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Association of gestational cardiovascular health with infant neurodevelopment: A prospective study in Hefei of Anhui, China

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ABSTRACT

We investigate the prospective the association of gestational cardiovascular health (CVH) with infant neurodevelopment, and whether such relation was mediated by cord blood metabolites. The data come from the prospective birth cohort study in Hefei of Anhui, China. A total of 1714 mother-infant pairs are included from March 2018 and June 2021. CVH was evaluated at 24 to 28 gestational weeks by the combination of five metrics: body mass index, blood pressure, total cholesterol, glucose, and smoking. Cord blood samples were collected at delivery for the detection of related indicators. Infant neurodevelopment at 12 months was assessed by the Ages and Stages Questionnaire Edition 3 (ASQ-3). We stratified the status of CVH into three levels, ideal, intermediate, and poor. Compared with the ideal CVH, poor CVH was associated with infant communication domain failure (RR = 2.06; 95 %CI, 1.24–3.42) and cord blood C-peptide levels (β = 0.09; 95 %CI, 0.06–0.13) were higher. Cord blood C-peptide level with infant communication domain failure risk increased (RR = 3.43, 95 %CI: 2.11–5.58). Mediation analysis showed that cord blood C-peptide mediated 13.9 % of the effect. Key findings indicated that maternal poor CVH at 24 to 28 weeks gestation was associated with an increased risk of infant neurodevelopment at ASQ-3 failure in the communication domain, and cord blood C-peptide might mediate this association. The findings, if confirmed by replications, specific nursing cares among pregnant women with poor CVH, might have implications for the offspring neurodevelopment prevention strategies targeting.

1. Introduction

Neurodevelopmental disorders affect about 10 % of children worldwide (Thapar et al., 2017). Based on the developmental origin hypothesis of health and disease, the neurodevelopmental trajectory of offspring may be influenced by metabolic disorders during pregnancy (Barker, 2007; Monk et al., 2019; Lippert and Bruning, 2022). Singly and inseparate studies, metabolic risk factors, such as obesity (Josefson et al., 2020), diabetes (Wang et al., 2019), and hypertension (Palatnik et al., 2022), during pregnancy have been significantly associated with increased neurodevelopmental disorders risks among offspring. Given these metabolic factors, which have been recognized as established cardiovascular metabolic risk factors (Vogel et al., 2021), tend to cluster in individuals and interact with each other. Therefore, comprehensive evaluation of multiple cardiovascular risk factors is necessary. However, the evidence to comprehensively assess the association between multiple cardiovascular risk factors and infant neurodevelopment is still limited.

Abbreviations: ASQ-3, Ages and Stages Questionnaire Edition 3; ASD, Autism spectrum disorder; BMI, body mass index; BP, blood pressure; CVH, cardiovascular health; CVD, cardiovascular disease; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; GDM, gestational diabetes mellitus; HAPO, Hyperglycemia and Adverse Pregnancy Outcome; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; OGTT, oral glucose tolerance test; RR, relative risk; SD, standard deviations; TC, total cholesterol; TG, triglyceride.

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Pregnancy is an important period to assess cardiovascular health because maternal cardiometabolic risk factors may have unique impacts on maternal and infant health. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Studies (Perak et al., 2021a; Perak et al., 2021b), combined cardiovascular metabolic metrics: body mass index (BMI), blood pressure (BP), total cholesterol (TC) level, glucose level, and smoking to evaluate gestational cardiovascular health (CVH), which has gradually been recommended to apply to women during pregnancy (Brown et al., 2018). The current study found that better gestational CVH was associated with offspring positive health outcomes, including less adverse birth outcomes (Perak et al., 2021b) and greater healthy cardiometabolic (Perak et al., 2021a). However, its relevance for neurodevelopment in offspring remains unknown.

Maternal metabolic environment determines the intrauterine metabolic environment, which controls fetal metabolic (Qiao et al., 2018; Bowman et al., 2019). Measuring metabolic markers in cord blood can understand fetal metabolic status to a certain extent (Lee et al., 2020). Previous study has shown that high cord blood C-peptide levels are associated with impaired neurodevelopment in infancy (Wang et al., 2021). C-peptide, which is secreted by pancreatic β -cells along with equimolar levels of insulin, reflects the function of offspring β -cells and is also used to diagnose fetal hyperinsulinemia (Heding, 1975; Kühl et al., 1982). Studies have shown that maternal cardiovascular metabolism risk fastors are related to higher cord blood C-peptide levels and an increased risk of fetal hyperinsulinemia (Metzger et al., 2008; Dube et al., 2012). Therefore, we hypothesize that cord blood metabolites may mediate the association between gestational CVH and offspring neurodevelopment.

In this study, we aimed to assess the association of gestational CVH with infant neurodevelopment. Moreover, we further explored whether metabolic markers of cord blood could mediate this relation.

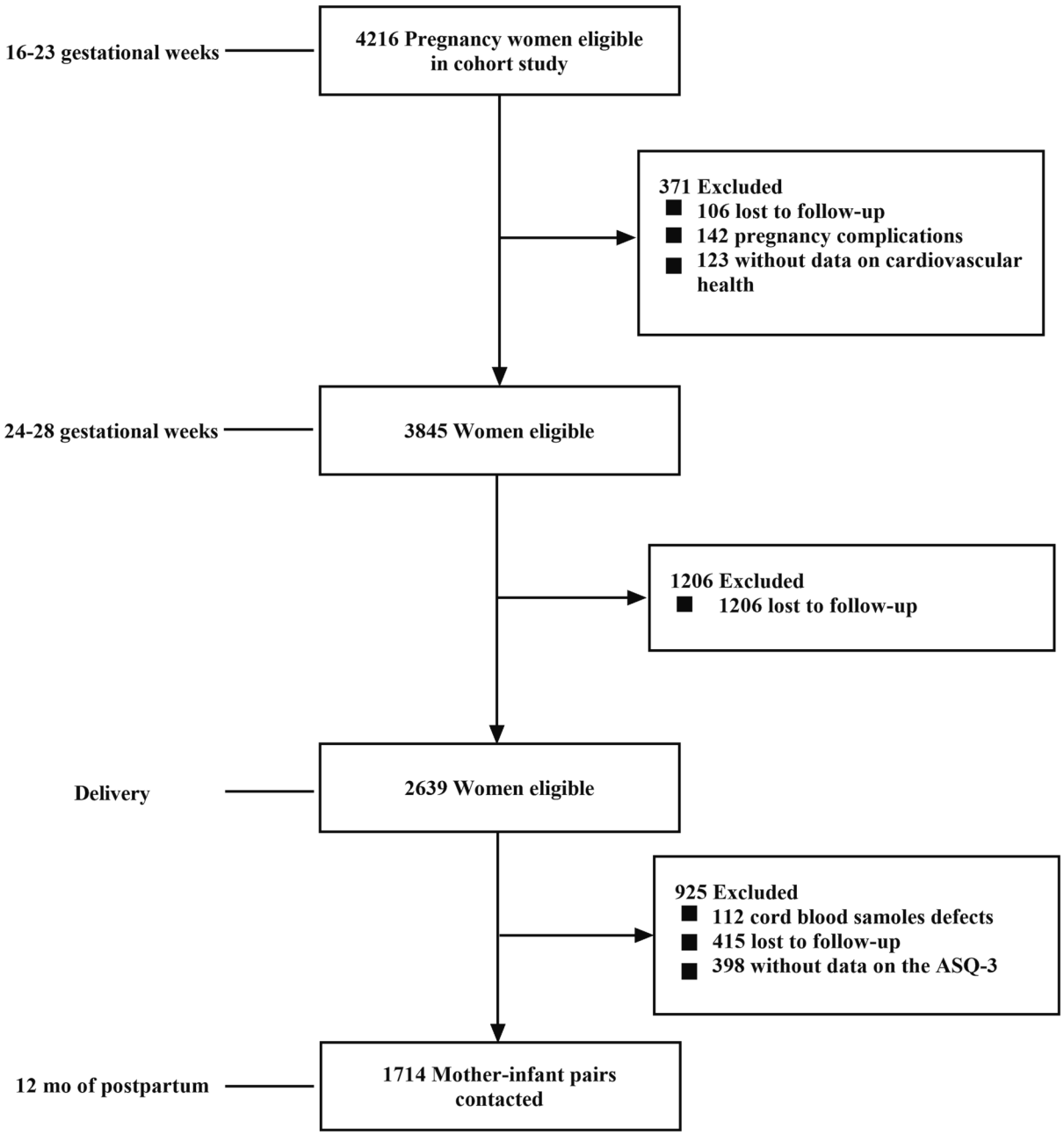

Fig. 1. Flow chart of included study sample.

2. Methods

2.1. Participants

In this prospective birth cohort, from March 2018 and June 2021, a total of 4216 participants aged 18 to 45, between 16 and 23 weeks of gestation, were conducted at three hospitals in Hefei, China. The enrolled participants were interviewed face-to-face and completed a questionnaire including demographic and lifestyle characteristics. We extracted perinatal health status and infant basic characteristics from the electronic medical records. In addition, the cord blood was collected during delivery, and the Ages and Stages Questionnaires Edition 3 (ASQ-3) was completed 12 months postpartum. Finally, we obtained 1714 mother-infant pairs' s complete data, including cord blood samples. The flowchart of study participants is presented in Fig. 1. All study participants had written informed consent and ethical approval was granted by the Ethics Committee of Anhui Medical University (No. 20180092).

2.2. Assessment of gestational CVH

Gestational CVH was described using the combination of five metrics: BMI, BP, TC, glucose, and smoking according to the HAPO study (Perak et al., 2021a; Perak et al., 2021b). Each CVH index was classified and coded as poor (0), intermediate (1), and ideal (2), according to the corresponding reference standard. BMI was defined in the following categories (kg/m^2): ≤28.4 (ideal), 28.5–32.9 (intermediate), and ≥33 (poor). Ideal BP was defined as systolic blood pressure (SBP) < 120 mm Hg and diastolic blood pressure (DBP) < 80 mm Hg. SBP 120–139 mm Hg or DBP 80–89 mm Hg as intermediate, SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg as poor. TC levels are less than 260 mg/dL as ideal, 260 to 299 mg/dL as intermediate, and 300 mg/dL or greater as poor. Glucose (mmol/L): ideal: non-gestational diabetes mellitus (GDM), poor: GDM: fasting ≥ 5.1, 1-h oral glucose tolerance test (OGTT) ≥ 10, 2-h OGTT ≥ 8.5. Smoking was defined as poor and non-smoking as ideal. In this study, information on smoking was collected from questionnaires, and (BMI, BP, TC, and glucose) at 24 to 28 gestational weeks were obtained from the medical records. We stratified the status of CVH into three levels, ideal, intermediate, and poor, where ideal status was defined as ideal for all five individual metrics, poor status as poor for all, and the rest as intermediate.

2.3. Assessment of offspring developmental outcomes

Infant neurodevelopment screening was assessed by using the ASQ-3 scale. The ASQ-3 was divided into five domains and each domain contained six items. Each item was faithfully filled in by the guardian combined with the actual situation of the infant under the guidance of professional training personnel. The rating scale of each item was: yes (10 points), sometimes yes (5 points), and no (0 points). The sum of the scores of the six items in each energy zone was the corresponding energy zone score. The cutoff point was described as a score in any domain that was less than 2 standard deviations from the mean score in that domain. Infants have not passed the developmental assessment screening and may have neurodevelopmental delays when their scores were below the cutoff point (Romero Otalvaro et al., 2018).

2.4. Cord blood biomarkers

We measured cord blood biomarkers including serum C-peptide, TC, triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C). C-peptide was measured by immunoassay (AutoDELFIA, PerkinElmer). TC, TG, LDL-C, and HDL-C were tested by automatic biochemical analyzer (Beckman Coulter, Brea, CA, USA).

2.5. Confounding variables

The study confounding variables were included according to previous reports in the literature (Craig et al., 2003; Tian et al., 2018; Chen et al., 2020; Yan et al., 2020; Xiang et al., 2023). The potential confounding variables were categorized into maternal and infant information. The information on maternal age, education level (<12 and ≥12 years of completed schooling), household income (<8000 and ≥8000 yuan), parity (primipara and multipara), family history of the disease (diabetes, hypertension, and heart disease), physical activity (<3 and ≥3 days/week), sedentary time (<8 and ≥8 h/day), gestational nutrient supplementation (folic acid, iron, and vitamin D), and infant information (breastfeeding and vitamin D supplementation) were reported using a standardized questionnaire. Prepregnancy BMI and infant characteristics include sex (male and female), mode of delivery (vaginal delivery and cesarean section), birth weight (g), and gestational week at birth and the season of delivery were obtained from medical records.

2.6. Statistical analysis

Data on the Characteristics of mothers and offspring were described using the percentage or means (standard deviations, SD). Multiple logistic regression modeling was performed to analyze the associations among different states of exposure to gestational CVH and development outcomes in offspring. The relationship of gestational CVH with cord blood metabolites was analyzed by linear regression model. All models were adjusted for confounding factors.

In addition, multiple logistic regression models were performed to estimate relationships between cord blood C-peptide and ASQ-3 domains with adjusting for potential confounding factors. The SPSS PROCESS plug-in was used to test the effect of cord-blood C-peptide on the association between gestational CVH and failure of the communication domain. We used causal mediation analyses to estimate the indirect effects. Decomposing total effects into direct and indirect paths calculates the proportion of the total effects that are mediated by the indirect path. Statistical analyses were conducted using SPSS 26.0 software (IBM Corp, Armonk, NY, USA).

3. Results

A total of 1714 mother-infant pairs were included in the analysis. Table 1 presents the basic characteristics of mothers and offspring. The mean age of the pregnant mothers was 29.7 ± 4.3 years. Of the subjects analyzed, 91.0 % (1560) had ideal BMI, 72.6 % (1244) had ideal BP, 78.4 % (1343) had ideal TC, 79.3 % (159) had ideal glucose and 99.4 % (1703) had ideal smoking. The proportions of gestational CVH in the ideal, medium and poor groups were 43.2 %, 30.5 % and 26.3 %, respectively.

Table 2 presents the associations of gestational CVH to infant neurodevelopment. In multivariate logistic regression analysis, compared with ideal CVH, poor CVH was related to an increased incidence of neurodevelopmental failure in the communication domain (RR = 2.06, 95 % CI 1.24–3.42), after adjustment for covariates. Infants born to mothers with poor CVH had greater odds of communication domain failure than those born to mothers with ideal CVH (9.6 % vs 4.6 %). However, there was no significant association between gestational CVH and other ASQ-3 domains. Compared with gestational ideal CVH group, cord blood C-peptide levels (β = 0.09; 95 %CI, 0.06–0.13) were higher in gestational poor CVH group (Fig. 2).

As shown in Table 3, the risk of developmental delay in the communication domain increased with each 1-unit increase in cord blood C-peptide level (RR = 3.44, 95 %CI: 2.14–5.53 in model 1; RR = 3.43, 95 %CI: 2.11–5.58 in model 2). Further mediation analysis observed that the proportion of the relationship of gestational CVH with communication domain failure mediated by cord blood C-peptide was 13.9 % in Fig. 3.

Table 1
Characteristics of mothers and offspring (values are % yes or means (SD), N = 1714). A Prospective Study in Hefei of Anhui, China (2018–2021).

Characteristic	Mean ± SD or n (%)
Demographics	
Age, years	29.7 ± 4.3
Education ≥ 12 years	1160(67.7)
Household income ≥ 8000 yuan	260(15.2)
Prepregnancy BMI, kg/m^2	21.4 ± 2.9
Multipara	1077(62.8)
Family history of diabetes	157(9.2)
Family history of hypertension	564(32.9)
Family history of heart disease	75(4.4)
Gestational cardiovascular health	
BMI	
Intermediate	139(8.1)
Poor	15(0.9)
BP	
Intermediate	453(26.4)
Poor	17(1.0)
TC	
Intermediate	276(16.1)
Poor	95(5.5)
Poor glucose	355(20.7)
Poor smoking	11(0.6)
CVH	
Intermediate	523(30.5)
Poor	450(26.3)
Pregnancy lifestyle factors	
Physical activity < 3 days /week	924(53.9)
Sedentary time ≥ 8 h/day	745(43.4)
Folic acid supplement < 3 days /week	131(7.6)
Iron supplement < 3 days /week	1492(87.0)
Vitamin D supplementation < 3 days /week	801(46.7)
Characteristics of infants	
Gestational age at birth, weeks	39.6 ± 1.4
Birth weight, g	3405.7 ± 461.6
Male infant	907(52.9)
Cesarean section	586(34.2)
Season of delivery in winter and spring	879(51.3)
Exclusive breastfeeding	375(21.9)
Vitamin D supplement	1297(75.7)

Abbreviations: BMI, body mass index; BP, blood pressure; TC, total cholesterol; CVH, cardiovascular health.

Table 2
Associations of Gestational CVH with neurodevelopmental delays in offspring at 12 months. A Prospective Study in Hefei of Anhui, China (2018–2021).

ASQ-3	Ideal CVH	Intermediate CVH		Poor CVH	
	n (%)	n (%)	*RR* (95 % CI)	n (%)	*RR* (95 % *CI*)
Communication	34 (4.6)	25 (4.8)	1.02 (0.58,1.78)	**43 (9.6)**	**2.06 (1.24,3.42)**
Gross motor	35 (4.7)	30 (5.7)	1.23 (0.74,2.04)	15 (3.3)	0.68 (0.37,1.28)
Fine motor	31 (4.2)	30 (5.7)	1.59 (0.96,2.64)	16 (3.6)	0.76 (0.40,1.42)
Problem solving	24 (3.2)	19 (3.6)	1.08 (0.57,2.06)	14 (3.1)	0.61 (0.28,1.31)
Personal social	34 (4.6)	18 (3.4)	0.71 (0.38,1.33)	19 (4.2)	0.82 (0.43,1.55)

The logistic regression analyses were adjusted for maternal age, education, household income, prepregnancy BMI, multipara, family history of the disease (diabetes, hypertension, and heart disease), physical activity, sedentary time, gestational nutrient supplementation (folic acid, iron, and vitamin D), gestational age at birth, infant sex, birth weight, cesarean section, the season of delivery, breastfeeding, and infant vitamin D supplementation.

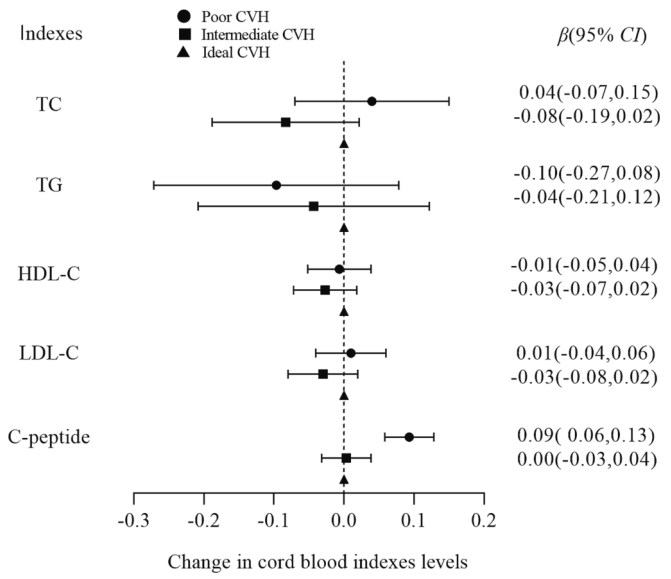

Fig. 2. The relationship between gestational CVH and cord blood glycolipid metabolism indexes. A Prospective Study in Hefei of Anhui, China (2018–2021). Adjusted for maternal age, education, household income, prepregnancy BMI, multipara, family history of the disease (diabetes, hypertension, and heart disease), physical activity, sedentarytime, gestational nutrient supplementation (folic acid, iron, and vitamin D), gestational age at birth,infant sex, birth weight, cesarean section, the season of delivery.

Table 3
Association between cord blood C-peptide level and infant neurodevelopment at 12 months of age. A Prospective Study in Hefei of Anhui, China (2018–2021).

ASQ-3	Model 1		Model 2	
	RR(95 %*CI*)	*P value*	*RR*(95 %*CI*)	*P value*
Communication	**3.44(2.14,5.53)**	**<0.001**	**3.43(2.11,5.58)**	**<0.001**
Gross motor	0.78(0.33,1.79)	0.546	0.75(0.32,1.74)	0.506
Fine motor	1.61(0.86,3.02)	0.139	1.58(0.84,2.99)	0.158
Problem solving	1.34(0.59,3.03)	0.488	1.24(0.54,2.83)	0.607
Personal social	0.67(0.26,1.69)	0.393	0.68(0.27,1.72)	0.411

Model 1 adjusted for maternal age, education, household income, prepregnancy BMI, multipara, family history of the disease (diabetes, hypertension, and heart disease), physical activity, sedentary time, gestational nutrient supplementation (folic acid, iron, and vitamin D), gestational age at birth, infant sex, birth weight, cesarean section, the season of delivery.
Model 2 further adjusted for breastfeeding, and infant vitamin D supplementation based on Model 1.

4. Discussion

In this prospective birth cohort study, we found that gestational poor CVH at 24 to 28 weeks gestation was related to an increased risk of infant neurodevelopment at ASQ-3 failure in the communication domain, which was linked to autism spectrum disorder (ASD) in children in previous study (McNally Keehn et al., 2021). Compared to ideal CVH, lipid metabolism indicators of fetal cord blood exposed to gestational poor CVH did not change, while C-peptide was significantly elevated. Mediation analysis found that the contribution of gestational CVH to communication domain failure mediated by cord blood C-peptide was 13.9 %.

As recommended by the American Heart Association (AHA) and American College of Obstetricians and Gynecologists (ACOG), CVH evaluation is beneficial for better monitoring of health status during pregnancy and throughout the life course (Brown et al., 2018). Previous HAPO studies showed gestational CVH was related to adverse pregnancy outcomes (Perak et al., 2021b) and offspring CVH (Perak et al., 2021a).

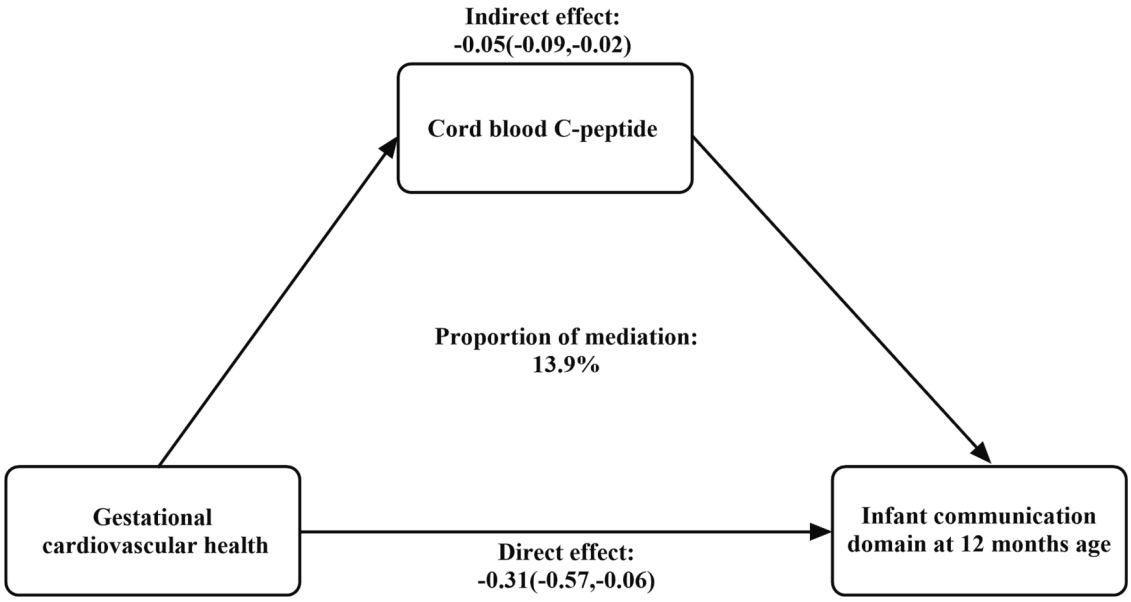

Fig. 3. Mediation analysis for the role of cord blood C-peptide levels in the association between gestational CVH and infant neurodevelopment at 12 months of age. A Prospective Study in Hefei of Anhui, China (2018–2021). Adjusted for maternal age, education, household income, prepregnancy BMI, multipara, family history of the disease (diabetes, hypertension, and heart disease), physical activity, sedentary time, gestational nutrient supplementation (folic acid, iron, and vitamin D), gestational age at birth, infant sex, birth weight, cesarean section, the season of delivery, breastfeeding, and infant vitamin D supplementation.

The Screening for Pregnancy Endpoints study (SCOPE) showed that maternal cardiovascular metabolism health was associated with shorter telomeres in their children (McAninch et al., 2020). Another prospective cohort study also found higher risks of cardiovascular disease (CVD) in offspring born to mothers with both hypertensive disorders and a history of diabetes or CVD (Huang et al., 2021). In this study, we first reported the association between gestational CVH and infant neurodevelopment outcomes. This finding extended previous research on the effects of gestational CVH on offspring health.

We found that gestational poor CVH was related to higher cord blood C-peptide levels. Fetal hyperinsulinemia, cord blood C-peptide level above the P_{90}, which played an important role in mediating pregnancy complications and programming offspring development (Hufnagel et al., 2022). Our finding suggested the risks of communication domain delay were higher among infants in 12 months exposed to newborns with fetal hyperinsulinemia. High levels of C-peptide generally indicate increased endogenous insulin secretion due to insulin resistance, which inhibits glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis, from inhibiting glucose production (Yoon et al., 2014). Hence, this results in a lack of alternative fuel for brain function, which increased hypoglycemic damage and neurological disorders (Francesca Menni et al., 2001; Meissner et al., 2003). In addition, the human placenta is a very important organ for pregnancy health and fetal development. Maternal metabolic disorders may adversely affect placental growth and development, which lead to vascular changes that pose potential concerns to the fetus as fetal hypoxia (Hosni et al., 2021; Huang et al., 2021).

This study has several strengths. First, in this prospective cohort study, we were able to examine the association of gestational CVH with infant neurodevelopment, and simultaneously evaluate the possible mediating effect of cord blood C-peptide. Second, our study measured multiple cord blood biological indicators such as fetal glucolipid metabolic indexes which can better suggest the potential mechanism of CVH affecting fetal neural development. Third, we have controlled for a large number of confounding factors of prepregnancy (eg, educational level, prepregnancy BMI, and physical activity) and the postpartum period (eg, gestational age at birth and breastfeeding). Fourth, ASQ-3 evaluation can indicate specific long-term neurodevelopmental disorders in offspring, such as communication domain failure of ASQ-3 is associated with ASD in children (McNally Keehn et al., 2021).

Several limitations should also be acknowledged in this study. First, observational studies can only demonstrate an association, for the sake of a cautious interpretation of our study findings, still needs to be replicated in other observational studies and verified in future randomized controlled trial studies. Second, our study assessed neurodevelopment only at 12 months of age with a relatively short follow-up, and thus it is difficult to understand the association of maternal CVH with offspring neurodevelopment across developmental stages. Finally, ASQ-3 evaluation is not a clinical diagnosis of neurodevelopment, which may be biased by misclassification.

5. Conclusion

Our study suggests that maternal poor CVH at 24 to 28 weeks gestation was associated with an increased risk of infant neurodevelopment at ASQ-3 failure in the communication domain, and cord blood C-peptide might mediate this association. The findings, if confirmed by replications, specific nursing cares among pregnant women with poor CVH, might have implications for the offspring neurodevelopment prevention strategies targeting.

Funding

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7. Ethics approval

Our study protocol was approved by the Ethics Committee of Anhui Medical University (No. 20180092). All participants provided informed consent.

CRediT authorship contribution statement

Qiong Li: Writing – review & editing, Writing – original draft,

Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Haixia Wang:** Writing – review & editing, Validation, Conceptualization. **Qiaolan Yang:** Writing – review & editing, Supervision, Conceptualization. **Lei Zhang:** Writing – review & editing, Investigation, Conceptualization. **Feicai Dai:** Writing – review & editing, Investigation, Conceptualization. **Lijun Yu:** Writing – review & editing, Investigation, Conceptualization. **Lin Wu:** Writing – review & editing, Investigation, Conceptualization. **Jinfang Ge:** Writing – review & editing, Supervision, Conceptualization. **Peng Zhu:** Writing – review & editing, Project administration, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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