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Broader autism phenotype as a risk factor for postpartum depression: Hamamatsu Birth Cohort (HBC) Study

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ABSTRACT

The broader autism phenotype (BAP), which refers to the expression of behavioral and cognitive propensities that are milder but qualitatively similar to those defining autism spectrum disorder, can play a crucial role in postpartum depression (PPD). We investigated whether pregnant women's BAP would increase the risk for PPD, using a representative birth cohort in Japan. Pregnant women were enrolled in the Hamamatsu Birth Cohort (HBC) Study during their mid-gestation ($N = 841$) and were followed up until 3 months after delivery. BAP was measured mainly during the 2nd trimester of the pregnancy by using the Broader Phenotype Autism Symptoms Scale. Participants scoring 9 points or higher on the Edinburgh Postnatal Depression Scale at least once during the first 3 months after childbirth were diagnosed with PPD. Among participants, 128 (15.2%) women were found to have PPD. Multiple logistic regression analyses showed that BAP were associated with PPD (OR = 1.19, 95% CI [1.07–1.31]), even after controlling for other potential confounders. In addition, the association was not moderated by history of depression and/or anxiety disorders, including concurrent depressive and anxiety symptoms during pregnancy. The findings suggest that pregnant women with BAP have an elevated risk for PPD.

1. Introduction

Postpartum depression (PPD) is one of the most commonly observed psychiatric conditions in women after childbirth (Kendell, Chalmers, & Platz, 1987; O'Hara & McCabe, 2013). In the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR: American Psychiatric Association, 2000), PPD had been defined as a depressive disorder with the specifier "postpartum onset". It has been reported that the prevalence of PPD ranges from approximately 10 to 20% in Western countries (Davey, Tough, Adair, & Benzies, 2011; O'Hara & McCabe, 2013) as well as in Asian countries (Matsumoto et al., 2011; Wan et al., 2009). However, a substantial proportion of women with PPD are overlooked

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(Gjerdingen & Yawn, 2007). This is problematic because PPD leads to a variety of negative outcomes, including maternal health problems (e.g., lower levels of self-rated general health; Dennis, 2004), poor parenting (Field, 2010; Paulson, Dauber, & Leiferman, 2006), and delay in children's behavioral development in later life (Hay, Pawlby, Waters, & Sharp, 2008). Therefore, it is important to identify risk factors for PPD to maintain the well-being of mothers and their families.

Studies have reported that some psychosocial factors increase the risk for PPD. Such risk factors include history of psychiatric illness, lack of social support, advanced age, and primiparity (Matsumoto et al., 2011; Milgrom et al., 2008; Mori et al., 2011; O'Hara & McCabe, 2013; Robertson, Grace, Wallington, & Stewart, 2004).

However, other researchers have focused on the biological and genetic basis of PPD. For example, it has suggested that serotonin-system dysfunctions have been associated with risk of depression and PPD (Riccio et al., 2011; Skalkidou, Hellgren, Comasco, Sylvén, & Sundström Poromaa, 2012). Variability in the repeat sequence of HTTLPR, which is a promoter region of serotonin transporter gene (SLC6A4), is associated with autism spectrum disorder (ASD) and related conditions (Cook & Leventhal, 1996), particularly among multiplex families (Devlin et al., 2005). In addition, abnormalities in expression of the SLC6A4 have been specifically associated with PPD (Doornbos et al., 2009), but not with depressive symptoms at 32 weeks after giving birth (Sanjuan et al., 2008). These findings imply that PPD and ASD might share common biological and genetic mechanisms. One way to test this possibility is to investigate the possible association between PPD and the mother's ASD-like behaviors, also known as broader autism phenotype (BAP).

BAP refers to the expression of behavioral and cognitive propensities that are milder but qualitatively similar to those seen in ASD and is more common in relatives of individuals with ASD than in the general population (Piven, Palmer, Jacobi, Childress, & Arndt, 1997). BAP is considered a stable trait rather than a momentary state. Studies have suggested that individuals with BAP have deficits in social motivation and communication, impairments in facial processing and executive functioning, and lower levels of motor imitation and language (Dawson et al., 2002, 2005; Piven et al., 1997; Sucksmith, Roth, & Hoekstra, 2011); all of these characteristics are also seen in individuals with ASD. In addition, it has been shown that individuals with higher levels of BAP are at increased risk for psychiatric disorders, such as major depressive disorder and depressive symptoms (Ingersoll & Hambrick, 2011; Piven & Palmer, 1999; Yirmiya & Shaked, 2005). These findings suggest that pregnant women with BAP may be at an increased risk for developing PPD after giving birth.

The present study was designed to investigate the possible link between BAP and PPD among a representative sample of Japanese women. We are unaware of any studies that have investigated the possible risk of PPD conferred by BAP in pregnant women using birth cohort. Identifying such an association would also be beneficial in providing more efficacious intervention for a large number of PPD sufferers. We hypothesized that pregnant women with BAP, as defined in the Broader Phenotype Autism Symptoms Scale (BPASS; Dawson et al., 2007), would show an increased likelihood of developing PPD after controlling for known risk factors.

2. Method

This study was conducted as a part of an ongoing cohort study, the "Hamamatsu Birth Cohort for Mothers and Children" (HBC; Tsuchiya et al., 2010). A detailed summary of the methodology of the HBC is described below.

2.1. Participants

We consecutively contacted 962 pregnant women who were expected to give birth at our two research sites in Hamamatsu in mainland Japan, namely the Hamamatsu University Hospital and the Kato Maternity Clinic, and who gave birth between December, 2007 and December, 2010. Participants were representative of Japanese women in terms of age, socioeconomic status, and parity, and their children were representative in terms of birthweight and gestational age (Tsuchiya et al., 2010). All participants were given a complete description of the study and provided written informed consent to participate.

The participating women were followed from study entry, which took place during mid-pregnancy, to 3 months after childbirth. Participants were asked to complete an interview with our research team during mid-gestation and filled out the Edinburgh Postnatal Depression Scale (EPDS; Cox & Holden, 2003; Cox, Holden, & Sagovsky, 1987) to measure their depressive symptoms after childbirth. Following the literature (Evans, Heron, Francomb, Oke, & Golding, 2001; Kendell et al., 1987), participants were asked to complete the EPDS three times after delivery at 2–4, 5–7, and 8–12 weeks, and then to mail it back to our research center. Because the diagnosis of PPD was considered unreliable in respondents who completed the EPDS only once during the study period, 121 (12.6%) of the 962 participants were excluded from the analysis. The following values were derived for the group of women excluded ($n = 121$) and the group of women included ($n = 841$) in the analysis: the mean scores of the first observation of the EPDS (4.05 vs. 4.49 points), mean scores of the BPASS (13.42 vs. 13.24 points), mean age of the participants (29.9 vs. 30.9 years), mean age of the partners (32.5 vs. 32.8 years), average household income (5.62 vs. 6.04 million JPY), gender of the child (male 47.9% vs. 51.8%), and parity (primiparae 50.4% vs. 52.8%, respectively).

2.2. Outcome measures

At the time of our measurement, PPD was defined as a depressive disorder with a specifier of postpartum onset in the DSM-IV-TR (American Psychiatric Association, 2000), although this specifier was replaced with a new specifier "peripartum

onset" in the DSM-5 (American Psychiatric Association, 2013). Thus, our diagnosis of PPD is compatible with DSM-IV-TR instead of DSM-5.

In this study, PPD was detected using the EPDS (Cox & Holden, 2003; Cox et al., 1987), which is a paper-and-pencil questionnaire with 10 items. Each item was scored on a 4-point Lickert-type scale (0–3) and then the items were summed to give a depressive symptoms score; higher scores represent greater levels of depressive symptoms after childbirth. We defined participants who scored 9 points or higher on the EPDS at least once during the 3-month period (after delivery at 2–4, 5–7, and 8–12 weeks) as having PPD. The cut-off point of 8 and 9 for the Japanese version of EPDS has been verified in previous studies (Tamaki, Murata, & Okano, 1997; Yamashita, Yoshida, Nakano, & Tashiro, 2000; Yoshida, Yamashita, Ueda, & Tashiro, 2001); both the sensitivity and specificity of the Japanese version of the EPDS for identifying a major depressive episode have been shown to exceed 80%.

2.3. Measurement of risk factors

BAP was assessed using the BPASS (Dawson et al., 2007), which is a measure of autism-related traits via both direct observation and face-to-face interview through 11 items. This scale is appropriate for adults and children, irrespective of whether a diagnosis of ASD has been made. The BPASS comprises four domains. First, the social motivation domain measures social interest in peers and groups, such as self-perception of social comfort in groups and preference for time spent alone versus time spent with others across settings (two items). Second, the expressiveness domain assesses nonverbal social communication, such as the use of appropriate and integrated eye gaze, social smiling, facial expressions, and prosody (four items). Third, the conversational skills domain measures clinical observations of conversation skills, such as the occurrence of excessive detail that impedes conversation and decreased sensitivity to the listener (two items). Fourth, the flexibility/range of interests domain assesses breadth and intensity of interests, such as the preference for arranging a daily schedule and the physical environment in support of a particular hobby (three items).

Because the BPASS interview was conducted mainly during the 2nd trimester of the pregnancy, interviewers could not ascertain whether the participants would develop PPD. The BPASS was administered by highly trained interviewers and conducted individually with each participant to discuss their behavioral propensities. Lickert-type scales ranged from 1 to 5, 1 to 4, or 1 to 3 depending on the items; higher scores represent greater (more impaired) levels of BAP. The composite scores were summed to form a BAP scores (skewness = 1.02, kurtosis = 4.58, $\omega = 0.54$).

To check whether our use of the BPASS is reliable and valid, we adopted a subset of the participating women of this study at 3–6 years after childbirth ($n = 20$) and examined test–retest reliability and convergent validity of the BAP scores assessed by the BPASS. Test–retest reliability was investigated by intraclass correlation (ICC) using a BPASS over 3–6 years, and convergent validity was evaluated by Pearson correlation with the Subthreshold Autism Trait Questionnaire (24 items; Kanne, Wang, & Christ, 2012). The results were acceptable (ICC = 0.47 and $r = 0.42$, respectively).

2.4. Measurement of potential confounders

As for potential confounders that may account for the association between BAP and PPD, we opted for following factors that have been shown to have an elevated risk for PPD in the literature (Matsumoto et al., 2011; Milgrom et al., 2008; Mori et al., 2011; O'Hara & McCabe, 2013; Robertson et al., 2004) and are available in the HBC data set: (a) history of depression and/or anxiety disorders, (b) lack of emotional support from the partner, (c) parity, (d) age of the participating women, (e) age of the partners, and (f) annual household income. As with previous studies (Matsumoto et al., 2011; Mori et al., 2011), the past and current history of psychiatric diagnoses for the participants was evaluated during mid-gestation and confirmed by trained interviewers, using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1997). Among the varying patterns of psychiatric history, because prior history of depression and/or anxiety disorders have been consistently shown to be associated with an increased risk for PPD (Matsumoto et al., 2011; Milgrom et al., 2008; Mori et al., 2011; O'Hara & McCabe, 2013; Robertson et al., 2004), we focused on this risk factor. We defined history of depression as a current or past diagnosis of major depressive disorder, bipolar disorders, or dysthymia, and a history of anxiety disorders as a current or past diagnosis of panic disorder with or without agoraphobia, specific phobia, social phobia, obsessive compulsive disorder, or adjustment disorder. Among the 841 participants included in the analysis, 95 women (11.3%) had a history of depression and/or anxiety disorders.

2.5. Statistical analysis

First, we calculated Pearson correlation coefficients to confirm the associations of BAP with depressive symptoms after delivery at each time point (2–4, 5–7, and 8–12 weeks).

Second, we calculated the scores and proportions of risk factors in women with or without PPD. In addition, we conducted comparative analyses in the two groups using the *t*-test for mean scores (i.e., BAP), Mann–Whitney test for median scores (i.e., annual household income), or Chi-square test for categorical variables (i.e., history of depression and/or anxiety disorders, lack of emotional support from the partner, parity, age of the participating women, and age of the partners), and then calculated the odds ratios (ORs) of each potential risk factor.

Third, we conducted a series of logistic regression analyses to estimate the ORs of BAP for PPD: (a) an analysis using a crude model that did not control for any potential confounder, (b) an analysis using a first adjustment model that considered history of depression and/or anxiety disorders, lack of emotional support from the partner, and parity, and (c) an analysis using a final model that included all the remaining confounders.

In addition, to rule out the possibility that the possible association between BAP and PPD is moderated by concurrent depressive symptoms during mid-pregnancy, we examined whether an interaction term between BAP and history of depression and/or anxiety disorders would predict PPD, even after controlling for potential confounders. We also performed a supplemental analysis in which we broke BAP down into four domains proposed by Dawson et al. (2007) to investigate the associations between BAP traits and PPD in more detail, controlling for all confounders.

P-values of <0.05 were considered to be statistically significant. Stata version 12.1 was used for these analyses.

3. Results

3.1. Correlations of BAP with depressive symptoms after childbirth

As seen in Fig. 1, BAP were weakly but positively associated with depressive symptoms after childbirth at all measurement periods ($r = 0.14$, 95% CI [0.07–0.20], $P < 0.001$ for 2–4 weeks; $r = 0.16$, 95% CI [0.10–0.23], $P < 0.001$ for 5–7 weeks; $r = 0.16$, 95% CI [0.09–0.23], $P < 0.001$ for 8–12 weeks).

3.2. Characteristics of women with or without PPD

Table 1 shows the number of women with or without PPD, in addition to the scores and proportions of each potential risk factor of the two groups. Among the 841 women included in the analysis, 128 participants scored 9 points or higher on the EPDS at least once during the 3-month observation period after the childbirth. The overall cumulative incidence of PPD was 15.2% (95% CI [12.9–17.9]).

3.3. Does BAP increase the risk for PPD?

The final model with full adjustment indicated that BAP were associated with PPD (OR = 1.19, 95% CI [1.07–1.31]), even after controlling for history of depression and/or anxiety disorders, lack of emotional support from the partner, parity, age of the participating women, age of the partners, and annual household income (Table 2). Multicollinearity was not found because the variance inflation factor (VIF) for independent variables in the final model was 1.01–2.05.

We did not find a significant interaction effect between BAP and history of depression and/or anxiety disorders on PPD, controlling for potential confounders (OR = 0.99, 95% CI [0.78–1.27]; table not shown).

In the supplemental analysis, social motivation (OR = 1.40, 95% CI [1.09–1.80]) and expressiveness (OR = 1.35, 95% CI [1.03–1.75]) were associated with PPD; however, conversational skills (OR = 1.25, 95% CI [0.90–1.74]) and flexibility/range of interests (OR = 1.03, 95% CI [0.89–1.20]) were not associated with PPD, controlling for potential confounders (table not shown).

4. Discussion

The current study investigated whether BAP as stable autism-related behavioral and cognitive traits would increase the risk for developing PPD among a representative sample of Japanese pregnant women. Multiple logistic regression analyses revealed that BAP were positively associated with PPD, even after controlling for other potential confounders. To our knowledge, this is the first study to show that BAP measured during mid-pregnancy increases the likelihood of having PPD. In short, our findings indicated that the presence of BAP among pregnant women is associated with the emergence of PPD after giving birth.

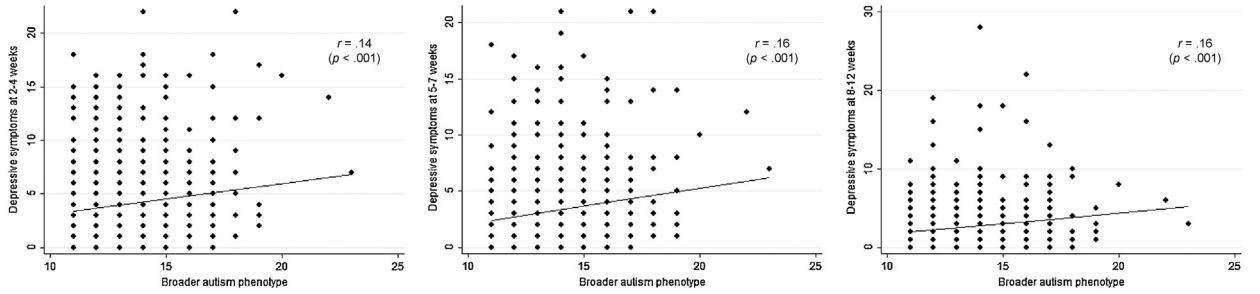

Fig. 1. Scatterplots showing the associations between broader autism phenotype and depressive symptoms after childbirth at 2–4, 5–7, and 8–12 weeks. Broader autism phenotype was measured by composite score of the Broader Phenotype Autism Symptoms Scale.

Table 1
Descriptive statistics of the risk factors for postpartum depression (PPD).

	Women with PPD ($n = 128$)		Women without PPD ($n = 713$)		p and effect size	OR and 95% CI
	n, M, or Md	%, SD, or QD	n, M, or Md	%, SD, or QD		
Broader autism phenotype[a, b]	13.77	2.08	13.14	1.74	$P < 0.001$, $d = 0.35$	1.19 [1.08–1.31][c]
History of depression/anxiety disorders					$P < 0.001$, $\varphi = 0.16$	
No	98	13.1	648	86.9		Reference
Yes	30	31.6	65	68.4		3.05 [1.88–4.94]
Emotional support from the partner[b]					$P = 0.17$, $\varphi = 0.05$	
Available	65	13.7	408	86.3		Reference
None	63	17.2	304	82.8		1.30 [0.89–1.90]
Parity					$P = 0.003$, $\varphi = 0.10$	
Multiparity	45	11.3	352	88.7		Reference
Primiparity	83	18.7	361	81.3		1.80 [1.22–2.66]
Age of the participating women					$P = 0.45$, $V = 0.06$	
<25 years	16	19.1	68	81.0		1.31 [0.70–2.46]
25–29 years	31	12.6	215	87.4		0.80 [0.49–1.31]
30–34 years	46	15.2	256	84.8		Reference
≥35 years	35	16.8	174	83.3		1.12 [0.13–0.25]
Age of the partner					$P = 0.43$, $V = 0.06$	
<25 years	12	23.1	40	76.9		1.81 [0.88–3.74]
25–29 years	28	14.7	162	85.3		1.05 [0.62–1.75]
30–34 years	42	14.2	254	85.8		Reference
≥35 years	46	15.2	257	84.8		1.08 [0.69–1.70]
Annual household income (million JPY)	5.60	1.13	5.50	1.43	$P = 0.79$, $r = 0.01$	0.97 [0.91–1.04] [c]

Note. M = mean; SD = standard deviation; Md = median; QD = quartile deviation; OR = odds ratio; CI = confidence interval.
[a] Composite score of the Broader Phenotype Autism Symptoms Scale.
[b] There was one missing observation in a participant without PPD.
[c] OR of continuous variables calculated for a 1-point increase.

Table 2
Logistic regression analyses predicting risk of postpartum depression from broader autism phenotype measured by composite score of the Broader Phenotype Autism Symptoms Scale.

	OR	95% CI	P
Crude[a]	1.19	1.08–1.31	<0.001
First adjustment[b]	1.18	1.07–1.31	0.001
Full adjustment[c]	1.19	1.07–1.31	0.001

Note. $N = 840$. OR = odds ratio; CI = confidence interval.
[a] No adjustment made for potential confounders.
[b] Adjusted for history of depression and/or anxiety disorders, lack of emotional support from the partner, and parity.
[c] Adjusted for history of depression and/or anxiety disorders, lack of emotional support from the partner, parity, age of the participating women, age of the partner, and annual household income.

Individuals who have higher levels of BAP can develop not only PPD, but also various psychiatric disorders. Studies have demonstrated that BAP and/or ASD is associated with major depressive disorder, anxiety disorders, obsessive compulsive disorder, hyperactivity, impulsivity, aggression, and self-injury (Gerdts & Bernier, 2011; Matson & Nebel-Schwalm, 2007; Sucksmith et al., 2011). However, we must note that the association between BAP and PPD, which we found in this study, did not reflect a link of past and/or current history of depression and/or anxiety disorders with PPD. Indeed, adjustment of history of depression and/or anxiety disorders as a confounder did not change the observed association between BAP and PPD, whereas history of depression and/or anxiety disorders was associated with a more than 3-fold increase in the risk of PPD. We also confirmed that the association between BAP and PPD was not moderated by history of depression and/or anxiety disorders. Therefore, the results suggest that BAP increases the likelihood of developing PPD, regardless of history of depression and/or anxiety disorders, including concurrent depressive symptoms during pregnancy.

The additional analysis revealed that two separable domains regarding social behaviors, namely social motivation and expressiveness, increased the risk for PPD, but not two other domains, namely conversational skills and flexibility/range of interests. Dawson et al. (2002, 2005), who originally developed BPASS, argued that impaired social motivation and expressiveness were based on dysfunction of the amygdala and prefrontal cortex. It is also reported that dysfunction of these brain areas may be associated with a later emergence of major depressive disorder (Heinz et al., 2005; Murray, Wise, & Drevets, 2011). To this point, the association between BAP and PPD might be attributable to specific social behaviors (i.e., social motivation and expressiveness) among pregnant women, which may be associated with depressive symptoms after childbirth by way of a neurobiological pathway. Unfortunately, we do not have any data to empirically investigate these possibilities, but they may provide important clues for future biological research.

Our findings have important clinical implications for prevention or early intervention of PPD. As shown in Table 2, a 1-point increase in the BAP represents an approximately 1.2-fold risk of developing PPD, corresponding to a two-fold increased risk after 5-point increase in the BPASS composite score. This implies that measuring BAP during pregnancy could help to educate caregivers about who are at increased risk for PPD among pregnant women. Since PPD continues to be overlooked (Gjerdingen & Yawn, 2007), early detection programs consisting of known predictors for PPD together with the BPASS would help those professionals to identify pregnant women who should receive preventive care prior to childbirth.

Furthermore, this study has implications for children with ASD whose mothers had PPD. Without any doubt, familial BAP is strongly associated with emergence of ASD among children (Gerdts, Bernier, Dawson, & Estes, 2013; Piven et al., 1997); on the other hand, PPD induced by BAP in the mother may also precipitate or facilitate the emergence of ASD in her child. In this regard, investigation into the association between mothers' PPD and children's ASD is warranted and would be of particular interest to elucidate the etiology of ASD in terms of the biological links between the mother and the child.

Several limitations in this study bear mention. First, the sample size was relatively modest. However, the ORs of BAP for PPD were statistically significant, while the estimates were not very large, indicating that type 2 errors due to limited sample size were not a concern. Second, the use of a self-report measure to diagnose PPD could have undermined the diagnostic accuracy. However, because previous studies which employed the EPDS with a cut-off point of 8 and 9 in Japan showed satisfactorily high sensitivity and specificity for major depressive disorder (e.g., Tamaki et al., 1997), using the self-report measure probably did not decrease the diagnostic accuracy in our study. Finally, scores of the BPASS in our study were slightly higher than in previous studies in the United States (Dawson et al., 2007; Gerdts et al., 2013). This may reflect cultural differences in the communication styles between East Asians and Euro-Americans, and thus future research is needed to investigate this possibility.

Despite these limitations, the strengths of this birth cohort study include the representativeness of the sample and the prospective design by interviewers who were blinded to the outcome. These methodologies would minimize selection bias and recall bias. Furthermore, our findings are considered highly valid because the BPASS assesses the autism-related behavioral and cognitive characteristics of participants based on direct observation and interview.

In sum, pregnant women with broader autism phenotype (BAP) showed an increased risk for developing postpartum depression (PPD). It is hoped that further investigations will clarify the underlying neurophysiological and psychological mechanisms of the association between BAP and PPD.

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Conflict of Interest

None of the authors have any conflict of interest to declare.

Contributors

R.A. performed the statistical analysis and wrote the first draft of the manuscript. K.J.T. contributed to all aspects of this study, including the design, data collection and analysis, and drafting. N.T. provided administrative support and critical comments on the study design, data collection, and drafting. T.H., Y.K., R.N., C.N., A.O., Y.S., S.T., and N.M. contributed to the preparation of the protocol, data collection, and interpretation of the results. All authors approved the final manuscript.

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