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Maternal diabetes in early pregnancy, and psychotic experiences and depressive symptoms in 10-year-old offspring: A population-based birth cohort study

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ABSTRACT

Epidemiological studies have suggested that maternal diabetes in pregnancy increases the risk of schizophrenia in offspring. A recent cohort study observed that maternal diabetes in early pregnancy is also associated with psychotic experiences in the general adolescent population. However, it remains unclear whether maternal diabetes in early pregnancy is specifically associated with psychotic experiences, or is generally associated with broader mental health problems, including depressive symptoms in adolescence. The present study investigated the longitudinal associations between maternal diabetes in early pregnancy, and psychotic experiences and depressive symptoms in 10-year-old offspring. Our data were derived from the Tokyo Early Adolescence Survey, a population-based survey of early adolescents (N = 4478) and their primary caregivers. Diabetes in early pregnancy was determined by records in the mother's Maternal and Child Health Handbook, documented during the pregnancy. Psychotic experiences and depressive symptoms were established through self-report by the offspring at 10 years of age. Diabetes in early pregnancy was associated with an increased risk of hallucination in the offspring (auditory hallucination [odds ratio {OR} 4.33, 95% confidence interval {CI} 1.12–16.75]; visual hallucination [OR 6.58, 95% CI 1.69–25.66]), even after adjusting for depressive symptoms and other covariates. However, the association between maternal diabetes and delusional thoughts was not significant and diabetes in early pregnancy was not associated with adolescent depressive symptoms. Our investigation suggests that maternal diabetes in early pregnancy may specifically affect the risk of hallucinatory experiences in adolescent offspring.

1. Introduction

Psychotic experiences are common in the general population (van Os et al., 2009) and highly prevalent in childhood and adolescence (Kelleher et al., 2012). Adolescent psychotic experiences have been prospectively associated with an increased risk of schizophrenia, (Dominguez et al., 2011; Fisher et al., 2013; Poulton et al., 2000; Welham et al., 2009), other mental health problems (Fisher et al., 2013), and suicidality in adolescence (Kelleher et al., 2014; Kelleher et al., 2013) and in adulthood (Bromet et al., 2017).

A neurodevelopmental model of schizophrenia postulates that prenatal neural anomalies alter the development of neural systems, leading to the emergence of schizophrenia later in life (Murray and Lewis, 1987; Weinberger, 1987). Human epidemiological and animal studies suggest that maternal hyperglycaemia in early pregnancy, due to gestational

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diabetes, may have adverse effects on neural development in the offspring (Van Lieshout and Voruganti, 2008). The early phase of pregnancy is a crucial period; the human central nervous system begins to develop at an early gestational age, and neuronal proliferation is nearly complete by 12 gestational weeks (Tau and Peterson, 2010). A meta-analysis of epidemiological studies revealed that maternal diabetes was the strongest risk factor (odds ratio [OR] = 7.76) for schizophrenia, among a range of prenatal and postnatal obstetric complications (Cannon et al., 2002). A recent birth cohort study also revealed that diabetes in early pregnancy (up to 11 gestational weeks) increased the risk of psychotic experiences by 3.4-fold in the general adolescent population aged 12 years (Zammit et al., 2009). However, it is unclear whether maternal diabetes is specifically associated with psychotic experiences, or more broadly with common mental health problems, including depressive symptoms. To our knowledge, there are no reports examining diabetes in pregnancy in relation to this wide range of outcomes in offspring (Du Preez et al., 2016), although a high rate of comorbidity between psychotic experiences and depressive symptoms in childhood and adolescence has been reported (Armando et al., 2010; Nishida et al., 2008; Sullivan et al., 2014; Wigman et al., 2011). There is also evidence of an association between first-trimester depression, gestational diabetes, and postpartum depression (Morrison et al., 2016; Hinkle et al., 2016), as well as the intergenerational transmission of depression (Weissman et al., 2006; Kendler et al., 1997). Therefore, it is important to control for psychotic and depressive symptoms in order to examine their respective effects. Furthermore, there are no previous reports investigating which specific psychotic symptoms (e.g., hallucinations vs. delusions) are associated with diabetes in early pregnancy.

The aims of the present study were: 1) to examine whether diabetes in early pregnancy is associated with an increased risk of psychotic experiences in 10-year-old offspring; 2) to investigate which specific psychotic experiences among 10-year-old offspring are associated with diabetes in early pregnancy; and 3) to examine whether diabetes in early pregnancy is associated with an increased risk of depressive symptoms.

2. Material and methods

2.1. Study design, sample, and survey procedure

This study utilised data from the Tokyo Early Adolescence Survey (T-EAS), originally designed as a baseline survey for the Tokyo Teen Cohort, which is an ongoing longitudinal cohort study (URL: http://ttcp.umin.jp/index.html). The T-EAS is a multidisciplinary survey of 10-year-old adolescents which aims to investigate their health and development (Kanata et al., 2016; Yamasaki et al., 2016). We randomly sampled early adolescents using the resident register in three municipalities in the metropolitan area of Tokyo, namely: Setagaya Ward, Mitaka City, and Chofu City. Eligible residents were those born between September 2002 and August 2004. The survey was conducted between October 2012 and January 2015. We sent letters of invitation to participants around the time of their tenth birthday, following which, a trained interviewer visited their homes. The survey was completed twice, over two visits. During the first visit, written informed consent from the primary caregiver (generally the mother) was obtained; participants were then asked to complete the questionnaires at home, before the second visit. During the second visit, the adolescent and primary caregiver were each asked to complete the self-report questionnaires separately (e.g. in different rooms) to avoid each party interfering in the other's answers to sensitive questions (e.g. psychotic experience). The questionnaires were enclosed in envelopes by the respondents immediately after completion. During the second visit, the interviewer also measured the height and weight of the adolescent, and the primary caregiver responded to a semi-structured interview. All data were collected anonymously.

2.2. Ethical approval

The T-EAS involves three research institutes: the Tokyo Metropolitan Institute of Medical Science (Approval No. 12-45), the University of Tokyo (Approval No. 10057), and SOKENDAI (The Graduate University for Advanced Studies) (Approval No. 2012002). This survey was approved by the ethics committees of the three institutes.

2.3. Participants

Among the 18,830 eligible pairs of adolescents and primary caregivers, 14,553 were randomly selected due to budget constraints. Of these, 4319 could not be contacted. Of the remaining 10,234 pairs who were contacted, 5756 adolescents or their parents refused to participate. Finally, 4478 pairs participated in the survey (response rate: 43.8%).

2.4. Outcomes

The main outcome measured was psychotic experiences, which were assessed by items derived from the schizophrenia section of the Diagnostic Interview Schedule for Children (DISC-C) (Costello et al., 1985), with an added question on visual hallucinations. A Japanese version of the DISC-C was developed using the translation and back translation method, and has been applied in previous studies conducted in Japan (Nishida et al., 2008; Nishida et al., 2010; Nishida et al., 2014; Oshima et al., 2010; Watanabe et al., 2012). Psychotic experiences were assessed by the following five items: i) “Have you ever heard voices that other people cannot hear?” (auditory hallucinations); ii) “Have other people ever read your thoughts?” (thought broadcasting); iii) “Have you ever had messages sent especially to you through the television or radio?” (special messages); iv) “Have you ever thought that people are following you or spying on you?” (persecutory thoughts); v) “Have you ever seen things that other people could not see?” (visual hallucinations). All responses were scored on a three-point scale: 0, no; 1, maybe; and 2, yes, definitely. Adolescents who answered “yes, definitely” to each item were categorised as having experienced each psychotic symptom, per a previous study (Nishida et al., 2010). Adolescents who answered “yes, definitely” to any of the five items were categorised as having experienced psychotic symptoms. In addition, we examined the association between maternal diabetes in pregnancy and adolescent psychotic experiences when the outcome measure was broader psychotic experiences, which includes the cases which responded “yes definitely”, and “maybe”. Adolescent depressive symptoms were assessed by the Short Mood and Feelings Questionnaire (SMFQ), a 13-item, self-report questionnaire and screening measure to assess the severity of depression. All responses were scored on a three-point scale: 0, not true; 1, sometimes; 2, true. All scores were summed, with the total possible points ranging from 0 to 26 (Kuo et al., 2005).

2.5. Exposures

The primary exposure variable was diabetes in early pregnancy. Cases were identified by entries in the participant's Maternal and Child Health (MCH) Handbook, which is a single booklet record of prenatal check-ups, delivery, child development, and vaccinations recorded by doctors, nurses, and mothers (Ichikawa et al., 2015). Information on having maternal diabetes was checked by mothers when they received the handbook and was confirmed by an obstetric doctor or a nurse when the mothers received their first prenatal check-up at an obstetric clinic, which is recommended and supported by the MCH Act in Japan. The MCH handbook is a unique data collection and prenatal support system in Japan that was based on the MCH Act and MCH Law of 1965, for the promotion of maternal, newborn, and infant health. Over 90% of all pregnant women in Japan are supposed to register within the 11th

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gestational week (Ministry of Health Labour and Welfare, 2016) and begin to record their health status, and receive regular prenatal check-ups at an obstetrics clinic, via the MCH handbook. The MCH Handbook is widely distributed in Japan; government records show that 98.1% of all pregnant mothers in Japan received the handbook before 20 gestational weeks in 2014 (Ministry of Health Labour and Welfare, 2016). In the present cohort, the handbooks were available for 98.0% (4387/4478) of the participants.

2.6. Other covariates

The covariates included maternal age, and age, sex, and cognitive ability of the child at age 10, as well as history of maternal antipsychotic drug use, and maternal obstetric complications which may be associated with the onset of schizophrenia (birth weight < 2000 g, and Caesarean section [Cannon et al., 2002]). Maternal obstetric complications were identified through records in the MCH Handbook. Maternal antipsychotic drug use history was identified by the MCH Handbook records, and responses to the self-report questionnaires about the condition of the mother when the child was 10 years of age. Adolescent cognitive ability was assessed using a short form of the Wechsler Intelligence Scale for Children (WISC-III), consisting of two subsets (Information, and Picture Completion) (Inada and Kamio, 2010). Since the two-item version provided sufficient reliability and validity using pooled sample data (Inada and Kamio, 2010), we developed an original formula for estimating the intelligence quotient (IQ) to fit the T-EAS, with specific regional and period characteristics. The full version of the WISC-III was administered by expert psychologists to 28 children from among the T-EAS participants one year after the initial survey. We then revised the formula for estimating IQ, which had good reliability for Information, and Picture Completion (Cronbach's $\alpha = 0.70$ and 0.54, respectively); The IQs estimated from the formula explained 78% of the variance in IQ scores from the full version of the WISC-III.

2.7. Statistical analysis

Logistic regression analysis was performed to test the associations between diabetes in early pregnancy and psychotic experiences in the offspring at 10 years of age. We calculated the ORs for overall psychotic experiences and each specific psychotic experience (auditory hallucinations, visual hallucinations, persecutory thoughts, and thought broadcasting). We then adjusted for the covariates and depressive symptoms. The specific psychotic experience of special messages was not included in the analysis as a dependent variable because no offspring of a mother with maternal diabetes in early pregnancy experienced this symptom. Linear regression analysis was conducted to test the association between diabetes in early pregnancy and depressive symptoms among the offspring, adjusting for the covariates and psychotic symptoms. The significance level (*P*-value) was set using 2-tailed 0.05-level tests. All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, New York, USA).

3. Results

The proportion of participating female adolescents from the 4478 primary caregiver and child pairs who gave consent to participate in the study was slightly lower than that of the 5756 pairs who refused consent (46.9%, and 49.8%, respectively; $\chi^2 = 8.10$, $P = 0.004$), although the adolescents' height, weight, and maternal age (42.0 years old) were similar to the general population data for Japanese 10-year-olds (Ando et al., 2018). Of the pairs who provided consent, 341 (7.6%) were excluded from the analyses due to incomplete responses to the questions of interest. The data from the remaining 4137 participants were analysed (mean age of offspring: 9.7 years, standard deviation {SD} 0.4; 47.1% female subjects). There were no differences among the excluded subjects (mean age of offspring: 9.7 years, SD 0.4; 44.0% female subjects), in terms of sex ($\chi^2 = 1.25$, $P = 0.263$), age ($\chi^2 = 0.089$, $P = 0.956$), and maternal diabetes in early pregnancy (0.3%; $\chi^2 = 0.081$, $P = 0.776$), although there were differences in terms of the main outcomes (psychotic experiences among the excluded subjects [prevalence rate: 38.0%, $\chi^2 = 13.72$, $P < 0.001$] and depressive symptoms: [SMFQ scores: 5.61, $t = 2.96$, $P = 0.003$]).

Table 1 shows the descriptive characteristics of the participants. Approximately one in four adolescents self-reported experiencing at least one psychotic symptom. Of all the adolescents, 15% experienced auditory hallucinations, approximately 10% experienced visual hallucinations and persecutory thoughts, and <3% experienced thought broadcasting, and special messages (2.6%, and 0.7%, respectively). The prevalence of diabetes in early pregnancy was <1%, while 12% of mothers underwent a Caesarean section, and approximately 1% of the total offspring had a birth weight under 2000 g.

Table 2 shows the results of logistic regression analyses. Diabetes in early pregnancy was associated with increased overall psychotic experiences, with an OR of 5.58 (95% confidence interval [CI] 1.39 to 22.36). The effect remained significant after adjusting for demographic variables (adjusted Model 1: OR = 5.90, 95% CI 1.46 to 23.80) and other perinatal obstetric complications (adjusted Model 2: OR = 5.89, 95% CI 1.46 to 23.74). After adjusting for these covariates and depressive symptoms, the association remained significant, and there was minimal attenuation of the OR (adjusted Model 3: OR 5.29, 95% CI 1.26 to 22.28). Maternal diabetes was significantly associated with auditory and visual hallucinations after full adjustment. Although the odds for delusional thoughts were increased, the association was not significant (Table 2). Additional analyses showed that maternal diabetes was not significantly associated with broader psychotic experiences (Table S1).

The results of the linear regression analyses are shown in Table 3. Exposure to diabetes in early pregnancy was not associated with offspring depressive symptoms at age 10, even after controlling for the covariates.

4. Discussion

To our knowledge, the present study is the first to investigate whether maternal diabetes in early pregnancy results in an increased risk of psychotic experiences and depressive symptoms among offspring at age 10. The present findings suggest that diabetes in early pregnancy is specifically associated with an increased risk of psychotic experiences among the offspring, particularly hallucinatory experiences (but not delusional thoughts). This effect was not explained by the presence of depressive symptoms, which were not associated with maternal diabetes in early pregnancy. The prevalence of psychotic experiences (22.7% in the present study, as measured by DISC-C 4 items) was slightly higher than that reported in a previous study involving 12–15-year-old

Table 1
Study participant characteristics.

N = 4137	
Female, n (%)	1950 (47.1)
Child age, mean years (SD)	9.7 (0.4)
Psychotic experiences, n (%)	1095 (26.5)
Auditory hallucinations, n (%)	616 (14.9)
Visual hallucinations, n (%)	444 (10.7)
Persecutory thoughts, n (%)	415 (10.0)
Thought broadcasting, n (%)	108 (2.6)
Special messages, n (%)	28 (0.7)
Maternal diabetes in early pregnancy, n (%)	9 (0.2)
Caesarean section, n (%)	500 (12.1)
Low birth weight, n (%)	53 (1.3)
Depressive symptoms, mean (SD)	4.8 (4.6)
Child estimated IQ, mean (SD)	107.9 (14.1)
Maternal age, mean (SD)	41.9 (4.2)
Maternal antipsychotic drug use history, n (%)	12 (0.3)

Abbreviations: IQ, intelligence quotient; SD, standard deviation.

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Table 2
Association between maternal diabetes in early pregnancy and psychotic symptoms in 10-year-old offspring.

	Unadjusted model			Adjusted model 1[b]			Adjusted model 2[c]			Adjusted model 3[d]		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Psychotic symptoms[a]	**5.58**	**(1.39–22.36)**	**0.015**	**5.90**	**(1.46–23.80)**	**0.013**	**5.89**	**(1.46–23.74)**	**0.013**	**5.29**	**(1.26–22.28)**	**0.023**
Auditory hallucinations	**4.60**	**(1.23–17.16)**	**0.023**	**4.92**	**(1.31–18.57)**	**0.019**	**4.87**	**(1.29–18.35)**	**0.020**	**4.33**	**(1.12–16.75)**	**0.034**
Visual hallucinations	**6.71**	**(1.79–25.06)**	**0.005**	**7.39**	**(1.96–27.88)**	**0.003**	**7.32**	**(1.94–27.61)**	**0.003**	**6.58**	**(1.69–25.66)**	**0.007**
Persecutory thoughts	**4.51**	**(1.12–18.10)**	**0.034**	**4.71**	**(1.16–19.15)**	**0.030**	**4.81**	**(1.18–19.54)**	**0.028**	4.09	(0.93–18.07)	0.063
Thought broadcasting	4.70	(0.58–37.89)	0.146	4.87	(0.60–39.75)	0.139	4.97	(0.61–40.63)	0.135	3.91	(0.45–33.79)	0.215

Abbreviations: CI, confidence interval; IQ, intelligence quotient; OR, odds ratio. **Bold**: $P < 0.05$.
[a] Experiencing psychotic symptoms: at least one of five specific symptoms (auditory hallucinations, visual hallucinations, persecutory thoughts, thought broadcasting, special message) was experienced.
[b] Adjusted for maternal age, child sex, child age, child's estimated IQ, and maternal antipsychotic drug use history.
[c] Adjusted for maternal age, child sex, child age, child's estimated IQ, maternal antipsychotic drug use history, birth weight < 2000 g, and Caesarean section.
[d] Adjusted for maternal age, child sex, child age, child's estimated IQ, maternal antipsychotic drug use history, birth weight < 2000 g, Caesarean section, and child's depressive symptoms at age 10.

participants assessed by the same measures (15.2%) (Nishida et al., 2010). However, this may be consistent with previous findings, showing that the prevalence of psychotic experiences among children 9–12 years of age was higher than that among adolescents aged between 13 and 18 years (Kelleher et al., 2012). The prevalence of diabetes in early pregnancy in the present study was 0.2%, which was comparable to the prevalence of pre-gestational diabetes (0.3–0.5% of pregnant women) reported in another study (Ornoy, 2005). Gestational diabetes is usually diagnosed after 24–28 gestational weeks (World Health Organization, 2013), although maternal diabetes before 20 gestational weeks was recorded in this study. This observation suggests that a substantial proportion of these diabetic mothers may have developed pre-gestational diabetes. This finding is consistent with that of a previous study showing a longitudinal association between diabetes in early pregnancy and overall psychotic experiences (Zammit et al., 2009). We found consistent results after controlling for adolescent depressive symptoms, and also demonstrated the association between diabetes in early pregnancy and specific definitive psychotic experiences (e.g., hallucinations but not delusions), while no association was found between diabetes in early pregnancy and depressive symptoms when adjusting for psychotic experiences.

4.1. Possible mechanisms

We postulated that the following variables were possible mechanisms linking diabetes in early pregnancy and psychotic experiences in the offspring. Hyperglycaemia in utero may affect perceptual abnormalities in early adolescence. Animal studies have shown that maternal diabetes can cause anatomical derangement of neural cells (Reece et al., 1994), aberrant activations of neural networks (Bhattacharya and Saraswati, 1991; Plagemann et al., 1998; Yamano et al., 1986), and abnormal behaviour in rats (Johansson et al., 1991; Kinney et al., 2003; Ramanathan et al., 2000). This may lead to increased oxidative stress due to impaired neural energy metabolism (Van Lieshout and Voruganti, 2008). Foetal exposure to maternal diabetes is associated with an increased risk of abnormal glucose homeostasis in the offspring, and is not solely attributable to genetic factors (Fetita et al., 2006). Exposure to hyperglycaemic conditions leads to the accumulation of advanced glycation end products (AGEs), which have been associated with the progression of diabetic complications even after good blood glucose control is achieved (Monnier et al., 1999), a phenomenon known as 'hyperglycaemic memory' (Engerman and Kern, 1987; Nathan et al., 2005). Previous findings have also suggested that AGEs contribute to the pathophysiology of schizophrenia (Arai et al., 2011; Arai et al., 2010; Bitanihirwe and Woo, 2011), and abnormal glucose metabolism in the thalamus and the pulvinar was associated with severity of hallucination among patients with schizophrenia (Hazlett et al., 2004). Therefore, diabetes in early pregnancy may be a key factor in the association between schizophrenia and abnormal glucose metabolism (Hasnain, 2016; Perry et al., 2016). In particular, perceptual abnormalities, especially specific ones, were affected by hyperglycaemia in utero, rather than delusions and depression. Delusions were suggested to be a direct representation of emotional concerns, and were formed and maintained by emotional disturbances (Freeman and Garety, 2003; Freeman et al., 2013). Hyperglycaemia in utero may not affect emotional problems in adolescent offspring, whereas it may specifically affect obvious hallucinatory experiences. Further research is needed in order to elucidate these mechanisms.

4.2. Strengths and limitations

We used perinatal records from the MCH Handbooks, allowing for the examination of longitudinal associations without recall bias. We randomly collected data from a large number of participants from the general adolescent population using resident registers in order to reduce the influence of selection bias. However, several study limitations should also be noted. First, the relatively low response rate (43.8%) was a limitation of the study. Response rates of population-based surveys in Japan have declined in the recent decade (from 70% to 50%) (Rindfuss et al., 2015). One reason would be that many apartment buildings in Tokyo have recently adopted an automated system that enables residents to talk with visitors at the locked gate via video. It allows potential respondents to refuse to participate before having a face-to-face encounter with the field worker (Rindfuss et al., 2015). Due to this

Table 3
Association between maternal diabetes in early pregnancy and depressive symptoms in 10-year-old offspring.

	Unadjusted model			Adjusted model 1[b]			Adjusted model 2[c]			Adjusted model 3[d]		
	B	95% CI	*P*	B	95% CI	*P*	B	95% CI	*P*	B	95% CI	*P*
Depressive symptoms[a]	1.92	(−1.07–4.92)	0.209	1.82	(−1.15–4.79)	0.229	1.86	(−1.11–4.83)	0.220	0.76	(−2.12–3.63)	0.605

Abbreviations: B, regression coefficient; CI, confidence interval; IQ, intelligence quotient.
[a] Short Mood Feeling Questionnaire total scores.
[b] Adjusted for maternal age, child sex, child age, child's estimated IQ, and maternal antipsychotic drug use history.
[c] Adjusted for maternal age, child sex, child age, child's estimated IQ, maternal antipsychotic drug use history, birth weight < 2000 g, and Caesarean section.
[d] Adjusted for maternal age, child sex, child age, child's estimated IQ, maternal antipsychotic drug use history, birth weight < 2000 g, Caesarean section, and child's psychotic symptoms at age 10.

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limitation, we could not overcome selection bias completely. There was a difference in the sex of the participants, compared to those who refused, as well as differences in the main outcomes between the analysed and excluded data. Although we adjusted as far as possible for these factors in the analyses, generalisation of the present findings to other adolescent populations should be approached with caution. Second, we used a self-report questionnaire to assess psychotic experiences among the children. It is possible that this tool overestimated the prevalence of psychotic experiences in comparison with the interview-based methods, although previous work demonstrated that self-report questionnaires for the assessment of psychotic experiences among the general adolescent population have a high degree of validity (Kelleher et al., 2011). Third, we did not have enough information about paternal and maternal risk factors (e.g., paternal diabetes, or paternal and maternal mental health status).Paternal and maternal psychotic experiences also could not be adjusted for in the study. Genetic confounding factors could not be confirmed based on our data. Fourth, we were only able to use the dichotomous information about diabetes only in early pregnancy (before 20 gestational weeks), which does not differentiate between pre-gestational and gestational diabetes, and could not investigate dose-response relationship between the severity of maternal diabetes, and the risk of psychotic experiences in offspring. In addition, we did not have detailed information on the conditions associated with maternal diabetes in pregnancy (e.g., severity, Type I or Type II diabetes). In the future, genetic information, detailed information about maternal diabetes (e.g. timing and severity), and biological markers should be used to confirm the association.

4.3. Implications

In conclusion, the results of our investigation suggest that diabetes in early pregnancy is associated with an increased risk of psychotic experiences in general and, specifically, auditory and visual hallucinatory experiences, in early adolescent offspring. Understanding the neurodevelopmental processes in the offspring of mothers with a history of diabetes in early pregnancy contributes to the development of strategies for the prevention of psychotic disorders. Further research is needed to determine the relationship between the severity and timing of maternal diabetes in pregnancy, and psychotic experiences, in order to develop effective prevention strategies for psychosis or other mental health problems in offspring during the perinatal period.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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CRediT authorship contribution statement

Syudo Yamasaki: Conceptualization, Data curation, Formal analysis, Writing - original draft. **Shuntaro Ando:** Conceptualization, Data curation, Formal analysis, Writing - original draft. **Marcus Richards:** Writing - review & editing. **Stephani L. Hatch:** Writing - review & editing. **Shinsuke Koike:** Conceptualization, Data curation, Writing - original draft. **Shinya Fujikawa:** Data curation. **Sho Kanata:** Data curation. **Kaori Endo:** Data curation. **Yuko Morimoto:** Data curation. **Makoto Arai:** Conceptualization, Writing - original draft. **Haruo Okado:** Conceptualization, Writing - original draft. **Satoshi Usami:** Formal analysis. **Toshiaki A. Furukawa:** Writing - review & editing. **Mariko Hiraiwa-Hasegawa:** Writing - review & editing. **Kiyoto Kasai:** Writing - review & editing. **Atsushi Nishida:** Conceptualization, Data curation, Formal analysis, Writing - original draft.

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References

Ando, S., Nishida, A., Usami, S., Koike, S., Yamasaki, S., Kanata, S., Fujikawa, S., Furukawa, T.A., Fukuda, M., Sawyer, S.M., Hiraiwa-Hasegawa, M., Kasai, K., 2018. Help-seeking intention for depression in early adolescents: associated factors and sex differences. J. Affect. Disord. 238, 359–365.

Arai, M., Yuzawa, H., Nohara, I., Ohnishi, T., Obata, N., Iwayama, Y., Haga, S., Toyota, T., Ujike, H., Arai, M., Ichikawa, T., Nishida, A., Tanaka, Y., Furukawa, A., Aikawa, Y., Kuroda, O., Niizato, K., Izawa, R., Nakamura, K., Mori, N., Matsuzawa, D., Hashimoto, K., Iyo, M., Sora, I., Matsushita, M., Okazaki, Y., Yoshikawa, T., Miyata, T., Itokawa, M., 2010. Enhanced carbonyl stress in a subpopulation of schizophrenia. Arch. Gen. Psychiatry 67, 589–597.

Arai, M., Koike, S., Oshima, N., Takizawa, R., Araki, T., Miyashita, M., Nishida, A., Miyata, T., Kasai, K., Itokawa, M., 2011. Idiopathic carbonyl stress in a drug-naive case of at-risk mental state. Psychiatry Clin. Neurosci. 65, 606–607.

Armando, M., Nelson, B., Yung, A.R., Ross, M., Birchwood, M., Girardi, P., Fiori Nastro, P., 2010. Psychotic-like experiences and correlation with distress and depressive symptoms in a community sample of adolescents and young adults. Schizophr. Res. 119, 258–265.

Bhattacharya, S.K., Saraswati, M., 1991. Effect of intracerebroventricularly administered insulin on brain monoamines and acetylcholine in euglycaemic and alloxan-induced hyperglycaemic rats. Indian J. Exp. Biol. 29, 1095–1100.

Bitanihirwe, B.K., Woo, T.U., 2011. Oxidative stress in schizophrenia: an integrated approach. Neurosci. Biobehav. Rev. 35, 878–893.

Bromet, E.J., Nock, M.K., Saha, S., Lim, C.C.W., Aguilar-Gaxiola, S., Al-Hamzawi, A., Alonso, J., Borges, G., Bruffaerts, R., Degenhardt, L., de Girolamo, G., de Jonge, P., Florescu, S., Gureje, O., Haro, J.M., He, Y., Hu, C., Karam, E.G., Kovess-Masfety, V., Lee, S., Lepine, J.P., Mneimneh, Z., Navarro-Mateu, F., Ojagbemi, A., Posada-Villa, J., Sampson, N.A., Scott, K.M., Stagnaro, J.C., Viana, M.C., Xavier, M., Kessler, R.C., McGrath, J.J., World Health Organization World Mental Health Survey Collaborators, 2017. Association between psychotic experiences and subsequent suicidal thoughts and behaviors: a cross-national analysis from the World Health Organization World Mental Health Surveys. JAMA Psychiat. 74, 1136–1144.

Cannon, M., Jones, P.B., Murray, R.M., 2002. Obstetric complications and schizophrenia: historical and meta-analytic review. Am. J. Psychiatry 159, 1080–1092.

Costello, E.J., Edelbrock, C.S., Costello, A.J., 1985. Validity of the NIMH Diagnostic Interview Schedule for Children: a comparison between psychiatric and pediatric referrals. J. Abnorm. Child Psychol. 13, 579–595.

Dominguez, M.D.G., Wichers, M., Lieb, R., Wittchen, H.U., van Os, J., 2011. Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: an 8-year cohort study. Schizophr. Bull. 37, 84–93.

Du Preez, A., Leveson, J., Zunszain, P.A., Pariante, C.M., 2016. Inflammatory insults and mental health consequences: does timing matter when it comes to depression? Psychol. Med. 46, 1–17.

Engerman, R.L., Kern, T.S., 1987. Progression of incipient diabetic retinopathy during good glycemic control. Diabetes 36, 808–812.

Fetita, L.S., Sobngwi, E., Serradas, P., Calvo, F., Gautier, J.F., 2006. Consequences of fetal exposure to maternal diabetes in offspring. J. Clin. Endocrinol. Metab. 91, 3718–3724.

Fisher, H.L., Caspi, A., Poulton, R., Meier, M.H., Houts, R., Harrington, H., Arseneault, L., Moffitt, T.E., 2013. Specificity of childhood psychotic symptoms for predicting schizophrenia by 38 years of age: a birth cohort study. Psychol. Med. 43, 2077–2086.

Freeman, D., Garety, P.A., 2003. Connecting neurosis and psychosis: the direct influence of emotion on delusions and hallucinations. Behav. Res. Ther. 41, 923–947.

Freeman, D., Dunn, G., Fowler, D., Bebbington, P., Kuipers, E., Emsley, R., Jolley, S., Garety, P., 2013. Current paranoid thinking in patients with delusions: the presence of cognitive-affective biases. Schizophr. Bull. 39, 1281–1287.

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Hasnain, M., 2016. Schizophrenia and metabolic dysregulation: shared roots? Lancet Psychiatry 3, 1003–1005.
Hazlett, E.A., Buchsbaum, M.S., Kemether, E., Bloom, R., Platholi, J., Brickman, A.M., Shihabuddin, L., Tang, C., Byne, W., 2004. Abnormal glucose metabolism in the mediodorsal nucleus of the thalamus in schizophrenia. Am. J. Psychiatry 161, 305–314.
Hinkle, S.N., Buck Louis, G.M., Rawal, S., Zhu, Y., Albert, P.S., Zhang, C., 2016. A longitudinal study of depression and gestational diabetes in pregnancy and the postpartum period. Diabetologia 59, 2594–2602.
Ichikawa, K., Fujiwara, T., Nakayama, T., 2015. Effectiveness of home visits in pregnancy as a public health measure to improve birth outcomes. PLoS One 10, e0137307.
Inada, N., Kamio, Y., 2010. Short forms of the Japanese version WISC-III for assessment of children with autism spectrum disorders. Jpn. J. Child Adolesc. Psychiatry 51, 11–19.
Johansson, B., Meyerson, B., Eriksson, U., 1991. Behavioral effects of an intrauterine or neonatal diabetic environment in the rat. Neonatology 59, 226–235.
Kanata, S., Koike, S., Ando, S., Nishida, A., Usami, S., Yamasaki, S., Morimoto, Y., Toriyama, R., Fujikawa, S., Sugimoto, N., Sasaki, T., Furukawa, T.A., Hiraiwa-Hasegawa, M., Kasai, K., 2016. Enuresis and hyperactivity-inattention in early adolescence: findings from a population-based survey in Tokyo (Tokyo Early Adolescence Survey). PLoS One 11, e0158786.
Kelleher, I., Harley, M., Murtagh, A., Cannon, M., 2011. Are screening instruments valid for psychotic-like experiences? A validation study of screening questions for psychotic-like experiences using in-depth clinical interview. Schizophr. Bull. 37, 362–369.
Kelleher, I., Connor, D., Clarke, M.C., Devlin, N., Harley, M., Cannon, M., 2012. Prevalence of psychotic symptoms in childhood and adolescence: a systematic review and meta-analysis of population-based studies. Psychol. Med. 42, 1857–1863.
Kelleher, I., Corcoran, P., Keeley, H., Wigman, J.T.W., Devlin, N., Ramsay, H., Wasserman, C., Carli, V., Sarchiapone, M., Hoven, C., Wasserman, D., Cannon, M., 2013. Psychotic symptoms and population risk for suicide attempt: a prospective cohort study. JAMA Psychiat. 70, 940–948.
Kelleher, I., Cederlof, M., Lichtenstein, P., 2014. Psychotic experiences as a predictor of the natural course of suicidal ideation: a Swedish cohort study. World Psychiatry 13, 184–188.
Kendler, K.S., Davis, C.G., Kessler, R.C., 1997. The familial aggregation of common psychiatric and substance use disorders in the National Comorbidity Survey: a family history study. Br. J. Psychiatry 170, 541–548.
Kinney, B.A., Rabe, M.B., Jensen, R.A., Steger, R.W., 2003. Maternal hyperglycemia leads to gender-dependent deficits in learning and memory in offspring. Exp. Biol. Med. 228, 152–159.
Kuo, E.S., Vander Stoep, A., Stewart, D.G., 2005. Using the Short Mood and Feelings Questionnaire to detect depression in detained adolescents. Assessment 12, 374–383.
Ministry of Health Labour and Welfare, 2016. Report on regional public health services and health promotion services. http://www.mhlw.go.jp/toukei/saikin/hw/c-hoken/14/dl/kekka1.pdf.
Monnier, V.M., Bautista, O., Kenny, D., Sell, D.R., Fogarty, J., Dahms, W., Cleary, P.A., Lachin, J., Genuth, S., the DCCT Skin Collagen Ancillary Study Group, 1999. Skin collagen glycation, glycoxidation, and crosslinking are lower in subjects with long-term intensive versus conventional therapy of type 1 diabetes: relevance of glycated collagen products versus HbA1c as markers of diabetic complications. Diabetes 48, 870–880.
Morrison, C., McCook, J.G., Bailey, B.A., 2016. First trimester depression scores predict development of gestational diabetes mellitus in pregnant rural Appalachian women. J. Psychosom. Obstet. Gynaecol. 37, 21–25.
Murray, R.M., Lewis, S.W., 1987. Is schizophrenia a neurodevelopmental disorder? BMJ (Clin. Res. Ed.) 295, 681–682.
Nathan, D.M., Cleary, P.A., Backlund, J.Y., Genuth, S.M., Lachin, J.M., Orchard, T.J., Raskin, P., Zinman, B., The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group, 2005. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N. Engl. J. Med. 353, 2643–2653.
Nishida, A., Tanii, H., Nishimura, Y., Kajiki, N., Inoue, K., Okada, M., Sasaki, T., Okazaki, Y., 2008. Associations between psychotic-like experiences and mental health status and other psychopathologies among Japanese early teens. Schizophr. Res. 99, 125–133.
Nishida, A., Sasaki, T., Nishimura, Y., Tanii, H., Hara, N., Inoue, K., Yamada, T., Takami, T., Shimodera, S., Itokawa, M., Asukai, N., Okazaki, Y., 2010. Psychotic-like experiences are associated with suicidal feelings and deliberate self-harm behaviors in adolescents aged 12–15 years. Acta Psychiatr. Scand. 121, 301–307.
Nishida, A., Shimodera, S., Sasaki, T., Richards, M., Hatch, S.L., Yamasaki, S., Usami, S., Ando, S., Asukai, N., Okazaki, Y., 2014. Risk for suicidal problems in poor-help-seeking adolescents with psychotic-like experiences: findings from a cross-sectional survey of 16,131 adolescents. Schizophr. Res. 159, 257–262.
Ornoy, A., 2005. Growth and neurodevelopmental outcome of children born to mothers with pregestational and gestational diabetes. Pediatr. Endocrinol. Rev. 3, 104–113.
Oshima, N., Nishida, A., Fukushima, M., Shimodera, S., Kasai, K., Okazaki, Y., Sasaki, T., 2010. Psychotic-like experiences (PLEs) and mental health status in twin and singleton Japanese high school students. Early Interv. Psychiatry 4, 206–213.
Perry, B.I., McIntosh, G., Weich, S., Singh, S., Rees, K., 2016. The association between first-episode psychosis and abnormal glycaemic control: systematic review and meta-analysis. Lancet Psychiatry 3, 1049–1058.
Plagemann, A., Harder, T., Lindner, R., Melchior, K., Rake, A., Rittel, F., Rohde, W., Dorner, G., 1998. Alterations of hypothalamic catecholamines in the newborn offspring of gestational diabetic mother rats. Dev. Brain Res. 109, 201–209.
Poulton, R., Caspi, A., Moffitt, T.E., Cannon, M., Murray, R., Harrington, H., 2000. Children's self-reported psychotic symptoms and adult schizophreniform disorder - a 15-year longitudinal study. Arch. Gen. Psychiatry 57, 1053–1058.
Ramanathan, M., Jaiswal, A.K., Bhattacharya, S.K., 2000. Hyperglycaemia in pregnancy: effects on the offspring behaviour with special reference to anxiety paradigms. Indian J. Exp. Biol. 38, 231–236.
Reece, E.A., Pinter, E., Homko, C., Wu, Y.K., Naftolin, F., 1994. The yolk sac theory: closing the circle on why diabetes-associated malformations occur. J. Soc. Gynecol. Investig. 1, 3–13.
Rindfuss, R.R., Choe, M.K., Tsuya, N.O., Bumpass, L.L., Tamaki, E., 2015. Do low survey response rates bias results? Evidence from Japan. Demogr. Res. 32, 797–828.
Sullivan, S.A., Wiles, N., Kounali, D., Lewis, G., Heron, J., Cannon, M., Mahedy, L., Jones, P.B., Stochl, J., Zammit, S., 2014. Longitudinal associations between adolescent psychotic experiences and depressive symptoms. PLoS One 9, e105758.
Tau, G.Z., Peterson, B.S., 2010. Normal development of brain circuits. Neuropsychopharmacology 35, 147–168.
Van Lieshout, R.J., Voruganti, L.P., 2008. Diabetes mellitus during pregnancy and increased risk of schizophrenia in offspring: a review of the evidence and putative mechanisms. J. Psychiatry Neurosci. 33, 395–404.
van Os, J., Linscott, R.J., Myin-Germeys, I., Delespaul, P., Krabbendam, L., 2009. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. Psychol. Med. 39, 179–195.
Watanabe, N., Nishida, A., Shimodera, S., Inoue, K., Oshima, N., Sasaki, T., Inoue, S., Akechi, T., Furukawa, T.A., Okazaki, Y., 2012. Help-seeking behavior among Japanese school students who self-harm: results from a self-report survey of 18,104 adolescents. Neuropsychiatr. Dis. Treat. 8, 561–569.
Weinberger, D.R., 1987. Implications of normal brain development for the pathogenesis of schizophrenia. Arch. Gen. Psychiatry 44, 660–669.
Weissman, M.M., Wickramaratne, P., Nomura, Y., Warner, V., Pilowsky, D., Verdeli, H., 2006. Offspring of depressed parents: 20 years later. Am. J. Psychiatry 163, 1001–1008.
Welham, J., Scott, J., Williams, G., Najman, J., Bor, W., O'Callaghan, M., McGrath, J., 2009. Emotional and behavioural antecedents of young adults who screen positive for non-affective psychosis: a 21-year birth cohort study. Psychol. Med. 39, 625–634.
Wigman, J.T.W., Lin, A., Vollebergh, W.A.M., van Os, J., Raaijmakers, Q.A.W., Nelson, B., Baksheev, G., Yung, A.R., 2011. Subclinical psychosis and depression: co-occurring phenomena that do not predict each other over time. Schizophr. Res. 130, 277–281.
World Health Organization, 2013. Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy. WHO Press, Geneva.
Yamano, T., Shimada, M., Fujizeki, Y., Kawasaki, H., Onaga, A., 1986. Quantitative synaptic changes on Purkinje cell dendritic spines of rats born from streptozotocin-induced diabetic mothers. Brain Dev. 8, 269–273.
Yamasaki, S., Ando, S., Koike, S., Usami, S., Endo, K., French, P., Sasaki, T., Furukawa, T.A., Hiraiwa-Hasegawa, M., Kasai, K., Nishida, A., 2016. Dissociation mediates the relationship between peer victimization and hallucinatory experiences among early adolescents. Schizophr. Res. Cogn. 4, 18–23.
Zammit, S., Odd, D., Horwood, J., Thompson, A., Thomas, K., Menezes, P., Gunnell, D., Hollis, C., Wolke, D., Lewis, G., Harrison, G., 2009. Investigating whether adverse prenatal and perinatal events are associated with non-clinical psychotic symptoms at age 12 years in the ALSPAC birth cohort. Psychol. Med. 39, 1457–1467.

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