WOMEN'S HEALTH

Linking birth experience and perinatal depression symptoms to neuroanatomical changes in hippocampus and amygdala

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Childbirth is a life-changing event in a mother's life. While the transition to motherhood has recently been recognized as one of the most neuroplastic periods in adulthood, no study has yet explored whether the hippocampus and amygdala change during the peripartum in relation to childbirth experience and perinatal depression symptoms. In this longitudinal neuroimaging study, we assessed 88 first-time gestational mothers in late pregnancy and early postpartum and 30 nulliparous control women. We used optimized high-resolution MRI scans to quantify volumetric changes in the hippocampus and amygdala, along with their substructures. We found that increases in depression symptoms during the peripartum were positively correlated with changes in the right amygdala. A more challenging birth experience was associated with bilateral increases in hippocampal volume. These findings show that studying the neuroanatomical changes during the transition to motherhood can inform not only about adaptive processes but also about potential vulnerabilities, highlighting the importance of tracking perinatal experiences to enhance women's health.

INTRODUCTION

Each minute, about 300 women give birth, leading to approximately 140 million births every year (*1*). At the physiological level, the transition to motherhood involves a profound transformation of women's entire bodies, including their brains (*2*, *3*). Consistent with nonhuman animal models, the limited but compelling literature in humans recognizes pregnancy as a period of profound neuroplasticity (*4*). Longitudinal magnetic resonance imaging (MRI) studies have observed a reduction in cortical volume during gestation, followed by a partial recovery in the postpartum period (*5*–*9*). The key moment in this dynamic trajectory occurs around the peripartum period, with childbirth potentially marking the turning point.

Beyond the cortical mantle, research in murine models also highlights the involvement of key subcortical structures in the maternal brain circuit. These include the ventral striatum, hypothalamus, the amygdala, and the hippocampus (*10*). In humans, longitudinal studies measuring volume changes from preconception to postpartum have reported significant reductions in the hippocampus (*5*, *6*, *8*), the ventral striatum (*11*), and the hypothalamus (*12*), linking the volume changes of the latter two with responsiveness to infant cues and maternal-fetal attachment and nesting behavior, respectively. The hippocampus and amygdala are essential for emotional regulation and memory formation (*13*), yet it remains unknown whether changes in these structures are related to the birth experience, one of the most emotionally intense and memorable moments in a mother's life (*14*).

Childbirth is a transformative event that can profoundly affect a woman's life in just a few hours. Its multidimensional nature means each birth experience varies from mother to mother and birth to birth. The mother's psychological and physiological state, in interaction with external environmental factors, shapes childbirth into a deeply subjective experience (*15*). While some women perceive their parturition as a positive experience—feeling intense joy, pride, and accomplishment (*16*)—others describe it as traumatic (*17*). A distressing and complicated birth experience can lead to symptoms of post-traumatic stress or postpartum depression (*18*, *19*). Estimates suggest that between 7 and 44% of mothers describe their childbirth as traumatic (*20*), 10% develop childbirth-related post-traumatic stress disorder (*18*), and 17% experience postpartum depression (*21*). Notably, major depression and post-traumatic stress disorder have been linked to structural alterations in the hippocampus and amygdala (*22*, *23*). However, no studies have yet explored how peripartum changes in the anatomy of these structures relate to childbirth experiences and perinatal depression symptoms.

The aims of the current neuroimaging study are twofold. First, we will test whether the hippocampus and amygdala go through neuroanatomical changes during the peripartum. In line with observations in the cortical mantle, we expect to find reduced volumes in these structures during late pregnancy, with partial recovery in the early postpartum period. Second, we will explore whether these volumetric changes are linked to childbirth experience and peripartum depression symptoms. To approach these aims, we conducted a longitudinal study with 88 first-time gestational mothers assessed at late pregnancy and early postpartum. At each session, we acquired high-resolution T2-weighted MRI scans to quantify the volume of hippocampus, amygdala, and their substructures, along with self-administered questionnaires evaluating prenatal and postnatal depression symptoms

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and childbirth experience. In addition, we also included 30 nulliparous women evaluated at a similar time interval as a control group. Throughout the paper, the term "women" refers to females whose biological sex aligns with their gender identity, and "mothers" specifically denotes women who have undergone pregnancy and childbirth.

RESULTS

Volume changes in amygdala and hippocampus

During the late pregnancy session, pregnant women exhibited lower volumes in the global right amygdala compared to nulliparous women (Table 1). Substructure analyses revealed that pregnant women had smaller volumes than controls in the right laterobasal nucleus and both superficial nuclei of the amygdala, as well as in the hippocampal subfields: left cornus ammonis 4 (CA4), right subicular complex, and left and right fimbriae (table S1). In the early postpartum session, only the hippocampal subicular complexes were reduced in mothers compared to controls (Table 1 and table S1). None of the cross-sectional group differences at late pregnancy and early postpartum survived multiple comparisons.

From late pregnancy to early postpartum, longitudinal increases were observed in the global right amygdala, its laterobasal nucleus, the left and right superficial nuclei, and both hippocampal fimbriae, while decreases were noted in both hippocampal fissures and the right hippocampal tail, in mothers compared to controls (Table 1 and table S1). After correcting for multiple comparisons, significant differences persisted in the global right amygdala, both superficial amygdalar nuclei, right fimbria, and both hippocampal fissures. Similar results in both cross-sectional and longitudinal group differences were obtained in additional analyses that accounted for multiple

Table 1. Volumetric hippocampal and amygdala differences in mothers and controls. Descriptives and group comparison statistics of the volumetric (cubic millimeters) differences at session 1 [pregnancy session ("Prg")], session 2 [postpartum session ("Post")], and in longitudinal changes ("Prg-to-Post") in mothers and nulliparous women ("controls"). The adjusted linear mixed effect models correspond to "subcortical structure volume ~ session * group + (1 | Participant)." Effect sizes were calculated as the signed partial eta squared (η_p^2) associated with the correspondent Wald *F* tests. Degrees of freedom (DoF) were obtained using Satterthwaite's approximation. False discovery rate was applied across all hemispheric global and substructure volumes for each contrast. *F*-stat., *F*-statistic; *P* value, uncorrected *P* value; SD, standard deviation.

		Controls		Mothers		Group differences		
Subcortical structure	**Statistic**	**Session 1**	**Session 2**	**Session 1 (Prg)**	**Session 2 (Post)**	**Session 1 (Prg)**	**Session 2 (Post)**	**Session 1-to-2 (Prg-to-Post)**
Left whole hippocampus	Mean	3297	3286.8	3199.6	3208.3			
	SD	241.1	237.3	246.6	241.2			
	F-stat.					3.62	2.35	3.84
	DoF					1118.08	1118.08	1116
	P value					0.06	0.13	0.053
	Signed η_p^2					−0.03	−0.019	0.032
Right whole hippocampus	Mean	3253.8	3244.8	3159.9	3152.2			
	SD	260.9	265.6	251.2	246.8			
	F-stat.					3.11	3.02	0.02
	DoF					1117.64	1117.64	1116
	P value					0.081	0.085	0.88
	Signed η_p^2					−0.026	−0.025	0.00019
Left whole amygdala	Mean	1819.4	1803.5	1771.1	1769.3			
	SD	143.1	143.6	151	153.3			
	F-stat.					2.33	1.17	1.84
	DoF					1122.35	1122.35	1116
	P value					0.13	0.28	0.18
	Signed η_p^2					−0.019	−0.0095	0.016
Right whole amygdala	Mean	1977.9	1939.9	1886.3	1885.9			
	SD	178.8	156	181.1	175			
	F-stat.					6.11	2.12	7.39
	DoF					1124.36	1124.36	1116
	P value					0.015*	0.15	0.0076**
	Signed η_p^2					−0.047	−0.017	0.06

*P value < 0.05. **False discovery rate–corrected P value < 0.05.

comparisons and potential confounders such as age, intracranial volume, sleep quality, and perceived stress levels (table S2).

To account for potential covariates that specifically affect the mothers' group—namely, gestational weeks at birth and postpartum time—we fitted a model using only the mothers' sample. Longitudinal comparisons revealed increases from pregnancy to postpartum in the left superficial nuclei of the amygdala, left hippocampal CA3, right hippocampal tail, and both hippocampal fimbriae. We also observed decreases in both hippocampal fissures. After correcting for multiple comparisons, only increases in the hippocampal fimbriae and decreases in the right hippocampal tail and fissure remained significant (table S3).

When exploring the effect of parturition type, we found longitudinal differences between vaginal deliveries and scheduled C-sections in the right hippocampal-amygdala transition area (HATA). Further differences were observed between emergency C-sections and vaginal deliveries in left hippocampal CA4, right fimbria, and right HATA, as well as between emergency and scheduled C-sections in both HATA. However, none of these differences remained significant after correcting for multiple comparisons (table S4). Comparisons between women who initiated labor—either vaginal delivery or emergency C-section—and those who did not showed a difference in the right HATA that did not survive multiple comparisons (table S5).

Perinatal depression symptoms and birth experience

At the pregnancy session, participants reported a mean depression score of 4.38 (SD 3.84) on a scale from 0 to 30, with higher scores meaning greater symptoms of depression. This score significantly increased to 5.89 (SD 4.75) at the postpartum session [$F(1, 87) = 11.12$; $P = 0.0013$; and signed effect size = 0.113]. Individual scores showed that 10 participants (11.36%) exhibited moderate depression symptoms during late pregnancy, while 15 participants (17.05%) showed these symptoms at the postpartum session (Fig. 1A). The mean score in the birth experience survey was 3.23 (SD 0.94) on a scale from 1 to 7, with higher scores indicating a more challenging birth experience. Notably, we found that a worse birth experience was associated with greater increases in depression symptoms across peripartum ($R = 0.23$ and $P = 0.03$; Fig. 1B).

Correlations between hippocampal and amygdalar volumes, depression symptoms, and birth experience

We found significant associations between mothers' scores on the birth experience questionnaire and volumetric changes in both the left and right hippocampus (Fig. 2A). Specifically, the worse the childbirth experience, the greater the increases in hippocampal volumes. In addition, increases in the right amygdala were positively associated with increases in depressive symptoms (Fig. 2B). All these correlations survived multiple comparisons. No other significant associations were detected (fig. S1), although a positive trend was noted between the right amygdala volume changes and birth experience (fig. S1B). Supplementary analyses using partial correlations, which accounted for postpartum time and gestational weeks at birth, confirmed the same pattern of associations (table S6), which were also corrected for multiple comparisons.

Post hoc analyses of hippocampal subfields revealed that a worse birth experience was associated with greater volume increases in the right CA1, right dentate gyrus, right HATA, and left CA4 (Fig. 2C

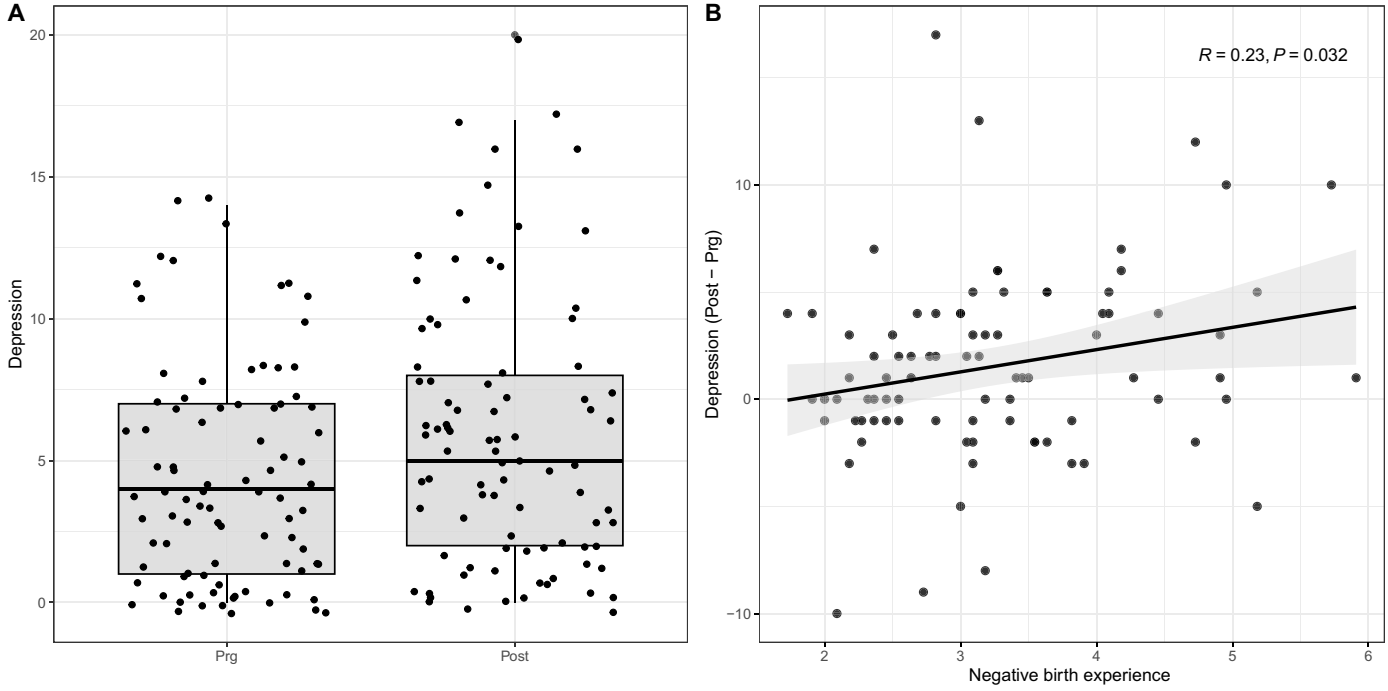

Fig. 1. Perinatal depression symptoms and correlation between birth experience and perinatal depression symptoms in first-time gestational mothers ($N = 88$). (**A**) Boxplots showing the distribution of the depression symptoms scores at late pregnancy (Prg) and early postpartum (Post) sessions. The center line of the boxplot represents the median, the box encloses the lower and upper quartiles, and the whiskers extend to the minimum and maximum values within a range of 1.5 times the interquartile range. Horizontal jitter (width = 0.35) was added to the data points for better visualization. (**B**) Correlation between birth experience and the difference in depression symptoms scores between pregnancy (Prg) and postpartum (Post). The black line and shaded area represent the least squares regression line and the 95% confidence interval, respectively. At the top, the Pearson correlation coefficient (*R*) and its associated two-tailed *P* value (*P*) are displayed.

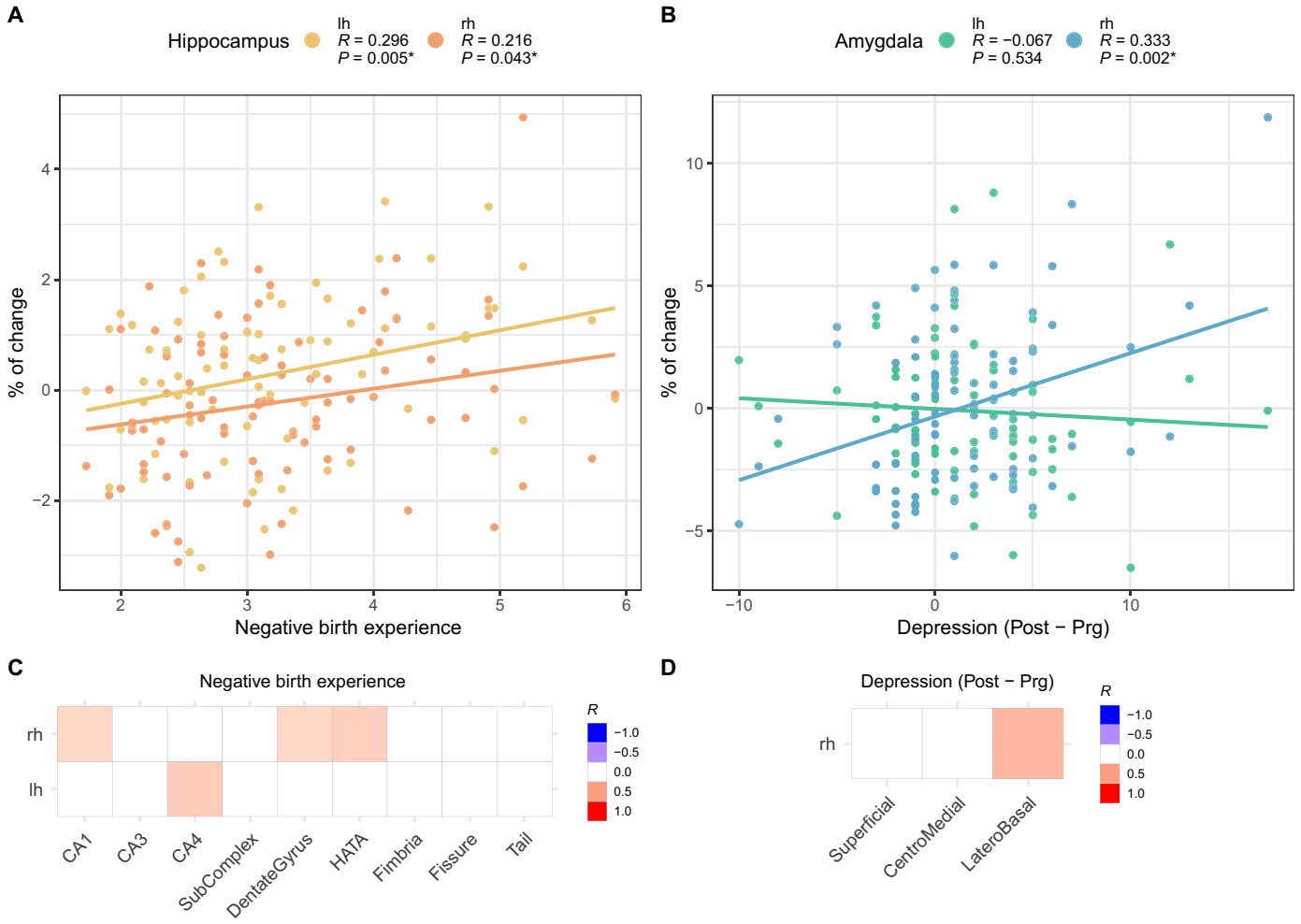

Fig. 2. Correlations in gestational mothers ($N = 88$) between longitudinal changes in hippocampal and amygdala volumes and birth experiences and depression symptoms variables. Scatterplots with least square regression lines depict volume changes relative to pregnancy on the *y* axis and psychological variables on the *x* axis. (**A**) Whole hippocampal changes and birth experiences. (**B**) Whole amygdala changes and the difference in depression levels. Asterisks indicate Pearson coefficients surviving a two-tailed *P* value < 0.05 after false discovery rate (FDR) correction. Correlation matrices (**C** and **D**) illustrate the associations between birth experience and depression variables and the percentage of change in hippocampal subfields and amygdala nuclei. Filled squares represent the Pearson coefficients of those correlations surviving a two-tailed uncorrected *P* value of 0.05. lh, left hemisphere; rh, right hemisphere; Post, Postpartum session; Prg, pregnancy session, *R*, Pearson's correlation coefficient; *P*, uncorrected *P* value; CA, cornu ammonis; SubComplex, subicular complex; HATA, Hippocampal-and-Amygdala Transition Area.

and fig. S2). For the amygdala nuclei, increased depression symptoms were associated with volume increases in the right laterobasal nucleus (Fig. 2D and fig. S3).

DISCUSSION

This neuroimaging study examined changes in hippocampal and amygdalar volumes from late pregnancy to early postpartum in relation to birth experience and changes in perinatal depression symptoms. We found that the larger the increase in the right amygdala volume, the greater the increase in symptoms of perinatal depression and that the worse the birth experience, the larger the bilateral volume increase in the hippocampus.

In a previous study, we found that third-trimester pregnant women had lower cortical thickness compared to nulliparous controls, with the difference attenuating at 1 month postpartum (*7*). Here, we tested whether the hippocampus and amygdala follow the same trajectory. We found that the direction of the volume changes aligns with that observed in the cortex: a lower volume at late pregnancy compared to controls and a volume increase between late pregnancy and early postpartum. However, most of these differences did not survive multiple comparisons correction. Although unlikely, it is possible that these subcortical regions might be spared from the widespread neurological effects exerted by pregnancy (*7*, *8*). Instead, we believe that the lack of statistical significance may arise from the following nonmutually exclusive reasons.

First, these subcortical regions might exhibit different dynamics of changes than those observed at the cortical level. While previous studies have examined hippocampal (*5*, *6*, *24*, *25*) and amygdala (*24*, *26*, *27*) volumes at preconception or postpartum time points, only one report included measures during the gestational period (*8*). Using a precision dense-sampling design, Pritschet *et al.* measured whole hippocampal and subfield volumes in a woman from preconception throughout gestation and up to 2 years postpartum. The authors observed a

reduction in hippocampal volume during pregnancy. Their graphs indicate that this decline reaches its nadir around the second trimester, after which it begins to rise. This contrasts with the turning point observed in the cortical mantle, which occurs around birth (*7*–*9*). Furthermore, the plots for some hippocampal subfields suggest no changes between the third trimester of gestation and the early postpartum. Thus, it is possible that the time points of the current study—third trimester and first month postpartum—may not be optimal for capturing the dynamic progression of changes in these subcortical regions. While no prior studies have tracked the amygdala's dynamic trajectory during gestation, it is plausible that a similar pattern could occur in this neighboring and highly connected structure. Further dense-sample studies with larger cohorts are needed to determine whether the pattern of changes in these structures diverges from that consistently reported in the cortex.

Second, high intersubject variability in hippocampal and amygdala volume and volumetric changes may overshadow potential cross-sectional and longitudinal effects. According to our data, childbirth experience and postpartum depression symptoms could be key sources of variability within the mother's group. While brain changes across the transition to motherhood have been linked to adaptive processes that facilitate maternal care (*5*, *6*, *11*, *12*), peripartum can also be a vulnerable period for women's mental health (*28*). Mild and transient mood changes are common after childbirth, a 10% of women develop childbirth-related posttraumatic stress disorder (*18*), and a 17% experience postpartum depression (*21*). Yet, peripartum changes in key regions for memory and emotional processing remain largely unexplored in relation to birth experiences and depressive symptoms. Consistent with Ahmadpour *et al.* (*29*), we found that a negative birth experience correlates with increased symptoms of postpartum depression. Although these variables correlated, they were linked to changes in distinct subcortical structures: the hippocampus for birth experience and the amygdala for perinatal depressive symptoms.

When comparing pregnancy and postpartum brain images, we found that a poorer birth experience correlated with increased hippocampal volumes, especially in the left CA1 and CA4 and the right HATA subfields. Studies in murine models show that stress can alter both hippocampal structure and function (*30*). Thus, a negatively perceived birth experience could act as a significant stressor, potentially driving the observed volumetric changes. However, a negative birth experience can be influenced by precipitating factors—such as unexpected medical interventions, health complications, loss of control, and lack of support—as well as by predisposing factors, such as fear of childbirth or a history of mental disorders (*31*, *32*). These predisposing factors may heighten the hippocampus's susceptibility to perceiving and encoding emotionally intense situations as adverse, and this, in turn, potentiates the neural changes. Together, we cannot determine whether: (i) negative childbirth experiences render changes in the hippocampus; (ii) hippocampal susceptibility bias toward more negative childbirth experience; or (iii) both possibilities interact. Collecting birth experiences closer to the time of childbirth might provide greater insight into this. Overall, this initial evidence highlights the importance of including the childbirth experience as a key variable in neuroscience research, particularly in the field of maternal brain.

We found that peripartum increases in depression symptoms are linked to amygdala volume changes. According to functional MRI analysis, the amygdala is one of the brain regions that most consistently differentiates patients with and without major depression (*33*) as well as mothers with and without postpartum depression (*34*). Mothers with postpartum depression show reduced connectivity between the amygdala and other cortical regions (*35*, *36*), as well as amygdalar hypoactivity in response to negative stimuli (*37*, *38*). Structural imaging modalities, however, have received less attention. The scarce literature indicates no anatomical brain differences between healthy mothers and mothers with postpartum depression nor any associations with depression levels in cross-sectional analysis during the postpartum period (*39*, *40*). In contrast, our longitudinal study focusing on the peripartum period revealed volume increases in the right amygdala and its laterobasal nucleus that positively correlated with an increase in depressive symptoms. These results suggest that longitudinal and prospective designs across the maternal transition will be essential to detect brain signatures of perinatal depression symptoms.

Outside the context of maternal brain literature, studies have reported volumetric differences in hippocampal and amygdala volumes in patients with post-traumatic stress disorder and depression, respectively, compared to controls. These cross-sectional studies typically show reduced volumes in patients with these disorders (*22*, *23*). Although this finding might seem to conflict with our correlational results, where worse depressive symptomatology and birth experience relate to larger volumetric increases, we must acknowledge that these publications examine different populations, refer to different mental disorders, derive mostly from cross-sectional data, and are limited by several confounding variables—including medication status and chronicity of the disorder.

To our knowledge, peripartum amygdala and hippocampal volume changes in relation to depressive symptoms and birth experience have not been previously studied. Our exploratory approach on the correlational data prevents us from making strong assumptions about the potential directionality of the findings. From the observed correlations, different alternatives emerge. The increased volume associated with adverse birth experiences and peripartum depressive symptoms might reflect either stressor-induced damage, a maladaptive response to these stressors, or even an adaptive mechanism to mitigate the negative resulting effects. Regardless of the directionality, our results add to the growing body of recent research that positions pregnancy as a highly plastic period and support the notion that a plastic brain is also a vulnerable brain.

Despite the evidence presented in this study, several limitations should be considered when interpreting the results. First, the lack of preconception measures limits our ability to assess baseline brain characteristics. Second, although the MRI high-resolution sequences and the toolboxes used for segmentations were optimized to quantify volume in these subcortical regions, these processes are still subject to inherent limitations of test-retest reliability (*41*). Third, comparisons between parturition types should be interpreted cautiously, given the uneven and low sample sizes in the C-section groups. Fourth, the use of self-reported questionnaires restricts the information that participants can report. Combining this information with medical records and personal interviews could better capture the complexity of childbirth and depression experiences. Last, although we assessed depressive symptoms and screened for mental health disorders, none of the participants reported a diagnosis of postpartum depression or post-traumatic stress disorder, encouraging future neuroimaging studies to specifically target these populations.

To conclude, this study revealed that a perceived adverse childbirth experience is associated with pregnancy-to-postpartum increases in the

hippocampal volume of first-time mothers and that increases in depressive symptoms correlate with increases in right amygdala volume. Overall, our findings suggest that neuroanatomical changes during the transition to motherhood can capture not only adaptive processes but also inform us about potential vulnerabilities. Likewise, the results advocate for a multifaceted understanding of parturition that encompasses not only mechanical, immunoendocrine, psychological, and sociocultural factors but also neural ones. Furthermore, this research underscores the critical importance of collecting data about perinatal experiences, both to advance our understanding of the maternal brain and to improve women's health before, during, and after childbirth.

MATERIALS AND METHODS

Experimental design

In this longitudinal study, we analyzed neuroimaging data from a group of first-time gestational mothers and a group of nulliparous women as a control group. Mothers underwent structural MRI scans of their brains at two sessions: the first one during the third trimester of pregnancy (Prg; mean 36.26 gestational weeks, SD 0.94) and the second one during the first month postpartum (Post; mean 21.33 postpartum days, SD 7.74). Age-matched nulliparous women were also assessed at an equivalent time interval (mean 44.37, SD 10.22, days). The MRI acquisitions included whole-brain T1-weighted images and high-resolution coronal T2-weighted images focused and aligned on the hippocampus and amygdala. Self-reported psychological variables and sociodemographic information were collected at both sessions for both groups and stored in the Qualtrics platform. For the mothers group, we also collected obstetric and parenting information. For more details about the protocol, see (*7*).

No statistical methods were used to predetermine sample sizes. Our sample was drawn from a larger longitudinal project aimed at examining the effects of the peripartum period on the human brain (*7*). Participants were recruited in the Madrid area (Spain) through the group's social media channels, including Instagram (@neuro.maternal) and X (@neuromaternal), as well as by word-of-mouth. Participants were assigned to either the experimental or control groups based on their pregnancy status. Data collection and analysis were not performed blind to the conditions of the experiments. We excluded females who had previous pregnancies beyond the first trimester or fostered children or had an estimated intelligence quotient below 80, as determined by the Wechsler Adult Intelligence Scale IV (WAIS-IV) Digit Span subtest scores (*42*). Those with a reported history of neurological disorders or psychiatric conditions, as provided by the Mini-International Neuropsychiatric Interview (*43*), were also excluded.

Here, we focused on unpublished acquired brain scans designed to investigate the hippocampus and amygdala. The original sample comprised 110 mothers (mean age 33.12, SD 3.98, years) and 34 controls (mean age 33.32, SD 4.56, years) from whom pregnancy and postpartum T1-weighted images were acquired. However, T2-weighted coronal images were not collected for seven mothers due to discomfort during the brain scanning. Ten participants (7 mothers and 3 controls) were discarded due to motion artifacts, and 14 more (11 mothers and 3 controls) were excluded because of processing errors in the automatic segmentation of the hippocampus or amygdala (see the "Image processing" section). The flowchart of the participants can be depicted in fig. S4. Thus, the final sample for this study consisted of 88 first-time gestational mothers with a mean age of 32.99 (SD 3.88) years and 30 controls with a mean age of 33.56 (SD 4.61) years.

Mothers and controls did not differ in terms of age ($t_{116} = 0.66$, $P = 0.51$), intersession time ($t_{116} = -1.31$, $P = 0.19$), WAIS-IV digits ($t_{115} = 1.13$, $P = 0.26$), or educational level ($\chi^2_{2,118} = 2.98$, $P = 0.56$). Among the mothers' group, 90.9% became pregnant via natural conception (80 women), while 9.1% conceived using assisted reproduction methods (8 women), including in vitro fertilization (6.8%, 6 women), artificial insemination (1.1%, 1 woman), and intracytoplasmic sperm injection (1.1%, 1 woman). Regarding childbirth, 80.7% delivered vaginally (71 women), 10.2% had an emergency C-section (9 women), and 9.1% had a scheduled C-section (8 women). All births were singletons, with an equal sex distribution among the infants (50% male, 50% female). During the first month postpartum, 77.3% of the mothers (68 women) breastfed exclusively, 18.2% (16 women) combined breastfeeding with formula feeding, and 4.5% (4 women) chose formula feeding. None of the mothers reported a diagnosis of postpartum depression in the second session when asked in the self-administered questionnaire. For a comprehensive overview of participant demographics and the mother's obstetric characteristics, please see Table 2.

This research was approved by the Ethics Committee at the Instituto de Investigación Sanitaria del Hospital Gregorio Marañón (ref: 106/19), in accordance with the Declaration of Helsinki guidelines, and adhered to data protection regulations. All participants signed a consent form before participating in the study and received monetary compensation for their time and travel expenses. Further details regarding the study design and data acquisition protocol can be found elsewhere (*7*).

Image acquisition

For each participant and session, two structural MRI images were acquired using a 3 Tesla Siemens MAGNETOM Vida with a Head-and-Neck 20 channel coil located in the Hospital Beata Maria Ana in Madrid (Spain). T1-weighted images were obtained using a magnetization-prepared rapid gradient-echo sequence in the sagittal plane. The image acquisition parameters were as follows: voxel size, 1 mm × 0.9375 mm × 0.9375 mm; field of view, 176 mm × 240 mm × 240 mm; echo time, 4.4 ms; repetition time, 9.8/2300 ms; inversion time, 900 ms; flip angle, 8°; GeneRalized Autocalibrating Partial Parallel Acquisition (GRAPPA) acceleration factor, 2; percent sampling, 80%; and acquisition time, 265 s. High-resolution T2-weighted images were acquired using a turbo spin echo sequence oriented perpendicularly to the anterior-posterior long axis of the hippocampus in the coronal plane. The T2-weighted image acquisition parameters were as follows: in-plane resolution, 0.390625 × 0.390625 mm; slice thickness, 2 mm; field of view, 175 mm × 68 mm × 175 mm; echo time, 50 ms; repetition time, 8.82 s; flip angle, 122°; in-plane parallel reduction factor, 2; percent sampling, 100%; and acquisition time, 264 s.

Image processing

T1-weighted brain images were processed using the recon-all longitudinal stream in FreeSurfer version 7.1.1 (*44*). This workflow starts with a cross-sectional processing of the images at each Prg and Post session, which includes skull stripping, bias field correction, gray and white matter segmentations, and cortical surface reconstruction based on the segmented brain tissues. Subsequently, for each participant, an individual unbiased template was created from the cross-sectional processed images (*45*). Then, the participant's Prg and Post scans were registered to that individual template and longitudinally processed (*46*). Segmentation-based total intracranial volume (sbTIV) was estimated using the longitudinal processing in Sequence Adaptive Multimodal SEGmentation (SAMSEG) provided in FreeSurfer 7.4.1 (*47*).

Table 2. Sample demographic and obstetric characteristics. Medical birth induction refers to the use of medical substances to initiate or accelerate labor. Of note, this variable has missing data from seven mothers. Instrumental birth refers to the use of forceps, spatula, or cupping glass during the delivery. Nondelivery companion indicates whether the participant was alone in the delivery room during childbirth. Skin-to-skin contact is defined as the practice of placing the newborn on the mother's chest immediately after birth and allowing them to remain there for at least 50 min. Range reports the minimum and maximum values. *N* = sample size.

	Controls, *N* = 30			Mothers, *N* = 88		
Characteristic	**Mean (SD)**	**Range**	**# Participants (%)**	**Mean (SD)**	**Range**	**# Participants (%)**
Age at session 1 (years)	33.53 (4.61)	26.10–45.98		32.99 (3.88)	24.10–39.93	
Gestational weeks at pregnancy session				36.26 (0.94)	33.14–38.71	
Gestational weeks at parturition (weeks)				39.78 (1.01)	37.10–41.50	
Postpartum time (days)				21.33 (7.74)	7.00–43.00	
Time between sessions (days)	44.37 (10.22)	31–70		47.33 (10.90)	27–71	
Education						
School			0 (0%)			4 (4.5%)
Professional training			5 (16.7%)			11 (12.5%)
University degree			10 (33.3%)			30 (34.1%)
Master			13 (43.3%)			41 (46.6%)
PhD			2 (6.7%)			2 (2.3%)
Premature rupture of membranes						
Spontaneous						37 (46.25%)
Artificial						43 (53.75%)
Birth medical induction						50 (68.5%)
Instrumental birth						18 (27.5%)
Episiotomy						23 (28.75%)
Kristeller maneuver						14 (17.5%)
Nondelivery companion						4 (4.5%)
Skin-to-skin contact						77 (88%)
Depression symptoms at session 1						
Score				4.35 (3.84)	0–14	
% Above cutoff for moderate symptoms						10 (11.36%)
Depression symptoms at session 2						
Score				5.89 (4.75)	0–20	
% Above cutoff for moderate symptoms						15 (17.05%)
Birth experience score				3.23 (0.94)		

Volume segmentations of the hippocampal substructures and the nuclei of the amygdala were performed with the Freesurfer's Hippocampal Subfields and Nuclei of Amygdala Segmentation tool (*48*, *49*). The tool used high-resolution coronal T2-weighted images as input for the segmentation. These images were processed within the T1-weighted image space generated by Freesurfer's longitudinal workflow without multispectral segmentation. The volumes of the whole hippocampus and the 12 segmented subfields, along with the whole amygdala and the 9 segmented nuclei, were automatically determined using a Bayesian inference approach and a probabilistic atlas. This atlas merges manually delineated ultrahigh resolution ex vivo MRI data with in vivo MRI data. The segmentation is performed at a higher subvoxel isotropic resolution of 0.33 mm, and volume quantification is done using the posterior probabilities (soft segmentations) to take into account partial volume effects. All segmentations were visually inspected. Images with clear segmentation errors—either extending beyond target regions or failing to include complete substructure—were discarded. Uncertain cases were flagged for potential exclusion and jointly reviewed with independent raters to reach a consensus.

In this study, the substructures examined in each hemisphere included the CA1, CA3, CA4, subicular complex, fimbria, hippocampal fissure, HATA, hippocampal tail, and dentate gyrus of the hippocampus as well as the superficial, centromedial, and lateralbasal nucleus

of amygdala. Specific details regarding the aggregation of these substructures from the original segmentation (*48*–*50*) are provided in Fig. 3 and Table 3.

Psychological evaluations

This study examined the levels of prenatal and postnatal depression in mothers, as well as their birth experiences. Depression levels were assessed using the Edinburgh Depression Scales (*51*, *52*), a 10-item screening test designed to identify mothers at risk for perinatal depression. Participants responded on the basis of their feelings during the past 7 days, with total scores ranging from 0 to 30. Lower values indicate a normal range, with minimal to no symptoms of depression. Scores between 10 and 20 suggest the presence of mild to moderate depressive symptoms, and scores higher than 20 indicate severe depressive symptoms. Birth experience was measured using the Birth Experience Questionnaire (*53*). This questionnaire captures important dimensions of the perinatal experience through 10 items. It assesses mothers' perceptions of stress, pain, fear, sense of control, and partner support during childbirth. Birth experience score is rated on a scale from 1 to 7, with higher scores indicating a more challenging birth experience.

In addition, sleep quality and perceived stress levels were assessed for both mothers and controls at each session. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (*54*), a self-reported questionnaire consisting of 19 items designed to measure overall sleep quality over the past month across seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. A global score was computed by summing all components, with scores ranging from 0 to 21, where higher scores indicate poorer sleep quality. Perceived stress levels were measured using the Perceived Stress Scale (*55*), a self-reported questionnaire consisting of 14 items, designed to assess how individuals perceive different life situations as stressful. Scores range on a scale from 0 to 40, with higher scores indicating higher perceived stress.

Statistical analyses

Neuroimaging analyses

We used univariate linear mixed effects models to examine group differences in hippocampus and amygdala volumes between first-time gestational mothers and nulliparous women. The dependent variables in these models included the hemispheric volumes of the whole hippocampus and amygdala as well as their aggregated substructures, with group (mothers and controls), session (Prg and Post), and their interaction as the independent variables. Random intercepts were included to account for subject-specific differences.

Several supplementary analyses were performed. First, we repeated both global and substructure analyses incorporating age at the pregnancy session, sbTIV, sleep quality, and perceived stress scores and their session interaction as mean-centered fixed effects covariates. Then, we examined longitudinal volumetric differences among mothers at the global and substructure levels. These models included session, age at the pregnancy session, sbTIV, postpartum days, gestational week at birth, and their interaction with the session as independent variables, along with random intercepts. Last, we analyzed volumetric differences—at both the whole structure and substructure levels—between mothers based on the birth type (vaginal delivery and emergency and scheduled C-sections) and on whether they initiated the first stages of labor (labor versus scheduled C-sections). These random-intercept models also included age at the pregnancy session, sbTIV, postpartum days, gestational week at birth, and their session interaction as fixed effect covariates.

For all fitted models, signed effect sizes were computed as partial eta squared, considering the sign of the parameter. Results were corrected for multiple comparisons using the Benjamini and Hochberg false discovery rate (FDR) (*56*) with $q = 0.05$.

Psychological analyses

We adjusted a random-intercept linear mixed effects model to examine longitudinal changes in depression scores from pregnancy to postpartum sessions. The adjusted model included the depression scores as the dependent variable and the session as the independent variable. We also computed a Pearson correlation to explore the relationship between depression changes and birth experience scores. Changes in depression levels were computed as the difference between the depression levels at postpartum and pregnancy sessions.

Correlational analyses between neuroimaging and psychological data

We used Pearson correlations to explore potential relationships between changes in the whole hippocampus and amygdala volumes and changes in depression levels and birth experience scores. Volumetric changes were computed as the percentage of change relative to the pregnancy session. We considered as significant P values surviving the Benjamini and Hochberg FDR correction with $q = 0.05$. In addition, we also computed Pearson partial correlations adjusting for maternal covariates such as the postpartum days and gestational week at birth. For those significant Pearson correlations, we conducted a post hoc analysis by computing similar Pearson correlations with the corresponding hippocampal subfields and amygdala nuclei.

Table 3. Overview of hippocampal and amygdala parcellations. Hippocampal subfields and amygdala nuclei from Iglesias *et al.* and the final aggregated substructures.

Aggregated substructures	Original substructures and nuclei (*48*, *49*) using F60 parcellation	Subcortical structure
No aggregated	CA1, CA3, CA4, fimbria, hippocampal fissure, hippocampus-amygdala-transition-area, and hippocampal tail	Hippocampus
Subicular complex	Parasubiculum, presubiculum, and subiculum	Hippocampus
Dentate gyrus	Granule cell layer of the dentate gyrus and the molecular layer	Hippocampus
Superficial nucleus	Cortical nucleus, anterior amygdaloid area, and cortical amygdaloid transition	Amygdala
Centromedial nucleus	Central nucleus and medial nucleus	Amygdala
Lateralbasal nucleus	Lateral nucleus, basal nucleus, accessory basal nucleus, and paralaminar nucleus	Amygdala

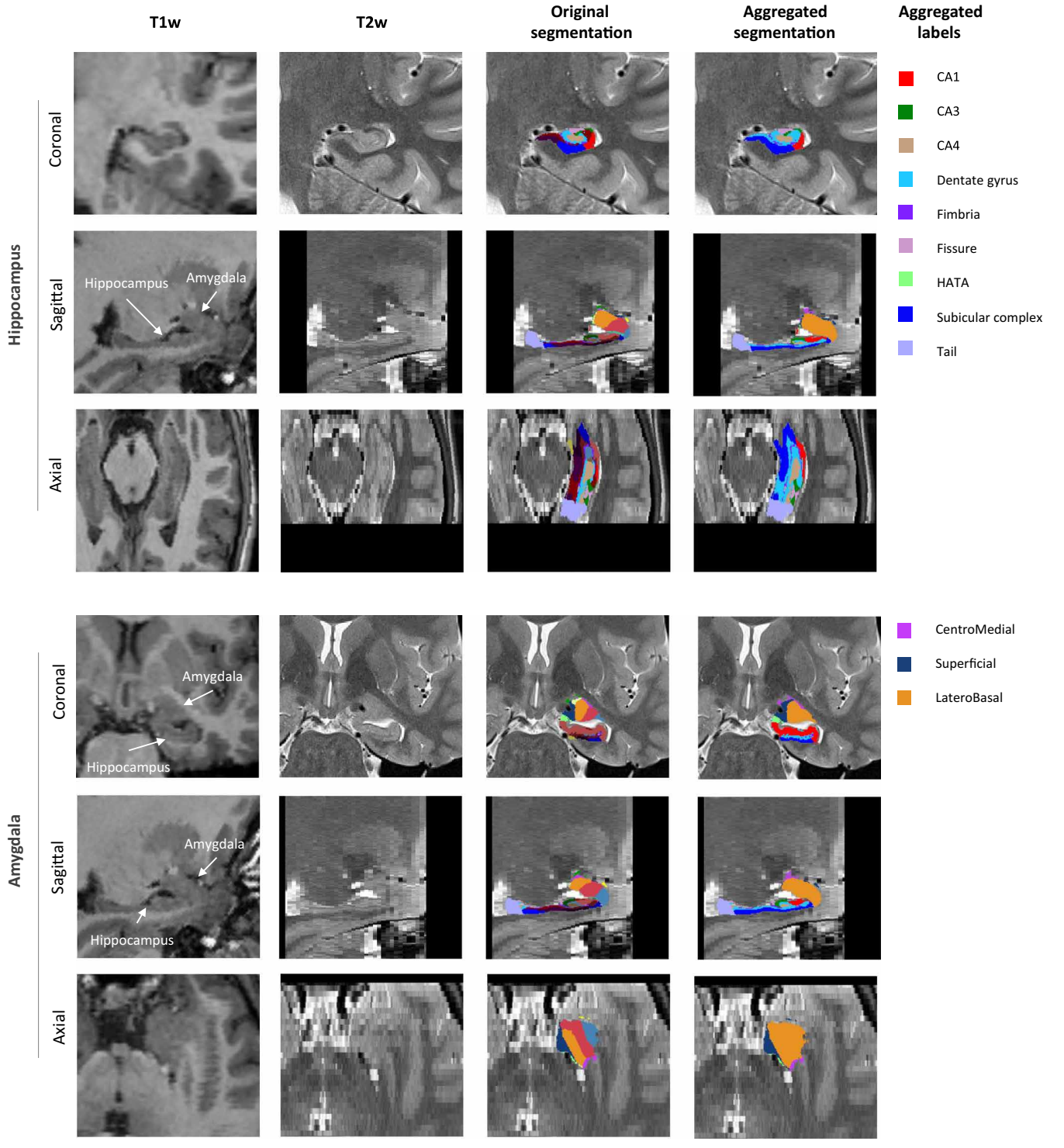

Fig. 3. Hippocampal and amygdalar substructures: Original segmentations and final aggregations. Sample slices showing the left hippocampus and amygdala, along with their substructures. The subcortical structures are shown in three views (coronal, sagittal, and axial), one per row. From left to right columns, the slices correspond to the whole-brain T1-weighted (T1w) magnetic resonance images, the high-resolution coronal T2-weighted (T2w) magnetic resonance images focused on the hippocampus and amygdala, the original segmentation from (*48*, *49*), and the aggregated segmentation used in this study and its labels (see also Table 2). Segmentations are represented with the voxel size used in the segmentation process, i.e., 0.33-mm isotropic.

Software

Statistical analyses were performed in RStudio, under the *R* version 4.2.1. To adjust linear mixed effects models, we used the fslmer (version 0.0.0.9002) library. To compute the Pearson normal and partial correlations, as well as to correct for FDR correction, we used the stats (version 4.2.1) and ppcor (version 1.1) libraries. For the plots, we used the following libraries: ggplot2 (version 3.4.2), ggpubr (version 0.4.0), gcorrplot (version 0.1.3), and cowplot (version 1.1.1). Additional used packages were as follows: dplyr (version 1.1.4), tidyr (version 1.2.0), feather (version 0.3.5), reshape2 (version 1.4.4), and gtsummary (version 1.6.1).

Supplementary Materials

This PDF file includes:

Figs. S1 to S4
Tables S1 to S6

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