

JAMA | Original Investigation

# 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

Francesca Crovetto, MD, PhD; Fàtima Crispi, MD, PhD; Rosa Casas, PhD; Andrés Martín-Asuero, PhD; Roger Borràs, MSc; Eduard Vieta, MD, PhD; Ramon Estruch, MD, PhD; Eduard Gratacós, MD, PhD; for the IMPACT BCN Trial Investigators

**IMPORTANCE** Being born small for gestational age (SGA) is a leading cause of perinatal morbidity and mortality with no effective prevention or therapy. Maternal suboptimal nutrition and high stress levels have been associated with poor fetal growth and adverse pregnancy outcomes.

**OBJECTIVE** To investigate whether structured interventions based on a Mediterranean diet or mindfulness-based stress reduction (stress reduction) in high-risk pregnancies can reduce the percentage of newborns who were born SGA and other adverse pregnancy outcomes.

**DESIGN, SETTING, AND PARTICIPANTS** Parallel-group randomized clinical trial conducted at a university hospital in Barcelona, Spain, including 1221 individuals with singleton pregnancies (19-23 weeks' gestation) at high risk for SGA. Enrollment took place from February 1, 2017, to October 10, 2019, with follow-up until delivery (final follow-up on March 1, 2020).

**INTERVENTIONS** Participants in the Mediterranean diet group (n = 407) received 2 hours monthly of individual and group educational sessions and free provision of extra-virgin olive oil and walnuts. Individuals in the stress reduction group (n = 407) underwent an 8-week stress reduction program adapted for pregnancy, consisting of weekly 2.5-hour sessions and 1 full-day session. Individuals in the usual care group (n = 407) received pregnancy care per institutional protocols.

**MAIN OUTCOMES AND MEASURES** The primary end point was the percentage of newborns who were SGA at delivery, defined as birth weight below the 10th percentile. The secondary end point was a composite adverse perinatal outcome (at least 1 of the following: preterm birth, preeclampsia, perinatal mortality, severe SGA, neonatal acidosis, low Apgar score, or presence of any major neonatal morbidity).

**RESULTS** Among the 1221 randomized individuals (median [IQR] age, 37 [34-40] years), 1184 (97%) completed the trial (392 individuals assigned to the Mediterranean diet group, 391 to the stress reduction group, and 401 to the usual care group). SGA occurred in 88 newborns (21.9%) in the control group, 55 (14.0%) in the Mediterranean diet group (odds ratio [OR], 0.58 [95% CI, 0.40-0.84]; risk difference [RD], -7.9 [95% CI, -13.6 to -2.6];  $P = .004$ ), and 61 (15.6%) in the stress reduction group (OR, 0.66 [95% CI, 0.46-0.94]; RD, -6.3 [95% CI, -11.8 to -0.9];  $P = .02$ ). The composite adverse perinatal outcome occurred in 105 newborns (26.2%) in the control group, 73 (18.6%) in the Mediterranean diet group (OR, 0.64 [95% CI, 0.46-0.90]; RD, -7.6 [95% CI, -13.4 to -1.8];  $P = .01$ ), and 76 (19.5%) in the stress reduction group (OR, 0.68 [95% CI, 0.49-0.95]; RD, -6.8 [95% CI, -12.6 to -0.3];  $P = .02$ ).

**CONCLUSIONS AND RELEVANCE** In this randomized trial conducted at a single institution in Spain, treating pregnant individuals at high risk for SGA with a structured Mediterranean diet or with mindfulness-based stress reduction, compared with usual care, significantly reduced the percentage of newborns with birth weight below the 10th percentile. Due to important study limitations, these findings should be considered preliminary and require replication, as well as assessment in additional patient populations, before concluding that these treatments should be recommended to patients.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: [NCT03166332](https://clinicaltrials.gov/ct2/show/study/NCT03166332)

JAMA. 2021;326(21):2150-2160. doi:10.1001/jama.2021.20178

← Editorial page 2137

+ Supplemental content

+ CME Quiz at [jamacmelookup.com](https://jamacmelookup.com)

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Group Information:** The IMPACT BCN Trial Investigators appear in Supplement 4.

**Corresponding Author:** Eduard Gratacós, MD, PhD, BCNatal (Hospital Sant Joan de Déu and Hospital Clínic), Universitat de Barcelona, Sabino de Arana 1, 08036 Barcelona, Spain ([egratacos@ub.edu](mailto:egratacos@ub.edu)).

Infants who are small for gestational age (SGA), defined as birth weight below the 10th percentile, account for a large proportion of perinatal mortality and morbidity and poor neurodevelopment in children.<sup>1,2</sup> There is currently no effective prevention or therapy for SGA. Maternal lifestyle factors, including suboptimal nutrition and high levels of stress, may be associated with SGA and other obstetric complications.<sup>3,4</sup> This association is thought to potentially be mediated by effects on systemic and placental inflammation, oxidative stress, and cellular senescence, all involved in the pathophysiology of SGA.<sup>5</sup> However, no randomized clinical trials have evaluated the effect of interventions aimed at improving diet, reducing stress, or both on preventing SGA.

Mediterranean diet interventions may reduce adverse health outcomes, such as cardiovascular events, diabetes, cognitive decline, and other inflammatory-based diseases.<sup>6,7</sup> Two randomized trials using Mediterranean diet in pregnant women with obesity<sup>8</sup> or “normal weight”<sup>9</sup> reported significant reductions in the incidence of gestational diabetes. Although it was not a primary end point, one of these studies also suggested a reduction in the incidence of SGA.<sup>10</sup>

Mindfulness meditation and other mind-body therapies have emerged as helpful adjuncts for stress-related diseases, but there is limited evidence of their effects on objective health outcomes.<sup>11</sup> Mindfulness-based stress reduction (henceforth referred to as *stress reduction*) is a structured program that has been extensively used in medical research.<sup>12,13</sup> In pregnancy, small studies have reported that stress reduction was feasible and associated with lower perceived stress and anxiety.<sup>14</sup> However, no studies have evaluated the effect of stress reduction on pregnancy outcomes.

This study evaluated whether structured lifestyle interventions based on either Mediterranean diet or stress reduction reduce the incidence of birth weight below the 10th percentile and adverse pregnancy outcomes in individuals at risk for SGA.<sup>15</sup>

## Methods

### Trial Design

IMPACT BCN (Improving Mothers for a Better Prenatal Care Trial Barcelona) was a parallel, unblinded, 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. Details of the trial design are provided in the protocol<sup>16</sup> and available in [Supplement 1](#) and the statistical analysis plan is provided in [Supplement 2](#). The protocol was approved by the Hospital Clínic institutional review board (HCB-2016-0830). All individuals who agreed to participate provided written informed consent before randomization.

### Participant Selection

All individuals attending routine second trimester ultrasonography scans from 19 weeks 0 days' gestation through 23 weeks 6 days' gestation were screened for eligibility under the Royal College of Obstetricians and Gynaecologists criteria for being

## Key Points

**Question** Among pregnant individuals at high risk for small-for-gestational age (SGA) newborns, is a Mediterranean diet or mindfulness-based stress reduction effective in preventing SGA at delivery?

**Findings** In this randomized clinical trial that included 1184 individuals with singleton pregnancies, the percentage of newborns with birth weight below the 10th percentile was 14% in the Mediterranean diet group and 15.6% in the mindfulness-based stress reduction group, compared with 21.9% in the usual care group; both interventions resulted in a significantly lower percentage of SGA newborns compared with usual care.

**Meaning** Structured interventions based on a Mediterranean diet or mindfulness-based stress reduction significantly reduced the risk of SGA newborns in individuals at high risk for this condition; however, the findings require replication, as well as assessment in additional patient populations, before concluding that these treatments should be recommended to patients.

at high risk of developing SGA during pregnancy,<sup>15</sup> adapted with minor modifications in an institutional clinical protocol (eTable 1 in [Supplement 3](#)). Participants were recruited at this time of gestation to allow standardized approach with the maximal information about risk factors, exclude most congenital malformations and miscarriages, and focus the potential effects of the interventions in the second half of gestation. Inclusion criteria were age 18 years or older, fluency in Spanish language, singleton pregnancy, positive fetal heart rate at the time of ultrasonography, and high risk of newborns with SGA according to the adapted criteria of the Royal College of Obstetricians and Gynaecologists for SGA<sup>15</sup> (eTable 1 in [Supplement 3](#)). Exclusion criteria were fetal anomalies, including chromosomal abnormalities, structural malformations, and congenital infections, detected prenatally; neonatal malformations or congenital anomalies diagnosed after birth; inability to perform additional visits; participation in another trial; and maternal intellectual disability or other mental or major psychiatric disorders requiring therapy during pregnancy. Race and ethnicity groups were recorded to describe the study population, categorized by the participants from fixed categories in a self-reported questionnaire, to have information about the generalizability of the results of the trial.

### Randomization

Participants were randomized in a 1:1:1 ratio to one of the 3 study groups: a Mediterranean diet supplemented with extra-virgin olive oil and walnuts, a stress reduction program, or usual care without any intervention (control group). Randomization was performed immediately after the patient signed the informed consent form using a web-based system and a computer-generated random number. Details are provided in [Supplement 3](#).

### Interventions and Measurements

The interventions were nonpharmacological and based on counseling and behavioral training that was tested in previous studies.<sup>6,13</sup>

### Mediterranean Diet Program

The dietary intervention, adapted from the PREDIMED trial,<sup>6</sup> aimed to change the general dietary pattern rather than focus on changes in single foods or macronutrients. All participants received olive oil (2 L every month) and 15 g of walnuts per day (450 g every month) at no cost. Dietitians conducted face-to-face interviews at enrollment and monthly until the end of the intervention (34-36 weeks' gestation). The participant received dietary training and personalized advice to increase adherence to the Mediterranean diet (eTable 2 in Supplement 3), including recipes, a quantitative 1-week shopping list of food items according to the season of the year, and a weekly plan of meals with detailed menus that were also available on the trial website. Participants were encouraged to increase the intake of whole grain cereals ( $\geq 5$  servings/d); vegetables and dairy products ( $\geq 3$  servings/d); fresh fruit ( $\geq 2$  servings/d); and legumes, nuts, fish, and white meat ( $\geq 3$  servings/week), as well as olive oil use for cooking and dressings. To achieve a personalized goal, personal and individual recommendations were introduced in the participant's diet according to height, weight, culture, and dietary preferences. A 151-item food frequency questionnaire validated for this study population,<sup>17</sup> a 7-day dietary journal, and a 17-item dietary assessment score (eTable 2 in Supplement 3) were used to assess baseline and final Mediterranean diet adherence. Two weeks after each face-to-face visit, participants underwent telephone interviews. In addition, 4 monthly group sessions with up to 20 participants were held to increase adherence. Physical activity was not promoted and energy restriction was not specifically recommended. Additional details of the intervention are provided in Supplement 3.

### Mindfulness-Based Stress Reduction Program

The stress reduction program was based on the program described by Kabat-Zinn<sup>12</sup> and later adopted by health institutions and tested in clinical trials.<sup>13,18</sup> The stress reduction program was adapted for the pregnancy status of the participants; otherwise, it was consistent with previously described stress reduction programs for adults.<sup>18</sup> Stress reduction instructors all self-identified as women, shared several meditations focused on the participant's relationship with the fetus, encouraged informal "being with the baby" practices, and taught prenatal yoga positions. The 8-week program-structured intervention included weekly 2.5-hour sessions, 1 full-day session, and daily home practice. The stress reduction 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 sessions included didactic presentations, formal 45-minute meditation practices with various mindfulness meditations, mindful yoga, body awareness, and group discussion. Home practice was strongly encouraged and was recommended to consist of 45-minute daily formal practice (eg, sitting and walking meditation, body scanning, yoga stretching) and informal practice (eg, mindfulness of daily activities, the 3-minute breathing space). The stress reduction groups were composed of up to 25 participants and were led by 4 experienced, certified stress reduction instructors who

met regularly to monitor and optimize program implementation with the senior coordinators of the intervention (E.V. and A.M.). The instructors supported practice and were available for individual counseling throughout the 8-week program. A book and MP3s or CDs of formal meditations adapted to pregnancy were provided for home practice, as well as a handbook including several activities for each week of the stress reduction program. Participants could record their activities in a logbook, answer questions regarding the content of the week, and share what they had done in the next session. The trial website provided additional material. Stress reduction practices were encouraged after completion of the 8-week stress reduction period; instructors remained available and offered extra weekly sections, including meditations/yoga and experience-sharing among participants. Additional details of the intervention are provided in Supplement 3.

### Control (Usual Care) Group

Pregnant individuals randomized to the usual care group received usual pregnancy care as per institutional protocols.

### Adherence to the Interventions

All individuals included in the trial had a baseline visit (19 to 23.6 weeks' gestation) and a final visit (34 to 36 weeks' gestation) with a dietitian to assess the 151-item food frequency questionnaire,<sup>17</sup> the 7-day dietary journal, and the 17-item dietary assessment (score range, 0-17) (eTable 2 in Supplement 3). All participants also provided self-reported lifestyle questionnaires to measure their anxiety and mindful state (State-Trait Anxiety Inventory [STAI] anxiety and personality scores, with anchors from "not at all" to "very much so" [range, 0-80]; Perceived Stress Scale, with anchors from "never" to "very often" [range, score 0-40]; WHO Five Well Being Index, with anchors from "all of the time" to "at no time" [score range, 0-100]; and Five Facet Mindfulness Questionnaire [FFMQ], with anchors from "always true" to "never" [score range, 8-40 for the observation, description, awareness, and nonjudgmental facets and 7-35 for nonreactivity facet]). Specific details are provided in Supplement 3.

A high adherence to the Mediterranean diet intervention was defined as an improvement of at least 3 points in the final score of the 17-item dietary screener compared with the baseline score. Adherence to the stress reduction intervention was considered high if at least 6 of 9 stress reduction sessions were attended.

Aside from the study interventions, the 3 study groups received the same pregnancy care, including follow-up by maternal-fetal specialists, according to institutional guidelines. Study investigators did not participate in the clinical care of trial participants.

### Outcomes

The prespecified primary end point was the percentage of newborns who were SGA at birth, defined as birth weight below the 10th percentile for gestational age<sup>19</sup> according to local standards.<sup>20</sup>

The prespecified secondary end point was the percentage of newborns with adverse perinatal outcome, defined as

a composite of either preterm birth less than 37 weeks' gestation, preeclampsia, perinatal mortality, severe SGA (birth weight below the third percentile), neonatal acidosis, Apgar score below 7 at 5 minutes, or the presence of any major neonatal morbidity. Major neonatal morbidity was defined as the presence of intraventricular hemorrhage grade III/IV, necrotizing enterocolitis, periventricular leukomalacia, sepsis, bronchopulmonary dysplasia, or hypoxic-ischemic encephalopathy. Details on definitions for secondary composite outcome components are provided in [Supplement 3](#). Other preestablished secondary end points were Bayley-III score, blood pressure, and heart rate evaluated at 2 years of corrected postnatal age. Collection of outcomes related to infants at 2 years of postnatal age is ongoing.

A prespecified subgroup analysis was designed to assess the influence of several baseline variables in relation with the primary end point in each of the intervention groups (Mediterranean diet or stress reduction) vs the usual care group as follows: maternal age 40 years or younger/older than 40 years; White/not White; low/high socioeconomic status; prepregnancy body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) less than 30/greater than or equal to 30; chronic hypertension; diabetes; parity (multiparous/nulliparous); use of assisted reproductive technology; previous adverse obstetrical history; high risk of preeclampsia; smoking during pregnancy; yoga/relaxation during pregnancy; and baseline high/low total Mediterranean diet score.

Additionally, other prespecified exploratory outcomes (perinatal and neonatal data, questionnaires, and biomarkers) were evaluated and are listed in [Supplement 3](#).

Several prespecified biomarkers were evaluated in a subsample of randomly selected participants (30%) to assess the biological effects of the interventions. In 140 participants from each study group, plasma oleic,  $\alpha$ -linoleic, and  $\alpha$ -linolenic acids (biomarkers of walnut consumption) and urinary hydroxytyrosol metabolites (biomarkers of olive oil consumption) were measured at the baseline visit and a final visit. In 50 to 60 participants from each study group (excluding those receiving corticosteroid treatment), the 24-hour urinary cortisone/cortisol ratio (estimating the activity of 11 $\beta$ -hydroxysteroid dehydrogenase type 2) was measured at the baseline and final visits.

All end point-related medical records were examined by trained research staff members blinded to the intervention received.

### Sample Size Calculation

The study was powered for the primary outcome of SGA. Assuming that 30% of individuals would give birth to newborns affected by SGA,<sup>15</sup> it was hypothesized that the Mediterranean diet or stress reduction program could reduce the incidence of SGA by 30%, which corresponds to a 9% absolute risk difference. The 30% relative reduction in the primary outcome was set as a likely observed effect, based on expert opinions of the members of the steering committee and other maternal-fetal specialists at the hospital.<sup>21</sup> Assuming a type I error of 5% and aiming for a power of 80%, the sample size estimate for the primary outcome was 1101 participants (367 per study group).

The required sample size was also calculated for the secondary composite adverse perinatal outcome. It was assumed that an adverse perinatal outcome would occur in 15% of the participants<sup>22,23</sup> and that the interventions could reduce this percentage by 50%, which corresponds to an 8% absolute risk difference. Assuming a type I error of 5% and aiming for a power of 80%, the sample size estimate for the secondary outcome was 1218 participants (406 per group).

The larger sample size estimate of 1218 was adopted as the trial's enrollment target. Differences in the primary outcome were prespecified as confirmatory, while the findings on the secondary end points should be interpreted as exploratory.

### Statistical Analysis

In the full analysis set, participants were analyzed according to their randomization group, excluding those who withdrew consent for participation in the trial and those whose fetuses/neonates had a malformation diagnosed during pregnancy or in the postnatal period from analysis.

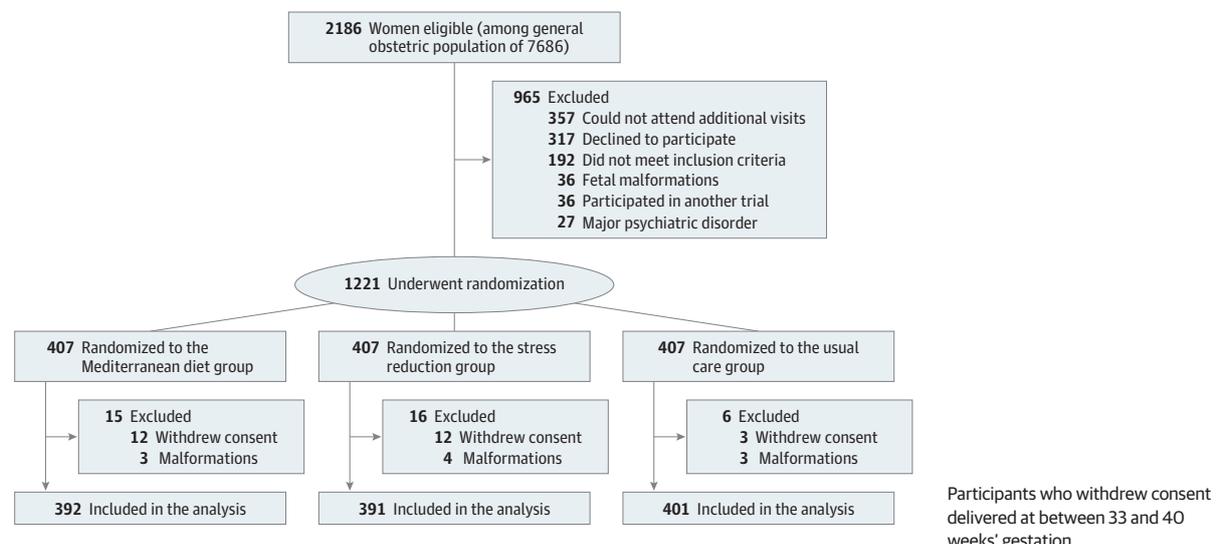
One interim analysis was performed at 50% sample recruitment using the O'Brien-Fleming approach. Members of the data monitoring committee, but not any investigator of the trial, were informed about the interim analysis. The 1-sided  $\alpha$  to indicate statistical significance adjusted at the nominal level was .0015 (2-sided  $\alpha$  = .0031) at the interim analysis and .0245 (2-sided  $\alpha$  = .0490) at the final analysis. The primary end point, the percentage of newborns with a birth weight below the 10th percentile, was analyzed and compared between groups using generalized linear models for binary response with an unadjusted model (1 for each intervention group); intervention effects were reported using odds ratios (ORs) with 95% CIs. Statistical significance was computed using the Wald test.

Hochberg adjustment for multiple comparisons was applied to the primary end point of each intervention group (Mediterranean diet or stress reduction) vs the usual care group. The *P* values for comparisons were put into descending order: if the highest *P* value was lower than the threshold (.0490), the study would be interpreted as positive for each intervention group vs no intervention; if the highest *P* value was higher than the threshold (.0490), the study would be interpreted as null for this study group and the next *P* value would need to be lower than .0245 (.0490/2) to conclude that there was a positive comparison of one of the intervention groups vs no intervention. For the main variable, missing data were imputed using the worst-case strategy.

For the analyses of the secondary end point, a logistic regression model was used; no imputations of missing data and no adjustments were made; all secondary statistical tests were applied with a 2-sided significance level of .05. Because of the potential for type I error due to multiple comparisons, findings on the secondary end point should be interpreted as exploratory.

Primary and secondary end points were also evaluated in the full analysis set (as previously defined but without the exclusion of fetal/neonatal malformation) and the per-protocol analysis (ie, excluding those individuals without high adherence to the intervention: improvement from baseline to final score <3 points for the Mediterranean diet group

Figure 1. Flow of Participants in a Study of the Effects of Mediterranean Diet or Mindfulness-Based Stress Reduction on Prevention of Small-for-Gestational Age Birth Weights



and attendance to less than 6 of 9 class sessions for the stress reduction group).

The subgroup analysis was performed according to a logistic regression model to test the intervention and subgroup interaction (including subgroup, intervention, and intervention  $\times$  subgroup as fixed effects in the model). The subgroup analyses should be interpreted as exploratory.

All other efficacy variables defined as exploratory outcomes in this study (described in Supplement 3) were analyzed as follows:  $\chi^2$  test was used for categorical variables and analysis of variance or analysis of covariance with baseline adjustment were used for continuous variables.

Details of the statistical analyses are provided in the statistical analysis plan in Supplement 2. The statistical software R, version 4.0.3 (R Foundation), and SPSS, version 26 (IBM), were used for data analyses.

## Results

### Baseline Characteristics

From February 2017 to October 2019, a total of 2186 pregnant individuals who attended second trimester ultrasonography scans were considered eligible for study inclusion. However, 965 of these individuals (44%) were excluded from recruitment to the trial because they did not fulfill the inclusion criteria, met at least 1 of the exclusion criteria, or declined to participate (Figure 1; eTable 3 in Supplement 3). Of the 1221 participants (median age, 37 [IQR, 34-40] years) who underwent randomization, 27 (2.2%) withdrew consent and 10 (0.8%) were excluded for a fetal/neonatal malformation diagnosed after randomization. Two participants were lost to follow-up. Study groups were similar with regard to baseline characteristics (Table 1; eTable 4 in Supplement 3).

### Primary End Point

SGA occurred in 88 of 401 participants (21.9%) in the control group compared with 55 of 392 (14%) in the Mediterranean diet group (odds ratio [OR], 0.58 [95% CI, 0.40 to 0.84]; risk difference,  $-7.9$  [95% CI,  $-13.6$  to  $-2.6$ ];  $P = .004$ ) and 61 of 391 (15.6%) in the stress reduction group (OR, 0.66 [95% CI, 0.46 to 0.94]; risk difference,  $-6.3$  [95% CI,  $-11.8$  to  $-0.9$ ];  $P = .023$ ) (Table 2; eTable 5 in Supplement 3). The probabilities of SGA at birth by study group are shown in Figure 2 and eFigure 1 in Supplement 3. The results of the analysis of the full analysis set with the inclusion of those neonates with a malformation diagnosed after randomization is shown in eFigure 2 and eTable 6 in Supplement 3.

### Secondary End Point

The composite adverse perinatal outcome occurred in 105 of 400 participants (26.2%) in the control group compared with 73 of 392 (18.6%) in the Mediterranean diet group (OR, 0.64 [95% CI, 0.46 to 0.90]; risk difference,  $-7.6$  [95% CI,  $-13.4$  to  $-1.8$ ];  $P = .01$ ) and 76 of 390 (19.5%) in the stress reduction group (OR, 0.68 [95% CI, 0.49 to 0.95]; risk difference,  $-6.8$  [95% CI,  $-12.6$  to  $-0.3$ ];  $P = .02$ ). Details regarding the components of the adverse perinatal outcome are provided in Table 2 and eTable 5 in Supplement 3. The results of the analysis of the full analysis set with the inclusion of those neonates with a malformation diagnosed after randomization are shown in eFigure 2 and eTable 6 in Supplement 3.

### Subgroup Analyses

Baseline subgroup analyses of the primary outcome showed no significant differences in most outcomes (all  $P$  values for interaction  $>.05$ ), with the exception of smoking during pregnancy ( $P$  value for interaction = .01) (eFigure 3 in Supplement 3).

**Table 1. Baseline Characteristics of Participants in a Study of the Effects of Mediterranean Diet or Mindfulness-Based Stress Reduction on Prevention of Small-for-Gestational Age (SGA) Birth Weights**

Characteristic	No. (%)		
	Mediterranean diet (n = 392)	Stress reduction (n = 391)	Usual care (n = 401)
Age, median (IQR), y	37.2 (34.5-40.4)	37.6 (33.9-40.4)	37 (33.2-40.5)
Race and ethnicity <sup>a</sup>			
Asian	8 (2)	6 (1.5)	8 (2)
Black	8 (2)	7 (1.8)	7 (1.7)
Latin American	54 (13.8)	67 (17.1)	61 (15.2)
Maghreb	8 (2)	10 (2.6)	9 (2.2)
White	314 (80.1)	301 (77)	316 (78.8)
Socioeconomic status <sup>b</sup>			
High	234 (59.7)	214 (54.7)	229 (57.1)
Medium	138 (35.2)	146 (37.3)	143 (35.7)
Low	20 (5.1)	31 (7.9)	29 (7.2)
BMI before pregnancy, mean	24 (4.8)	24 (5)	23.9 (4.8)
Previous medical condition			
Autoimmune disease	59 (15.1)	53 (13.6)	70 (17.5)
Obesity <sup>c</sup>	47 (12)	48 (12.3)	46 (11.5)
Thyroid disorder	46 (11.7)	54 (13.8)	34 (8.5)
Diabetes	21 (5.4)	20 (5.1)	16 (4)
Minor psychiatric disorder <sup>d</sup>	13 (3.3)	19 (4.9)	19 (4.7)
Chronic hypertension	12 (3.1)	13 (3.3)	21 (5.2)
Chronic kidney disease	8 (2)	9 (2.3)	8 (2)
Obstetric adverse history			
Previous SGA birth	69 (17.6)	57 (14.6)	72 (18)
Previous preterm birth	27 (6.9)	19 (4.9)	22 (5.5)
Previous preeclampsia	26 (6.6)	21 (5.4)	21 (5.2)
Previous stillbirth	14 (3.6)	8 (2)	7 (1.7)
Nulliparous	215 (54.8)	228 (58.3)	231 (57.6)
Use of assisted reproductive technologies	98 (25)	97 (24.8)	102 (25.4)
During pregnancy			
Cigarette smoking	27 (6.9)	31 (7.9)	38 (9.5)
Alcohol intake	4 (1)	5 (1.3)	9 (2.2)
Drug consumption	3 (0.8)	1 (0.8)	1 (0.2)
Sports practice	74 (18.9)	84 (21.5)	79 (19.7)
Yoga or Pilates	66 (16.8)	58 (14.8)	74 (18.5)
Gestational age at randomization, mean (SD), wk	21.2 (0.7)	21.3 (0.7)	21.2 (0.7)

<sup>a</sup> Race and ethnicity were self-reported by the participants.

<sup>b</sup> Socioeconomic status was defined as low if participants reported having never worked or being unemployed for more than 2 years and having a partner with unqualified work or who was unemployed; high if they reported university studies regardless of whether they were working; and medium if any other situations.

<sup>c</sup> Obesity was defined as body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) greater than 30.

<sup>d</sup> Defined as disorders without treatment during pregnancy, either because they were minor disorders or were not active during pregnancy.

### Exploratory Outcomes

Details regarding the exploratory outcomes (perinatal and neonatal data) are reported in eTable 7 and eFigure 4 in Supplement 3.

### Adherence to the Mediterranean Diet Intervention

Participants in the 3 study groups reported similar baseline patterns of food and nutrient intake (eTables 8-10 in Supplement 3). At the final assessment, significant differences in the foods and nutrients were observed in the 151-item food frequency questionnaire and mean (SE) final score of the 17-item dietary assessment, which increased significantly for the Mediterranean diet group (12 [0.12]), while no significant differences were observed in mean (SE) scores in the other groups (usual care: 7.8 [0.12]; stress reduction: 8.0 [0.12]) (eTables 8-10 in Supplement 3). In the Mediterranean group, the mean (SD)

visit attendance throughout the intervention was 3.2 (1.3), and 350 participants (89.3%) attended baseline and final visits. The mean (SD) number of monthly group sessions attended was 1.8 (1.2) by a mean of 140 participants (38%). High adherence (increase of 3 or more points in the 17-item dietary assessment score) was observed in 243 of 392 participants (62%). Primary and secondary end points for participants with high adherence to Mediterranean diet intervention (eFigure 5 in Supplement 3) are reported in eTables 11 and 12 in Supplement 3. No relevant diet-related adverse events were reported (see Supplement 3).

### Adherence to the Stress Reduction Intervention

The 3 study groups showed similar baseline scores on lifestyle and well-being questionnaires (eTable 13 in Supplement 3). At the end of the intervention, participants in the stress

Table 2. End Points According to Trial Group in a Study of the Effects of Mediterranean Diet or Mindfulness-Based Stress Reduction on Prevention of Small-for-Gestational Age (SGA) Birth Weights

Outcome	No. (%)			Mediterranean diet vs usual care		Stress reduction vs usual care	
	Mediterranean diet	Stress reduction	Usual care	Risk difference (95% CI)	P value <sup>a</sup>	Risk difference (95% CI)	P value <sup>a</sup>
<b>Primary end point</b>							
SGA	55 (14)	61 (15.6)	88 (21.9)	-7.9 (-13.6 to -2.6)	.004	-6.3 (-11.8 to -0.9)	.02
<b>Secondary composite end point</b>							
Adverse perinatal outcome <sup>b</sup>	73 (18.6)	76 (19.5)	105 (26.2)	-7.6 (-13.4 to -1.8)	.01	-6.8 (-12.6 to -0.3)	.02
Preterm birth	24 (6.1)	26 (6.7)	29 (7.3)	-1.1 (-4.6 to 2.4)	.53	-0.6 (-4.1 to 3.0)	.75
Preeclampsia	22 (5.6)	24 (6.2)	37 (9.3)	-3.6 (-7.3 to 0.0)	.05	-3.1 (-6.8 to 0.6)	.11
Severe SGA	20 (5.1)	19 (4.9)	39 (9.8)	-4.7 (-8.3 to -1.0)	.01	-4.9 (-8.5 to -1.3)	.01
Perinatal death	0	1 (0.3)	6 (1.5)	-1.5 (-2.7 to -0.3)	.03	-1.2 (-2.5 to 0.1)	.12
Neonatal metabolic acidosis <sup>c</sup>	25 (6.5)	26 (6.8)	30 (7.7)	-1.2 (-4.9 to 2.4)	.50	-0.9 (-4.6 to 2.8)	.64
Major neonatal morbidity	9 (2.3)	6 (1.5)	8 (2)	0.3 (-1.7 to 2.3)	.78	-0.5 (-2.3 to 1.4)	.62
<b>Combination end point</b>							
Severe SGA and/or preeclampsia	37 (9.4)	38 (9.7)	69 (17.2)	-7.8 (-12.5 to -3.1)	.002	-7.5 (-12.2 to -2.8)	.002
Severe SGA and/or preeclampsia and/or perinatal death	37 (9.4)	38 (9.7)	70 (17.5)	-8.1 (-12.8 to -3.4)	.001	-7.8 (-12.5 to -3.0)	.002
Severe SGA and/or preeclampsia and/or perinatal death and/or preterm birth	55 (14.0)	55 (14.1)	86 (21.5)	-7.5 (-12.8 to -2.2)	.007	-7.4 (-12.7 to -2.1)	.007

<sup>a</sup> P values refer to logistic regression analysis.

<sup>b</sup> Missing data of 2 pregnancies (1 in the usual care group and 1 in the stress reduction group), imputed just for primary end point (n = 1182 [400 in the usual care group and 390 in the stress reduction group]).

<sup>c</sup> Data available for 1156 pregnancies (389 in the usual care group, 386 in the Mediterranean diet group, and 381 in the stress reduction group).

reduction group had significantly lower anxiety scores (mean [SE] STAI anxiety score, 12.6 [0.34]; mean [SE] STAI personality score, 13.7 [0.3]; eTable 13 in Supplement 3) and significantly higher mean (SE) scores on the well-being and mindful state-related questionnaires (WHO Five Well Being Index score, 67.2 [0.71]; FFMQ observation score, 27.7 [0.29]; FFMQ description score, 32.7 [0.24]; FFMQ awareness score, 30.8 [0.33]; FFMQ nonjudgmental score, 31.3 [0.25]; FFMQ nonreactivity score, 25 [0.22]; eTable 13 in Supplement 3) compared with the usual care group. The median (IQR) number of sessions attended was 6 (1-7). High adherence to the stress reduction intervention was recorded in 198 of 391 participants (50.6%). Primary and secondary end points for participants with high adherence to the stress reduction intervention (eFigure 5 in Supplement 3) are reported in eTable 11 in Supplement 3. No relevant mindfulness-related adverse event was reported (see Supplement 3).

### Biological Effects of the Interventions

Baseline levels of blood biomarkers of walnuts and urinary biomarkers of extra-virgin olive oil intake in 434 participants were similar in all study groups but were significantly increased by the end of the intervention in the Mediterranean diet group (eg, mean [SE]  $\alpha$ -linolenic acid of 0.53 [0.02], mean [SE] hydroxytyrosol of 1.75 [0.23]) compared with the same group at baseline and with the usual care group, as reported in eTable 14 and eFigures 6 to 8 in Supplement 3.

The baseline 24-hour urinary cortisone/cortisol ratio in 162 participants was similar in all groups but was significantly increased at the end of the intervention in the stress reduction group (mean [SD] of 1.83 [0.1]) compared with the same group

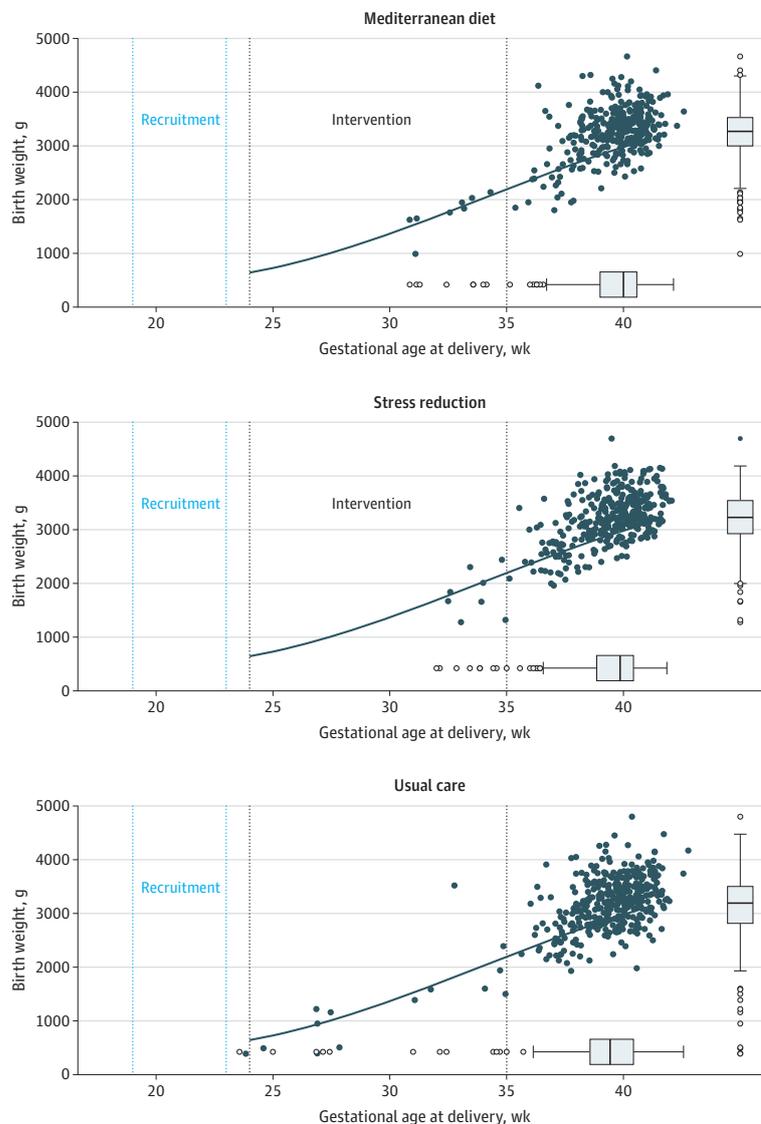
at baseline and with the usual care group, as shown in eTable 14 and eFigure 9 in Supplement 3.

## Discussion

In this randomized clinical trial that involved pregnant individuals at high risk for delivering newborns SGA, interventions based on Mediterranean diet or stress reduction, compared with usual pregnancy care, were associated with a reduction in the percentage of newborns who were born SGA, defined as birth weight below the 10th percentile.

Most studies on nutritional strategies in high-income settings have failed to show effects on SGA. A 2018 review<sup>24</sup> identified 70 randomized trials evaluating omega-3 addition in pregnancy that showed little or no difference in frequency of SGA. A substantial number of studies have evaluated associations between dietary patterns and birth weight,<sup>3</sup> but only a few were randomized trials. A clinical trial<sup>25</sup> of 290 healthy pregnancies reported that a cholesterol-lowering diet resulted in similar percentages of SGA as control participants. More recently, 2 randomized trials evaluated the effects of a supervised Mediterranean diet intervention on pregnancy outcomes.<sup>8,9</sup> The Esteem trial<sup>8</sup> used a Mediterranean diet from 18 weeks' gestation in 1252 pregnant individuals with obesity, chronic hypertension, or hypertriglyceridemia, observing no differences in SGA. The percentages of participants with BMI greater than 30 was 69.5% compared with 12% in the present study. The St Carlos trial<sup>9</sup> evaluated the effects of Mediterranean diet on gestational diabetes in 874 low-risk participants with a low BMI from 8 to 12 weeks' gestation. A 2019 subanalysis of this

Figure 2. Scatterplots of Birth Weight vs Gestational Age at Delivery in Each Study Group With Jitter Random Noise to Avoid Overlaps



Lines indicate the 10th birth weight percentile. For each study group, vertical box plot represents birth weight and horizontal box plot, gestational age at delivery. For each box plot, lines in the middle indicate the median; box ends, IQR; whiskers, values within 1.5× the IQR; and dots, values beyond the whiskers.

study<sup>10</sup> reported a statistically significant reduction in SGA (1.2% vs 5.7% in control participants;  $P < .001$ ). Some differences may explain the positive findings of the present study in comparison with others. First, it was designed and powered to address a difference in SGA and conducted in individuals at risk. Second, it used a structured and supervised Mediterranean diet intervention that was associated with significant changes in objective biomarkers of olive oil and walnut intake. Mediterranean diet pattern has been associated with antioxidant and anti-inflammatory properties.<sup>26,27</sup> Because SGA is associated with increased placental inflammation, oxidative stress, and aging, the results might be biologically related to the effects of the Mediterranean diet. Third, the study sample was predominantly composed of White individuals with low BMI and middle to high socioeconomic status, who may respond to the intervention tested while others do not.

To our knowledge, this is the first evidence that a cognitive intervention might improve pregnancy outcomes. Stress reduction is a plausible mechanism for the study findings. Maternal stress levels have been associated with increased SGA<sup>28</sup> and higher levels of cortisol and proinflammatory cytokines.<sup>29</sup> Increased inflammation, oxidative stress, and placental aging are pathogenic mechanisms involved in SGA.<sup>5</sup> In-line with previous studies in pregnant<sup>30</sup> and nonpregnant adults,<sup>31,32</sup> the stress reduction program was associated with improvements in anxiety and well-being scales and with increased estimated activity of a cortisol-deactivating enzyme compared with the other study groups.

SGA is considered a surrogate of fetal growth restriction and is a key target of global health policies. It is associated with stillbirth<sup>1</sup> and neonatal mortality and has neurologic<sup>33</sup> and cardiometabolic<sup>34</sup> long-term consequences into infancy

and adulthood. Additionally, severe SGA (ie, birth weight below the third percentile), which has been estimated to account for approximately two-thirds of all fetal deaths<sup>35</sup> among growth-restricted newborns, was reduced in this study. In the long term, a mean 100-g increase in birth weight as observed in this study has been associated with a 7% reduction in the likelihood of developing diabetes during adulthood.<sup>36</sup> Mediterranean diet and stress reduction were also associated with a significant decrease in the composite adverse outcome that included the main obstetric complications (ie, preeclampsia, preterm birth, and stillbirth).<sup>37</sup> The study was not powered to detect differences in the individual components of the composite adverse outcome.

### Limitations

The study has several limitations. First, the biological basis of the study hypotheses and results is speculative. Second, the effect size in the control group was smaller than anticipated. Third, there were some baseline imbalances in prognostic characteristics. There is the potential that the findings, in part, reflect a relatively worse outcome in the control group rather than beneficial effects in the intervention groups; however, the prognostic direction of the imbalances was not consistent. Fourth, the excess number of early births in the control group clustered extremely early in the intervention period, raising a question of whether the observed differences were due to the intervention or represent a chance outcome.

Fifth, cross-effects may have occurred between the intervention groups: a healthier diet may have improved mental well-being and vice versa. However, changes in oil metabolites were small in the stress reduction group and changes in anxiety/well-being levels were small in the Mediterranean diet group. Sixth, there was a lack of an attention control to en-

sure that control participants had the same number of visits and same amount of personal interaction as the intervention groups. Seventh, there were small differences in the number of participants responding to well-being questionnaires that may have caused attrition bias.

Eighth, the study was conducted in individuals with high-risk pregnancies and the interventions started in mid-pregnancy. Further research is required to ascertain the effects of these interventions in all pregnant individuals and starting earlier in pregnancy. Ninth, the study was conducted in a high-resource setting, and the findings may not be replicable in other settings. Tenth, the population had a low proportion of obesity, gestational diabetes, and large-for-gestational-age newborns. As suggested by this and previous studies,<sup>24,38</sup> the interventions tested might not be effective in patients with obesity or metabolic conditions.

In aggregate, given these limitations these findings should be considered preliminary unless and until they are replicated, including in more diverse populations.

### Conclusions

In this randomized trial conducted at a single institution in Spain, treating pregnant individuals at high risk for SGA with structured Mediterranean diet or with mindfulness-based stress reduction, compared with usual care, significantly reduced the percentage of newborns with birth weight below the 10th percentile. Due to important study limitations, these findings should be considered preliminary and require replication, as well as assessment in additional patient populations, before concluding that these treatments should be recommended to patients.

### ARTICLE INFORMATION

**Accepted for Publication:** October 22, 2021.

**Author Affiliations:** BCNatal Fetal Medicine Research Center (Hospital Clínic and Hospital Sant Joan de Déu), University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain (Crovetto, Crispi, Gratacós); Centre for Biomedical Research on Rare Diseases (CIBER-ER), Madrid, Spain (Crovetto, Crispi, Gratacós); Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición (CIBERON), Instituto de Salud Carlos III, Madrid, Spain (Casas, Estruch); Department of Internal Medicine Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Spain (Casas, Estruch); Instituto esMindfulness, Barcelona, Spain (Martín-Asuero); Cardiovascular Institute, Hospital Clínic, IDIBAPS, Universitat Autònoma de Barcelona, Barcelona, Spain (Borràs); Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain (Borràs, Vieta); Department of Psychiatry and Psychology, Hospital Clínic, Neuroscience Institute, IDIBAPS, University of Barcelona, Barcelona, Spain (Vieta).

**Author Contributions:** Drs Crovetto and Gratacós had full access to all of the data in the study and take responsibility for the integrity of the data and

the accuracy of the data analysis. Drs Crovetto and Crispi contributed equally.

**Concept and design:** Crovetto, Crispi, Martín-Asuero, Vieta, Estruch, Gratacós.

**Acquisition, analysis, or interpretation of data:** Crovetto, Crispi, Casas, Martín-Asuero, Borràs, Estruch, Gratacós.

**Drafting of the manuscript:** Crovetto, Crispi, Vieta, Gratacós.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Crovetto, Borràs, Estruch.

**Obtained funding:** Gratacós.

**Administrative, technical, or material support:** Crovetto, Martín-Asuero, Estruch.

**Supervision:** Crovetto, Crispi, Borràs, Vieta, Estruch, Gratacós.

**Other - responsible for the Mediterranean diet program:** Casas.

**Other - responsible for the mindfulness-based stress reduction program:** Martín-Asuero.

**Conflict of Interest Disclosures:** Dr Crovetto reported receiving personal fees from Centro de Investigaciones Biomédicas en Red sobre Enfermedades Raras for support for investigation (until July 2019) during the conduct of the study. Dr Crispi reported receiving grants from Hospital Clínic/Institut d'Investigacions Biomèdiques August Pi i Sunyer La Caixa foundation, Cerebra foundation,

and Agència de Gestió d'Ajudes Universitàries i de Investigació (AGAUR) during the conduct of the study. Dr Martín-Asuero reported receiving grants from La Caixa during the conduct of the study and book royalties from Editorial Planeta and Médecir Ediciones, nonfinancial support from Soc Andorrana Ciències, and personal fees from Instituto Guttmann and Technology Centre of Catalonia outside the submitted work and being the founder and owner of Instituto esMindfulness SL. Dr Borràs reported receiving personal fees from Fundació Privada per a la Recerca i la Docència Sant Joan de Déu during the conduct of the study. Dr Vieta reported receiving personal fees from Abbott, Allergan, Angelini, Sage, and Sanofi; and grants from Dainippon Sumitomo, Ferrer (money paid to his institution but no payment made as yet), and Janssen (money paid to his institution for trials on esketamine, JNJ-42165279, and MIJ821); and serving on advisory boards for and receiving personal fees from Lundbeck outside the submitted work. Dr Estruch reported receiving personal fees from Cerveza y salud, Fundació Dieta Mediterrània, Pernaud-Ricard, Instituto Cervantes, and nonfinancial support from Fundació de Investigación Sobre el Vino y Nutrición and Brewers of Europe; and grants from Grand Fountain Laboratories, Uriach Laboratories, Instituto de Salud Carlos III, EIT Digital, and JPI outside the submitted work. Dr Gratacós reported receiving grants from

CaixaResearch (LCF/PR/GN18/10310003), Cerebra Foundation for the Brain Injured Child, and AGAUR Catalonia government (2017 SGR No. 1531) during the conduct of the study and book royalties from Columna Edicions and Editorial Medica Panamericana and grants from Roche Diagnostics International (paid to his institution) outside the submitted work. No other disclosures were reported.

**Funding/Support:** 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); AGAUR under grant 2017 SGR No. 1531. Dr Crovetto has received support from Centro de Investigaciones Biomédicas en Red sobre Enfermedades Raras (CIBERER). Dr Nakaki has received support from a fellowship from "La Caixa" Foundation, Doctoral INPHINIT Retaining fellowship (LCF/BQ/DR19/11740018).

**Role of the Funder/Sponsor:** The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Group Information:** The IMPACT BCN Trial Investigators appear in Supplement 4.

**Data Sharing Statement:** See Supplement 5.

**Additional Contributions:** We thank the study participants for their personal time and commitment to this trial. We also thank all the medical staff, residents, midwives, and nurses of BCNatal, especially Laura Segales, BSc; Marta Dacal, MSc; Maria Laura Boutet, MD; Annachiara Basso, MD; Marta Larroya, MD; Marta Camacho, MD; Marta Garcia, MSc; Mireia Pascual, APRN; and Alba Camacho, APRN (BCNatal Fetal Medicine Research Center, Barcelona, Spain), for their support in the recruitment, interventions, and data collection of the trial; Carlos Galante, MSc (Department of Internal Medicine, Hospital Clinic, Barcelona, Spain, Barcelona, Spain), for his support in the Mediterranean diet intervention; Georgina Badosa, MSc; Amaia Helguera, BSc; and Sylvia Comas, MSc (Instituto esMindfulness, Barcelona, Spain), for their support in the stress reduction intervention; and Julian Lozano-Castellón, MSc; Anallely López-Yerena, MSc; Inés Domínguez-López, BSc; and Maria Marhuenda-Muñoz, MSc (School of Pharmacy and Food Sciences, University of Barcelona, Barcelona, Spain), for their support in the biomarkers analysis of Mediterranean diet compliance. We thank the Clinic-IDIBAPS Biobank for valuable management of samples. Laura Segales, Marta Dacal, Marta Garcia, Mireia Pascual, Alba Camacho, Carlos Galante, Georgina Badosa, Amaia Helguera, Sylvia Comas, Julian Lozano-Castellón, Anallely López-Yerena, Inés Domínguez-López, and Maria Marhuenda-Muñoz received economic compensation for their role in the study. Additionally, the members of the *IMPACT BCN Trial Investigators* group made the following contributions: C. Paules, A. Nakaki, K. Vellvé, and G. Casu were directly involved in participant recruitment and data collection; S. Castro-Barquero and T. Freita were dietitians involved in the Mediterranean diet program; A. M. Ruiz-León and R. M. Lamuela-Raventós were responsible for the analysis of fatty acids and hydroxytyrosol metabolites; M. T. Oller-Guzmán was a mindfulness-based stress reduction instructor who led several groups; A. Martínez-Arán and I. Morilla

were psychologists involved in the stress reduction program; A. Gomez-Gomez and O. J. Pozo were responsible for the analysis of the 24-hour urinary cortisone/cortisol ratio; M. C. Collado and M. Selma-Royo contributed to the analysis and interpretation of the biological effects of the interventions; M. Domenech helped to implement the Mediterranean diet program; A. Arranz was responsible for the postnatal follow-up; F. Figueras contributed to the study design and manuscript writing, and supervised the statistical analysis.

## REFERENCES

- Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. *BMJ*. 2013;346:f108. doi:10.1136/bmj.f108
- Sacchi C, Marino C, Nosarti C, Vieno A, Visentin S, Simonelli A. Association of intrauterine growth restriction and small for gestational age status with childhood cognitive outcomes: a systematic review and meta-analysis. *JAMA Pediatr*. 2020;174(8):772-781. doi:10.1001/jamapediatrics.2020.1097
- Raghavan R, Dreifelbis C, Kingshipp BL, et al. Dietary patterns before and during pregnancy and birth outcomes: a systematic review. *Am J Clin Nutr*. 2019;109(suppl\_7):s729-s756. doi:10.1093/ajcn/nqy353
- Traylor CS, Johnson JD, Kimmel MC, Manuck TA. Effects of psychological stress on adverse pregnancy outcomes and nonpharmacologic approaches for reduction: an expert review. *Am J Obstet Gynecol MFM*. 2020;2(4):100229. doi:10.1016/j.ajogmf.2020.100229
- Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth restriction. *Am J Obstet Gynecol*. 2018;218(25):s745-s761. doi:10.1016/j.ajog.2017.11.577
- Estruch R, Ros E, Salas-Salvadó J, et al; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. 2018;378(25):e34. doi:10.1056/NEJMoa1800389
- Valls-Pedret C, Sala-Vila A, Serra-Mir M, et al. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. *JAMA Intern Med*. 2015;175(7):1094-1103. doi:10.1001/jamainternmed.2015.1668
- H Al Wattar B, Dodds J, Placzek A, et al; ESTEEM study group. Mediterranean-style diet in pregnant women with metabolic risk factors (ESTEEM): a pragmatic multicentre randomised trial. *PLoS Med*. 2019;16(7):e1002857. doi:10.1371/journal.pmed.1002857
- Assaf-Balut C, García de la Torre N, Durán A, et al. A Mediterranean diet with additional extra virgin olive oil and pistachios reduces the incidence of gestational diabetes mellitus (GDM): a randomized controlled trial: the St. Carlos GDM Prevention Study. *PLoS One*. 2017;12(10):e0185873. doi:10.1371/journal.pone.0185873
- Assaf-Balut C, García de la Torre N, Durán A, et al. A Mediterranean diet with an enhanced consumption of extra virgin olive oil and pistachios improves pregnancy outcomes in women without gestational diabetes mellitus: a sub-analysis of the St. Carlos Gestational Diabetes Mellitus Prevention Study. *Ann Nutr Metab*. 2019;74(1):69-79. doi:10.1159/000495793
- Dossett ML, Fricchione GL, Benson H. A new era for mind-body medicine. *N Engl J Med*. 2020;382(15):1390-1391. doi:10.1056/NEJMp1917461
- Ludwig DS, Kabat-Zinn J. Mindfulness in medicine. *JAMA*. 2008;300(11):1350-1352. doi:10.1001/jama.300.11.1350
- Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: a meta-analytic review. *J Consult Clin Psychol*. 2010;78(2):169-183. doi:10.1037/a0018555
- Dhillon A, Sparkes E, Duarte RV. Mindfulness-based interventions during pregnancy: a systematic review and meta-analysis. *Mindfulness (N Y)*. 2017;8(6):1421-1437. doi:10.1007/s12671-017-0726-x
- The investigation and management of the small for gestational age fetus. Royal College of Obstetricians and Gynaecologists. Updated January 2014. Accessed November 11, 2021. [https://www.rcog.org.uk/globalassets/documents/guidelines/gtg\\_31.pdf](https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_31.pdf)
- Crovetto F, Crispi F, Borrás 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(1):362. doi:10.1186/s13063-021-05309-2
- Juton C, Castro-Barquero S, Casas R, et al. Reliability and concurrent and construct validity of a food frequency questionnaire for pregnant women at high risk to develop fetal growth restriction. *Nutrients*. 2021;13(5):1629. doi:10.3390/nu13051629
- Goyal M, Singh S, Sibinga EM, et al. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. *JAMA Intern Med*. 2014;174(3):357-368. doi:10.1001/jamainternmed.2013.13018
- American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics and the Society for Maternal-Fetal Medicine. ACOG practice bulletin No. 204: fetal growth restriction. *Obstet Gynecol*. 2019;133(2):e97-e109. doi:10.1097/AOG.0000000000003070
- Figueras F, Meler E, Iraola A, et al. Customized birthweight standards for a Spanish population. *Eur J Obstet Gynecol Reprod Biol*. 2008;136(1):20-24. doi:10.1016/j.ejogrb.2006.12.015
- Ross S, Milne J, Dwinell S, et al. Is it possible to estimate the minimal clinically important treatment effect needed to change practice in preterm birth prevention? results of an obstetrician survey used to support the design of a trial. *BMC Med Res Methodol*. 2012;12:31. doi:10.1186/1471-2288-12-31
- Bakalis S, Akolekar R, Gallo DM, Poon LC, Nicolaides KH. Umbilical and fetal middle cerebral artery Doppler at 30-34 weeks' gestation in the prediction of adverse perinatal outcome. *Ultrasound Obstet Gynecol*. 2015;45(4):409-420. doi:10.1002/ulog.14822
- Miranda J, Triunfo S, Rodriguez-Lopez M, et al. Performance of third-trimester combined screening model for prediction of adverse perinatal outcome. *Ultrasound Obstet Gynecol*. 2017;50(3):353-360. doi:10.1002/ulog.17317

24. Middleton P, Gomersall JC, Gould JF, Shepherd E, Olsen SF, Makrides M. Omega-3 fatty acid addition during pregnancy. *Cochrane Database Syst Rev*. 2018;11(11):CD003402. doi:10.1002/14651858.CD003402.pub3
25. Khoury J, Henriksen T, Christophersen B, Tonstad S. Effect of a cholesterol-lowering diet on maternal, cord, and neonatal lipids, and pregnancy outcome: a randomized clinical trial. *Am J Obstet Gynecol*. 2005;193(4):1292-1301. doi:10.1016/j.ajog.2005.05.016
26. Schwingshackl L, Morze J, Hoffmann G. Mediterranean diet and health status: active ingredients and pharmacological mechanisms. *Br J Pharmacol*. 2020;177(6):1241-1257. doi:10.1111/bph.14778
27. Ros E, Martínez-González MA, Estruch R, et al. Mediterranean diet and cardiovascular health: teachings of the PREDIMED study. *Adv Nutr*. 2014;5(3):s330-s336. doi:10.3945/an.113.005389
28. Bussi eres EL, Tarabulsy GM, Pearson J, et al. Maternal prenatal stress and infant birth weight and gestational age: a meta-analysis of prospective studies. *Dev Rev*. 2015;23:179-199. doi:10.1016/j.dr.2015.04.001
29. Lindsay KL, Buss C, Wadhwa PD, Entringer S. The interplay between maternal nutrition and stress during pregnancy: issues and considerations. *Ann Nutr Metab*. 2017;70(3):191-200. doi:10.1159/000457136
30. Guo P, Zhang X, Liu N, et al. Mind-body interventions on stress management in pregnant women: a systematic review and meta-analysis of randomized controlled trials. *J Adv Nurs*. 2021;77(1):125-146. doi:10.1111/jan.14588
31. Koncz A, Demetrovics Z, Takacs ZK. Meditation interventions efficiently reduce cortisol levels of at-risk samples: a meta-analysis. *Health Psychol Rev*. 2021;15(1):56-84. doi:10.1080/17437199.2020.1760727
32. Galante J, Friedrich C, Dawson AF, et al. Mindfulness-based programmes for mental health promotion in adults in nonclinical settings: a systematic review and meta-analysis of randomised controlled trials. *PLoS Med*. 2021;18(1):e1003481. doi:10.1371/journal.pmed.1003481
33. Figueras F, Oros D, Cruz-Martinez R, et al. Neurobehavior in term, small-for-gestational age infants with normal placental function. *Pediatrics*. 2009;124(5):e934-e941. doi:10.1542/peds.2008-3346
34. Crispi F, Miranda J, Gratac s 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(2S):S869-S879. doi:10.1016/j.ajog.2017.12.012
35. Pilliod RA, Cheng YW, Snowden JM, Doss AE, Caughey AB. The risk of intrauterine fetal death in the small-for-gestational-age fetus. *Am J Obstet Gynecol*. 2012;207(4):318.e1-318.e6. doi:10.1016/j.ajog.2012.06.039
36. Katanoda K, Noda M, Goto A, Mizunuma H, Lee JS, Hayashi K. Impact of birth weight on adult-onset diabetes mellitus in relation to current body mass index: the Japan Nurses' Health Study. *J Epidemiol*. 2017;27(9):428-434. doi:10.1016/j.je.2016.08.016
37. Brosens I, Pijnenborg R, Vercruyse L, Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. *Am J Obstet Gynecol*. 2011;204(3):193-201. doi:10.1016/j.ajog.2010.08.009
38. Poston L, Bell R, Croker H, et al; UPBEAT Trial Consortium. Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2015;3(10):767-777. doi:10.1016/S2213-8587(15)00227-2