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Mindfulness-based stress reduction intervention during pregnancy changes maternal brain

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Our aim is to evaluate the effect of a structured stress reduction intervention based on mindfulness during pregnancy on the maternal brain. We report a secondary analysis of IMPACT BCN, a randomized clinical trial including pregnant women randomly allocated to 8-week Mindfulness-Based Stress Reduction ($n = 41$) or usual care (without any intervention, $n = 35$). Maternal magnetic resonance (MR) was performed in the third trimester, cluster-wise analysis was used to assess cortical morphometric differences, and proton magnetic resonance spectroscopy (^{1}H-MRS) to evaluate the metabolic characteristics. Mindfulness status was evaluated using the Five Facet Mindfulness Questionnaire (FFMQ). Results showed that participants from Stress reduction group had significantly larger surface areas in the right superior frontal region as compared to the Usual care group (90%CI: 0.023–0.029, $p = 0.03$). The ^{1}H-MRS revealed that Stress reduction group participants, had higher concentrations of myo-inositol (adjusted mean difference D 0.37 mol/L, 95%CI 0.05–0.69) as compared to Usual care. Participants who had high mindfulness on FFMQ facets of non-judgmental (D 358.5 mm^2, 95%CI 53.5-663.6) and non-reactivity (D 362.3 mm^2, 95%CI 18.8-705.7) had larger right superior frontal area. In conclusion, Mindfulness-Based Stress Reduction program during pregnancy has a significant effect on maternal brain structure and is associated with metabolite concentration changes.

Keywords Mindfulness-based stress reduction, Pregnancy, Brain, MRI, Small-for-gestational age, Proton magnetic resonance spectroscopy

Abbreviations

IMPACT BCN	Improving mothers for a better PrenAtal care trial BarCeloNa
MBSR	Mindfulness-based stress reduction

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MR	Magnetic resonance
mI	Myo-inositol
FFMQ	Five facet mindfulness questionnaire
^{1}H-MRS	Proton magnetic resonance spectroscopy
SGA	Small-for-gestational age

Life during pregnancy is starting to be recognized as a more stressful period than previously thought. A recent study reported that approximately 1 in 5 pregnant women could be diagnosed with peripartum anxiety disorders[1]. Maternal stress and anxiety not only persist throughout pregnancy but also may increase over gestation[2], which are known to be associated with labor complications[3], hypertension and preeclampsia[4], as well as a high risk of depression[5]. Considering the physiology of pregnancy, non-pharmacological approaches are proposed to reduce stress and anxiety, such as yoga, exercise, meditation, including mindfulness and breathing[6]. Among these techniques, mindfulness has rapidly gathered evidence of reducing stress and anxiety during pregnancy[7].

Mindfulness-Based Stress Reduction (MBSR), a structured program based on Buddhist meditation, has been widely used in both clinical and medical research settings[8–11]. It aims to maintain awareness in the present moment and disengage oneself from a strong attachment to thoughts or emotions[12]. MBSR has been recognized as a solution for several medical symptoms such as chronic pain, hypertension, as well as anxiety and depressive disorders[8,13,14]. The effect of MBSR on the brain has also been studied. Hölzel et al. reported several studies showing that after an 8-week MBSR program, participants had a different morphometry in several brain regions, such as hippocampus, frontal lobe, cingulate cortex and insula, compared to controls[15–17]. Speaking of brain, recent studies have started to reveal the wonders of the pregnant brain, some reporting a cortical reduction in several brain areas during pregnancy[18,19].

During pregnancy, several studies have reported that MBSR is associated with lower perceived stress and anxiety[7,20]. However, there is scarce information on mindfulness's effect on pregnant women's brains. Recently, the randomized clinical trial IMPACT BCN (Improving Mothers for a better PrenAtal Care Trial BarCeloNa) showed that structured lifestyle interventions during pregnancy based on an MBSR program or a Mediterranean diet intervention reduced the incidence of newborns born small-for-gestational-age (SGA) and other adverse pregnancy outcomes[21], and reported changes in fetal brain development[22,23] and also a better neurodevelopment of infants at 2 years of age[24]. In a sub-analysis of this trial, we demonstrated that maternal anxiety and compromised sleep quality increase over gestation[2] whereas in the MBSR intervention group, participants reported significantly lower anxiety, better well-being and higher mindful state[21]. However, the effect of this intervention on maternal brain has not been explored yet. In this study, as part of the IMPACT BCN trial, we aimed to evaluate possible differences in brain morphometry and metabolite concentration of the pregnant women who underwent an 8-week MBSR program during pregnancy compared to pregnant women who had usual routine pregnancy care.

Results

Characteristics of the study population

Among the 1,221 pregnant women who were randomized in the clinical trial, 350 participants were randomly assessed for eligibility for the magnetic resonance (MR) study. A total number of 180 participants accepted and provided written informed consent for maternal brain MR. Dataset with root-mean-squared movement more than 2 mm were discarded from the study. For the objective of this study, we included the images from the Stress reduction group ($n = 42$) and the Usual care group ($n = 43$). After excluding the datasets which had suboptimal reconstruction quality, 41 datasets from the Stress reduction group and 35 datasets from the Usual care group were then analyzed. Figure 1 displays the flowchart of the study population.

The MR was performed at the mean (SD) of 36.6 (0.9) weeks of gestation with similar gestational age in both study groups and a similar distribution of the MR scanner (see Table 1). Participants from the Stress reduction group had higher percentage of unemployment (Stress reduction group (17.1% vs. 0%, $p = 0.01$) and higher presence of thyroid disease (19.5% vs. 2.9%, $p = 0.03$) (Table 1). There was no significant difference in pregnancy and outcomes between study groups (Table 1). Magnetic resonance spectroscopy (^{1}H-MRS) data were available for 28 participants out of 36 participants from Philips MR scanner ($n = 16$ Stress reduction group and $n = 13$ Usual care group participants). Five Facet Mindfulness Questionnaire (FFMQ) data were available for 66 participants ($n = 37$ Stress reduction group and $n = 29$ Usual care group). Among these participants, Stress reduction group mothers had higher scores at the end of the intervention in the facets of FFMQ 1 Observation and FFMQ 5 Non-reactivity, compared to Usual care group mothers (Table 2).

Cortical morphometry analysis results

Pregnant women from the Stress reduction group had significantly larger right superior frontal surface area (90%CI: 0.023–0.029, $p = 0.03$) (Fig. 2) as compared to participants from the Usual care group. No differences were found in the cortical thickness or the cortical volume of these areas nor other brain areas/volumes.

^{1}H-MRS results

All data fulfilled the quality control with mean (SD) of signal-to-noise ratio (SNR) 26.1 (3.56), estimated peak full width at half maximum (FWHM) 0.049 (0.007) ppm, and all Carmér-Rao lower values were less than 10 in all spectra. Stress reduction group mothers had significantly higher concentration of myo-inositol (mI) difference (0.37 mol/L, 95%CI: 0.05 to 0.69, significant after 10% false discovery rate correction) and higher mI/total creatine ratio (mI/tCr) (Mean difference 0.05, 95%CI: 0.001 to 0.09), compared to Usual care group women (Table 3). No differences were found in the remaining metabolites.

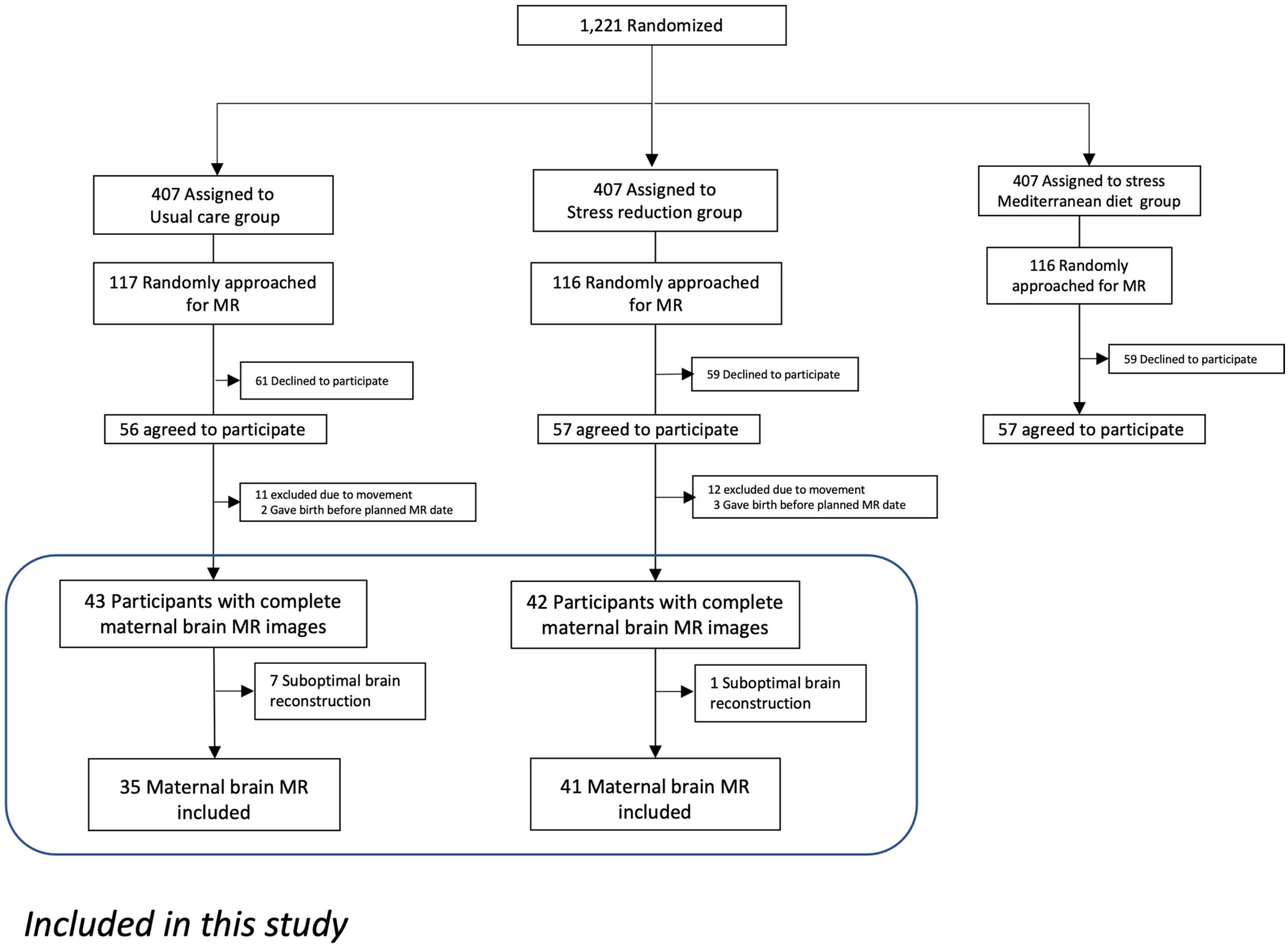


Fig. 1. Flow chart of the study population.

Association between cortical morphometry results and the FFMQ scores
Participants with high FFMQ 4 Non-judgmental and FFMQ 5 Non-reactivity scores had larger right superior frontal surface area compared to lower scores participants (adjusted mean difference: 358.5, 95%CI: 53.5 to 663.6 and adjusted mean difference: 362.3, 95%CI: 18.8 to 705.7, respectively) (Fig. 3). No associations were found in the remaining facets and the right superior frontal surface area.

Discussion
In this secondary analysis of the IMPACT BCN randomized clinical trial, pregnant women from the Stress reduction group showed a larger surface area in the right superior frontal region, compared to women from the Usual care group. In a subsample of participants, the Stress reduction group showed higher mI concentration in the anterior cingulate sulci region area compared to participants from the Usual care group. High mindfulness status on facets of Non-judgmental and Non-reactivity was also associated with a larger right superior frontal area. To our knowledge, this is the first study to assess the effect of a MBSR intervention during pregnancy on the brain morphometry and metabolic characteristics of a pregnant population.

MBSR is gathering positive evidence for the pregnant population with depression and anxiety symptoms[7,20]. However, studies mainly focus on MBSR's effect on psychological outcomes or the offspring's developmental outcomes[25]. Our results are the first evidence of MBSR's impact on pregnant individuals' brains.

Several studies report the association of MBSR with changes in several brain areas, such as hippocampus, insular cortex, amygdala, cingulate cortex and frontal cortex [16,17,26-28] in a non-pregnant population. For example, Hernández et al. reported the correlation between the depth of mental silence during the MR scan and the gray matter volumes in the medial prefrontal cortex[26]. Although the physiological mechanism of these alterations is still to be further explored[16], a research suggests that meditation is associated with neuroplasticity through increased neuronal connectivity across the brain[29]. MBSR has been reported to improve the activation and connectivity of the areas including the frontal cortex, which are involved in emotion regulation and self-referential processing[30–33].

In the current study, the area with a significant difference between the Stress reduction group and the Usual care group women was the superior frontal area. This area is typically involved in the regulation and monitoring of attention[34]. Considering that MBSR concentrates on the present-focused awareness, it is plausible that this

Characteristics	Usual Care $n=35$	Stress reduction $n=41$	p value
Age (years)	37.7 (5.0)	37.7 (4.0)	0.99
Race and ethnicity			0.07
Afro-American	0 (0.0%)	1 (2.4%)	
Asian	1 (2.9%)	0 (0.0%)	
Latin	0 (0.0%)	6 (14.6%)	
Maghreb	0 (0.0%)	1 (2.4%)	
White	34 (97.1%)	33 (80.5%)	
Study class: no/primary	1 (2.9%)	1 (2.4%)	0.91
Work status: yes/studying	35 (100.0%)	34 (82.9%)	0.01
Socio-economic status[a]			0.28
Low	1 (2.9%)	1 (2.4%)	
Medium	10 (28.6%)	19 (46.3%)	
High	24 (68.6%)	21 (51.2%)	
BMI before pregnancy (Kg/m^2)	23.1 (21.1–25.3)	21.7 (19.6–26.2)	0.53
Previous medical condition			
Thyroids disorders	1 (2.9%)	8 (19.5%)	0.03
Autoimmune disease	8 (22.9%)	5 (12.2%)	0.22
Diabetes mellitus	2 (5.7%)	0 (0.0%)	0.12
Chronic hypertension	2 (5.7%)	1 (2.4%)	0.46
Psychiatric disorders	3 (8.6%)	0 (0.0%)	0.06
Nulliparous	21 (60.0%)	28 (68.3%)	0.45
Assisted reproductive technologies	9 (25.7%)	12 (29.3%)	0.73
Cigarette smoking during pregnancy	6 (17.1%)	5 (12.2%)	0.54
Alcohol intake during pregnancy	7 (20.0%)	10 (24.4%)	0.65
Sports practice during pregnancy	10 (28.6%)	15 (36.6%)	0.73
Gestational age at recruitment (weeks)	20.8 (0.8)	21.0 (0.7)	0.16
Gestational age at MR (weeks)	36.4 (0.8)	36.7 (0.9)	0.29
MR scanner			0.26
Philips	19 (54.3%)	17 (41.6%)	
Siemens	16(45.7%)	24 (58.5%)	
Pregnancy outcomes			
Gestational diabetes	4 (11.4%)	3 (7.3%)	0.54
Gestational hypertension	1 (2.9%)	4 (9.8%)	0.23
Preeclampsia	3 (8.6%)	2 (4.9%)	0.52
Preterm birth	0 (0.0%)	0 (0.0%)	-

Table 1. Maternal characteristics of women according to the intervention groups with MR assessment. Data are expressed as mean (SD), median (IQR) or n (%). BMI: body mass index; MR: magnetic resonance; [a]Socioeconomical status: low (never work or unemployed > 2ys); medium (secondary studies & work); high (university studies & work).

region had higher activity/ connectivity and thus resulted in a different morphometry between the groups. However, difference was not found in other brain regions which previous studies reported altered in MBSR practitioners. One of the reasons for this could be the fundamental status of our population: pregnancy. In the past decade, researchers have challenged to reveal the characteristics of pregnant women's brains and proved the plasticity of the pregnant brain[19,35–37]. Specifically, Hoekzema et al. reported that pregnancy reduces the cortical volumes of the superior frontal gyrus[1,9] along with other brain regions. In relation with the mindfulness facets, the superior frontal area was larger among the participants with high mindfulness scores on the Non-judgmental and Non-reactivity facets. The Non-judgmental facet corresponds to the ability to take a non-evaluative stance towards inner emotions and thoughts, and the Non-reactivity facet corresponds to the ability to allow inner emotions and thoughts to come and go without being interfered by them[38,39]. As both facets are related to emotion regulation, there is a possibility that high mindfulness level on these two facets during pregnancy is more related to the superior frontal region than the other reported regions. Indeed, several observational studies report the relationship between mindfulness and functional connectivity changes in this area[30–32]. Among these changes, a recent review reports the increased connectivity between the anterior cingulate cortex region and the prefrontal cortex (related to the default mode network), which may relate to emotion regulation[33]. Interestingly, Chu et al. recently reported that pregnancy leads to an altered functional network between the precentral cingulate gyrus, the posterior cingulate gyrus and bilateral frontal lobe gyrus, and hypothesize that these changes may be one of

		Usual Care	Stress reduction		Mediterranean diet vs. Usual care
		n = 29	*n* = 37	p[c]	Difference (95%CI)
FFMQ 1: Observation	Baseline[a]	22.2 (6.47)	23.2 (7.45)		
	Final[b]	**23.2 (0.89)**	**28.5 (0.78)****	**< 0.0001**	**5.25 (2.93 to 7.56)**
FFMQ 2: Description	Baseline[a]	31.9 (5.52)	31.3 (5.87)		
	Final[b]	32.0 (0.78)	31.9 (0.69)	0.86	-0.19 (-2.22 to 1.85)
FFMQ 3: Awareness	Baseline[a]	31.8 (6.93)	29.2 (6.24)		
	Final[b]	30.9 (0.85)	30.1 (0.75)	0.48	-0.82 (-3.08 to 1.43)
FFMQ 4: Non-judgmental	Baseline[a]	28.8 (6.32)	29.3 (4.06)		
	Final[b]	30.0 (0.80)	31.0 (0.71)	0.37	0.97 (-1.13 to 3.06)
FFMQ 5: Non-reactivity	Baseline[a]	22.4 (4.37)	22.9 (4.34)		
	Final[b]	**22.1 (0.55)**	**23.7 (0.49)**	**0.04**	**1.55 (0.09 to 3.00)**

Table 2. Changes in five facet mindfulness questionnaires at baseline and final assessment by intervention group. *FFMQ* five facet mindfulness questionnaire, *CI* confidence interval, [a]Baseline values are observed means (SD). [b]Final values are baseline-adjusted (least-squares) means (SE) and comparison among groups done with ANCOVA analysis. [c]ANCOVA analysis. *$P < 0.05$ and **$P < 0.001$ final from baseline comparison.

the factors affecting the psychological status of pregnant individuals[40]. Our results may show effects of both the pregnancy and the intervention, consistent with what was described in those previous reports.

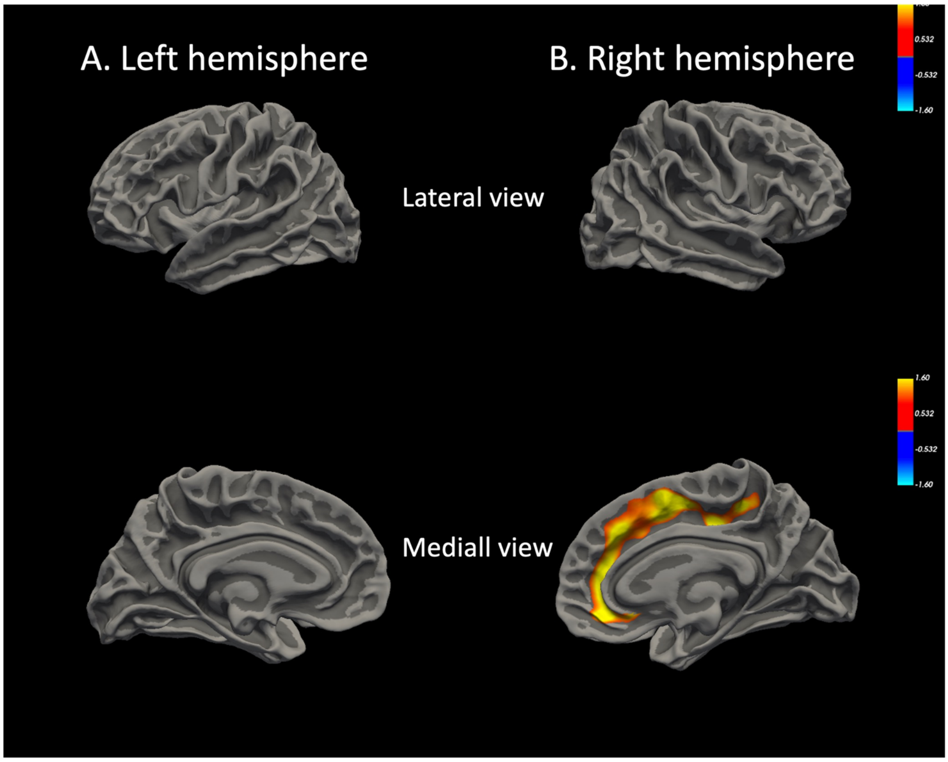
The metabolic characteristics of meditators were evaluated in an observational study by Fayed et al., which assessed the brain changes of long-term Zen meditators[41]. They selected three brain regions including the posterior cingulate gyrus and found that mI was increased in this region. In our exploratory assessment of the ^{1}H-MRS, we selected the anterior cingulate region due to its involvement in emotion regulation[26,42] and found higher mI concentration in the Stress reduction group compared to the Usual care group. Interestingly, regarding mI concentration in the anterior cingulate cortex, Urrila et al. report lower mI concentration in depressed individuals and a correlation between mI and total sleep time[43]. It is known that mI is mainly found in the glial cells such as astrocytes[44]; it not only serves as an osmotic regulator but also is a precursor for the synthesis of inositol phospholipids, which is implicated in the regulation of nuclear function and endo/exocytosis[45]. Therefore, our result may represent the difference in neuronal activity in mothers from the Stress reduction and the Usual care groups. On the other hand, elevation of the mI level can be also associated with neuroinflammation, presumed to reflect astrocyte and microglial activation[45]. Carmona et al. suspect that the mechanisms of the neuroanatomic remodeling during pregnancy may be similar to those observed during adolescence, which are synaptic pruning and myelination[46]. Synaptic pruning is controlled by diverse immune signalling mechanisms, including microglia and astrocyte activities[47] and lead to cortical thining as well as serve as a prerequisite for optimal area increases[48,49]. Thus, we may assume that the higher concentration of the mI in the Stress reduction group mothers may reflect the different astrocyte and microglial activity levels between the two groups.

It is worth mentioning that our metabolite concentration values slightly differ from previous reports which observed the anterior cingulate cortex[43,45]; specifically, lower mI concentrations are observed in our study. Sleep disturbances are common during pregnancy[2]. The high prevalence of sleep disturbance in pregnant women might be one of the reasons for the lower mI concentrations in our results. Moreover, there is little information on brain spectroscopy studies in pregnant brain[36,50,51]. Further research is warranted to define the metabolic characteristics of this population truly.

The major strength of this study is the well-structured intervention in a randomized clinical trial of a pregnant population. Additionally, despite the duration of the intervention being relatively short, we could be able to identify changes in women's brains due to an intervention during pregnancy. However, the study has several limitations. First, two different MR scanners were used. For this reason, MR scanner was included as a covariate in the adjusted model. Second, we lost around 20% of datasets due to the movement during the MR; although participants could choose their most comfortable position, the advanced gestational age may have caused difficulty for the participants to hold still in the scanner. Third, MR was performed only at the end of pregnancy. Since it focused on observing the brain at the end of intervention and it was not a longitudinal study[52], we could not assess the changes during pregnancy before the intervention. Fourth, we acknowledge that the percentage of the tissues may impact the concentration of the metabolites[53]. While the ^{1}H-MRS analysis, ratios of white matter, gray matter and cerebral-spinal fluid of each voxel could not be assessed, we showed the tCr ratio for adjustment[53,54]. Finally, although the maternal brain observation was prespecified in the study protocol, the main aim of the clinical trial was not the maternal brain evaluation. Therefore, the findings of this study shall be taken as preliminary and require further replication.

Conclusion

Structured lifestyle intervention based on MBSR during pregnancy significantly affects the maternal brain structure showing specifically larger area of the right superior frontal cortex and is associated with metabolism changes with higher concentration of mI in the anterior cingulate gyrus.



C.

Contrast	Regions	Hemisphere	MNI x	MNI y	MNI z	CWP	CWP low-high	Cluster size (mm2)
Stress reduction > Usual care	Superiorfrontal	Right	7.3	5.0	54.3	0.03	0.02326-0.02918	2270.36
Usual care > Stress reduction	-							

Fig. 2. Map and table of cortical surface area differences between Stress reduction group and Usual care group mothers. *CWP* clusterwise p-value, *CWPLow-High* 90% confidence interval for CWP, *MNI* Tal (XYZ) is the Talairach (MNI305) coordinate of the maximum. (**A**) Left hemisphere. (**B**) Right hemisphere: right superior frontal area, $p = 0.03$. Maternal brain surface on lateral and medial views. Images generated from a general linear model with total intracranial volume, maternal age, magnetic resonance protocol, nulliparity, maternal thyroid disease and work class. The color bar indicates logarithmic scale of p values (-log10). Red to yellow color reflects the increased area surface in the Stress reduction group participants as compared to Usual care group participants. (**C**) Cortical surface area difference between Stress reduction group and Usual care group participants.

	Usual care	**Stress reduction**			
	$n = 13$	$n = 16$	Mean difference (95%CI)	p value	Q value*
tNAA (mmol/Kg)	7.69 (0.42)	7.87 (0.34)	0.18 (-0.10 to 0.47)	0.20	0.37
tCho (mmol/Kg)	1.12 (0.17)	1.18 (0.15)	0.06 (-0.05 to 0.18)	0.29	0.37
tCr (mmol/Kg)	5.07 (0.62)	5.24 (0.41)	0.17 (-0.22 to 0.56)	0.37	0.37
mI (mmol/Kg)	**2.57 (0.45)**	**2.94 (0.39)**	**0.37 (0.05 to 0.69)**	**0.02**	**0.08**

Table 3. Proton magnetic resonance results of women according to the intervention groups. *tNAA* N-acetyl aspartate and N-acetylaspartateglutamate, *tCho* choline and phosphocholine, *tCr* creatine and phosphocreatine, *mI* myo-inositol. The concentration and the ratio values are shown as mean (SD). Concentration values are expressed as mmol/kg: mmol per kilogram wet weight. *Q-value is considered significant below 0.10.

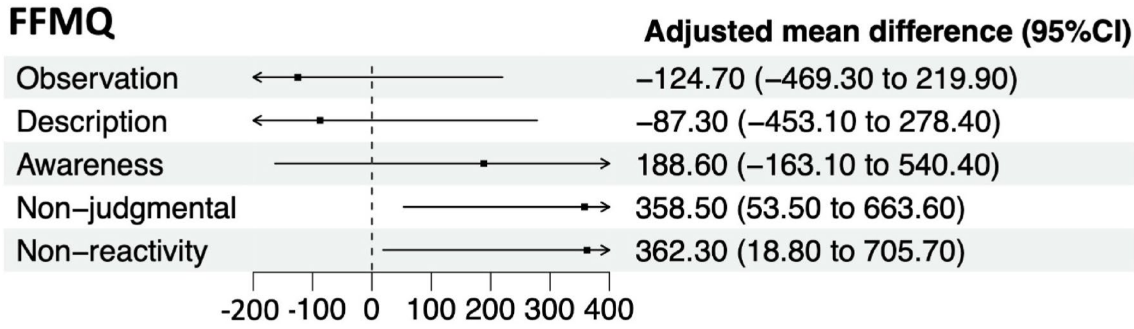


Fig. 3. Right superior frontal surface area differences between high mindfulness and low mindfulness. *FFMQ* five facet mindfulness questionnaire. Z scores higher than 0.4 was considered as High mindfulness group. High and Low mindfulness group sample sizes are: Observation: High $n=43$, Low $n=23$; Description: High $n=18$, Low $n=48$; Awareness: High = 18, Low $n=48$; Non-judgmental: High $n=33$, Low $n=33$; Non-reactivity: High $n=23$, Low $n=43$.

Materials and methods

Study population and design

The present study is a secondary analysis of a large randomized clinical trial, the IMPACT BCN[21] conducted at a large referral center for maternal-fetal and neonatal medicine in Barcelona, Spain. The enrollment of the main study took place from February 2017 to October 2019. The study population were pregnant women recruited at mid gestation (19-23.6 weeks) for being at high risk to have an SGA newborn, according to the criteria of the Royal College of Obstetrics and Gynaecologists[55]. Participants who agreed to take part in the trial were randomly allocated in a 1:1:1 ratio into three groups: a Mediterranean diet intervention group, a Stress reduction group based on a MBSR program, or usual care. Inclusion and exclusion criteria are reported elsewhere[21,56]. For this specific study, only women from the Stress reduction group and the Usual care group, who underwent a maternal brain MR were included. Specifically, at their 29–34 weeks of gestation visit, a sub-sample of randomly selected participants were recruited for an MR assessment, as specified in the trial protocol[21,56]. Inclusion criteria were individuals who participated in the IMPACT BCN trial and had no contraindications to MR, such as claustrophobia and metallic implants and devices. All individuals who agreed to participate provided written informed consent on the day of recruitment. The protocol was approved by the institutional review board Hospital Clínic Research Ethics Committee (HCB-2016-0830, HCB-2020-0267), and the trial was registered in ClinicalTrials.gov Identifier (NCT03166332). All research was performed in accordance with relevant guidelines and regulations and in accordance with the Declaration of Helsinki (last update: 64th WMA General Assembly, Fortaleza, Brasil, October 2013 and by the 75th WMA General Assembly, Helsinki, Finland, October 2024).

The Stress reduction program was based on the program proposed by Kabat-Zinn[12], later adopted by health institutions and tested in clinical trials[11,57]. The participants underwent an 8-weeks MBSR program adapted for pregnancy[56]. This intervention aimed to enhance nonjudgmental present-focused awareness and reduce rumination (dysregulated focus on the past) and anxiety. The program included weekly 2.5-hour sessions, one full-day session, and daily home practice. In each session, the participants had formal 45-minute mindfulness meditation practices (including several meditations focused on the participant's relationship with the fetus), mindfulness yoga with prenatal yoga positions, body awareness and group discussion. Home practice was strongly encouraged. The MBSR program was provided in groups of 25 participants and led by experienced, certified instructors. Briefly, they provided the participants with a book and MP3s or CDs of formal meditations adapted to pregnancy for home practice. Stress reduction practices were encouraged after completing the 8-week program, and the participants were offered extra weekly sessions with meditations/yoga and experience sharing among participants. Additional details of interventions are provided elsewhere[21,56].

The Usual care group received pregnancy care as per institutional protocols.

Maternal brain MR acquisition and processing

Data were acquired from two MR scanners between 32 weeks 0 days and 39 weeks 6 days of gestation. One scanner was a Siemens (Magnetom Trio Tim, Siemens Healthcare, Erlangen, Germany) 3T system equipped with a 32-channel head coil and the other was a Philips (Achieva, Philips Healthcare, Best, Netherlands) 3T system equipped with a 32-channel head coil. Anatomical images were acquired by high-resolution T1-weighted (T1-w) axial scans using a fast acquisition gradient echo sequence with magnetization preparation (MPRAGE) with the following protocol for Siemens: (repetition time (TR) = 2300 ms; echo time (TE) = 2. 08 ms; flip angle (A) = 8°; matrix size = 240 × 240 × 240; voxel size = 0.8 mm^3) and Turbo Field Echo (TFE) sequence with the following protocol for Philips: (TR = 8.1 ms; TE = 3.7ms; FA = 8°; matrix size = 240 × 240 × 180; voxel size = 1 mm3) were used for data collection. In addition, the participants from the Philips scanner were offered an additional sequence of proton magnetic resonance spectroscopy (^{1}H-MRS) as an exploratory study. It was obtained from the anterior cingulate gyrus region (Fig. 4) using single voxel PRESS technique, which was obtained using TR = 2000 ms, short TE = 35 ms, voxel size = 4 × 2 × 2 mm^{3}and partial water suppression with the CHESS module.

(a)

(b)

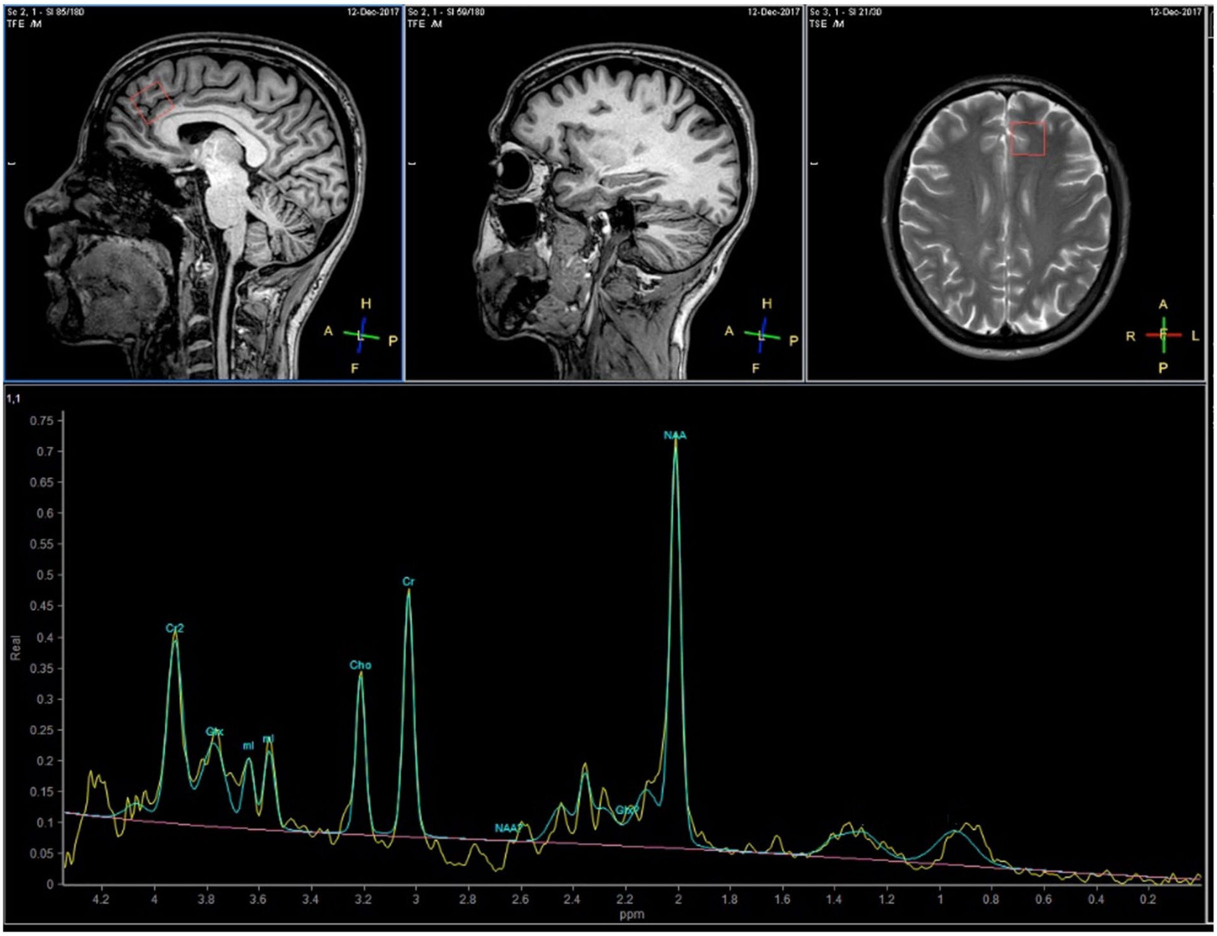


Fig. 4. Sample of voxel location and the spectra in the anterior cingulate cortex. (**a**) Location of the voxel position in the anterior cingulate gyrus, (**b**)Spectra obtained from the MR scanner. *Cr* creatine, *mI* myo-inositol, *Cho* choline, *NAA* N-acetyl aspartate.

The images were checked by a certified radiologist and discarded in case of quality problems or structural anomalies.

Offline MR processing for T1-weighted images

Cortical surface reconstruction was systematically executed using T1-w MR scans from each participant. This process was facilitated by the Freesurfer software package, specifically through the recon-all pipeline (Version 7.1; Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA). The technical procedures encompassed several stages: motion correction[58], removal of the skull and extraneous non-brain tissue[59], transformation to Talairach space[60,61], and segmentation of white matter along with deep grey matter structures[60,62]. This was followed by intensity normalization[63] and tessellation at the grey matter/white matter boundary, with subsequent automatic topological corrections[61]. Once reconstructions were generated, any that were deemed unsatisfactory were excluded. Metrics were gauged in alignment with Freesurfer's established criteria. Cortical volume was ascertained by subtracting the volume within the white surface from that inside the pial, excluding subcortical components. Cortical thickness was calculated by averaging the distance between points on the white surface and their closest counterparts on the pial surface[64]. Each vertex's determination was based on the average area of surrounding triangles, corresponding to the white surface's area. The Desikan-Killiany atlas facilitated the extraction of distinct cortical regions of interest for each metric. Beyond these metrics, Freesurfer also provides an estimate of the total intracranial volume by employing registration-based techniques. This is achieved by linearly transforming each participant's data to a template, a method detailed by Buckner et al.[65].

Offline MR processing for ^{1}H-MRS data

^{1}H-MRS data was processed for individual metabolite quantification by linear fitting with Linear Combination Model-Fitting (LC Model) version 6.1-4A[66,67]. The metabolites evaluated were: the concentrations of N-acetyl aspartate (N-acetyl aspartate and N-acetylaspartateglutamate, tNAA), a neuronal marker which is also localized in immature oligodendrocytes; total choline-containing compounds (choline and phosphocholine, tCho), which are essential for cell membrane turnover; total creatine (creatine and phosphocreatine; tCr), which is present in both neurons and glia and essential for energy metabolism; myo-inositol (mI), which functions as an osmotic regulator and it is also involved in second messenger neurotransmission[68,69]. In addition, ratios with tCr for the significant metabolites were assessed to confirm the concentration results. For quality control, we selected the dataset with clear visual identification of the main metabolite peaks (NAA, Cr, Cho), SNR > 5, estimated peak full width at half maximum (FWHM) < 0.1ppm and coefficient of variance of the metabolite concentration estimates (Carmér-Rao lower bounds) below 20%, as suggested by the manufacturer[70].

Five facet mindfulness questionnaire (FFMQ)

All participants from the trial were assessed on their mindfulness status in a baseline visit (20–24 weeks of gestation) and in a final visit (34–36 weeks of gestation), using the FFMQ[71,72]. This questionnaire consists of 39-item self-completed questions, classified into 5 facets: Observing (8 items), Describing (8 items), Acting with awareness (8 items), Non-judgmental (8 items) and Non-reactive (7 items). They anchor from 'always true = 5 points' to 'never = 1 point' with the score range 8–40 except for the Non-reactive facets which ranges from 7–35. Higher scores indicate higher levels of mindfulness. For additional analysis, the final FFMQ scores were converted into Z scores using the Usual care groups' mean and standard deviation of the baseline visit. Z scores higher than 0.4 was considered as high mindfulness status, following similar classification of Pearson et al.[71].

Statistical analysis

The normal distribution of variables was tested using the Shapiro-Wilk test and histograms. Student's t-test or the Mann-Whitney test as appropriate for continuous parameters, and chi-square test or Fisher exact test as appropriate for categorical parameters were used to assess differences between Stress reduction and Usual care group at baseline characteristics.

Brain MR structural evaluations, encompassing volume, thickness, and cortical area reconstructions, were standardized to a shared spherical atlas space, facilitating a detailed vertex-by-vertex cluster analysis. Datasets from both Stress reduction and Usual care group were juxtaposed using the general linear model, examining metric differences with covariates such as total intracranial volume, age, MR protocol, nulliparity and potential baseline differences (i.e. existence of the thyroid disorder and the employment status) among maternal characteristics. To manage the false discovery rate, general linear model outcomes underwent correction for multiple comparisons via the "mri_glmfit_sim" tool, setting a vertex-wise threshold at 1.3 and a cluster-wise p-threshold of < 0.05.

The mean difference of the ^{1}H-MRS results between the two intervention groups were analyzed with linear regression. For the exploratory nature of the ^{1}H-MRS analysis, we corrected for the multiple comparisons for the number of metabolites, with Benjamini & Hochberg method with the threshold of false discovery rate of 10%. As additional analysis, linear regression model with adjustment (total intracranial volume, age, MR protocol, nulliparity and potential baseline differences which are existence of the thyroid disorder and the employment status) was used to observe the associations between the significant region of interest and individual FFMQ facets level. Analysis of covariance (ANCOVA) was used to assess the changes in the FFMQ facets at the end of the intervention in each group by adjusting for the baseline values.

A p-value of < 0.05 was deemed indicative of statistical significance. Statistical analyses were performed using RStudio (version 1.4.1106, Rstudio) with software R (version 4.0.5, R Foundation), and statistical comparisons and adjusted means were computed with the emmeans library (v. 1.8.2).

Data availability

Data described in the manuscript, code book, and analytic code will be made available upon request and being approved by the Ethical Committee of the author's institute, with a signed data access agreement. To access this data, one should contact francesca.crovetto@sjd.es via email.

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Author contributions

FCro, FC and EG conceived and designed the study. FCro, IC, MG, LY, LB, NE, YG and AN had responsibility for day-to-day running of the trial including participant recruitment, data and sample collection, and data curation. FCro and FC and guarantying the correct execution of the trial. SCB was the dietitian involved in the

Mediterranean diet program, and RC and RE were responsible of the program. AMA and TOG was responsible for the Mindfulness-Based Stress reduction program. IM, AMÀ and EV were responsible for the stress reduction intervention. NB and RC gave supervision on the data interpretation. YG, AC, NT and AN performed the data processing and the statistical analysis. NT, AC and BG provided supervision on the imaging data processing and data results. AN, YG, FC, and FCro drafted the first version of the manuscript. All authors critically reviewed and approved the final version of the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Additional information
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