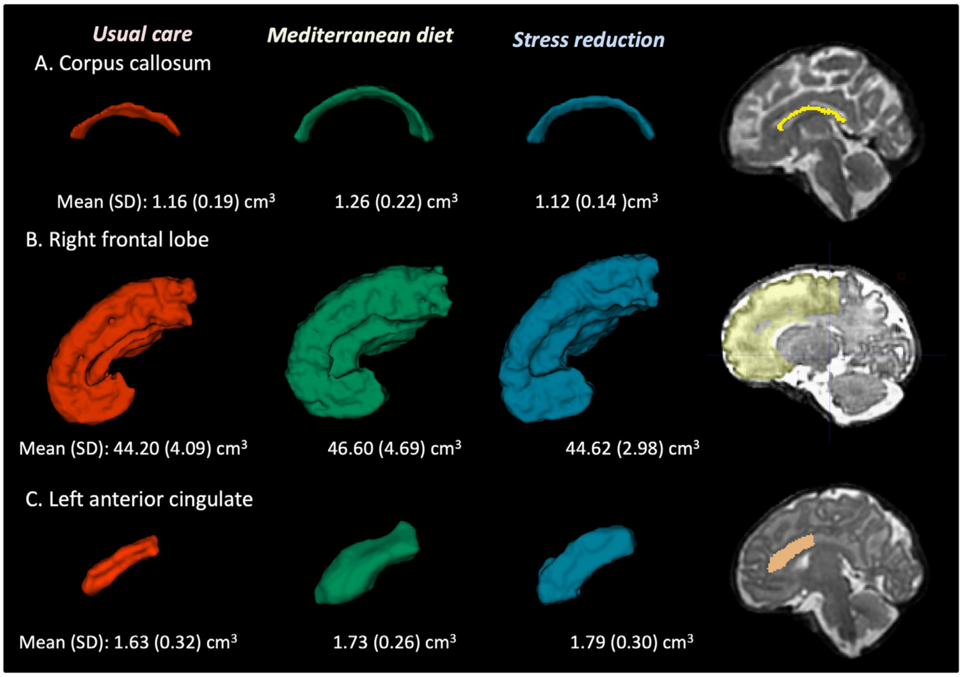
FIGURE 2
**Reconstructed brain images of regions with significant differences**




**A,** Corpus Callosum; **B.** Right frontal lobe; **C,** Left anterior cingulate lobe

*SD*, standard deviation.

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TABLE 3
**Neonatal Behavioral Assessment Scale examination of newborns according to the intervention groups**

| Cluster | Usual care n=226 | Mediterranean diet n=239 | Stress reduction n=227 | Mediterranean diet vs usual care | | Stress reduction vs usual care | |
|---|---|---|---|---|---|---|---|
| | | | | β (95% CI) | *P* value | β (95% CI) | *P* value |
| NBAS examination | | | | | | | |
| Days after birth | 45.9 (2.9) | 46.1 (3.2) | 45.8 (2.9) | | .39 | | .99 |
| NBAS clusters | | | | | | | |
| Habituation[a] | 7.5 (1.5) | 7.6 (1.2) | 7.1 (1.4) | −0.14 (−0.70 to 0.42) | .36 | 0.42 (−0.27 to 1.10) | .23 |
| Motor system | 6.4 (0.9) | 6.5 (1.0) | 6.5 (0.9) | −0.02 (−0.18 to 0.15) | .85 | −0.06 (0.22−0.11) | .17 |
| Autonomic stability | 7.4 (0.9) | 7.6 (0.7)[b] | 7.6 (0.8) | −0.15 (−0.31 to −0.002) | .04 | −0.11 (−0.27 to 0.05) | .17 |
| Social interactive organization | 7.5 (1.5) | 7.8 (1.3)[b] | 7.7 (1.1) | −0.27 (−0.53 to −0.02) | .03 | −0.23 (−0.47 to 0.02) | .07 |
| Range of status | 4.3 (1.1) | 4.5 (1.0)[b] | 4.3 (1.2) | −0.20 (−0.40 to −0.01) | .04 | −0.003 (−0.21 to 0.21) | .97 |
| Regulation of states | 6.0 (1.8) | 6.1 (1.8) | 6.5 (1.5)[c] | -0.11 (-0.45 to 0.22) | .52 | −0.49 (−0.80 to −0.18) | <.01 |

The data for n=692 participants are presented. Data are expressed as mean (SD). A higher score indicates better performance.

*P* values were calculated using linear models adjusted for mother's socioeconomic status, gestational age at delivery, birth weight, fetal sex, neonatal age at examination, and breastfeeding status.

*CI*, confidence interval; *NBAS*, Neonatal Behavioral Assessment Scale.

[a] For the habituation cluster, the data were available for 152 (22%) cases (67 Mediterranean diet, 48 stress reduction, 37 usual care); [b] Statistically significant difference between Mediterranean diet and usual care groups;; [c] Statistically significant difference between stress reduction and usual care groups.

*Nakaki. Mediterranean diet, stress reduction, and offspring neurodevelopment. Am J Obstet Gynecol MFM 2023.*

## Clinical and research implications

Although additional research is needed to confirm these findings, this randomized clinical trial demonstrated the potential of maternal structured lifestyle interventions during pregnancy to modify fetal and neonatal neurodevelopment.

## Strengths and limitations

The study has several limitations. First, MRI was performed in a relatively small subset of participants. Second, 2 different machines were used in the MRI analysis. To minimize the effect of this variation, a processing technique with super-resolution reconstruction was applied,[20] and the MRI machine was regarded as a covariate in the statistical analysis. Third, this study was not representative of a general pregnancy population because the participants had pregnancies at high risk for SGA neonates in a high-resource setting, and participants had a low proportion of obesity and gestational diabetes. Therefore, these findings might not be replicable in other settings. Fourth, the interventions tested were associated with improvements in the rate of SGA and other pregnancy complications in the original randomized trial.[16] It cannot be excluded that the effects observed were partly mediated by a reduction in pregnancy complications even if the rates of SGA in the subgroups analyzed in the present study were similar.

## Conclusion

In this randomized trial, applying structured interventions based on a Mediterranean diet or stress reduction to pregnant women at high risk for SGA neonates was associated with significant improvements in fetal brain volumes as assessed by MRI and neonatal neurobehavior as assessed by the NBAS at 1 to 3 months of age. These results need replication in future studies and in additional patient populations. ■


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## Supplementary materials

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