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Short Communication

Preconception maternal and paternal one-carbon metabolism homeostasis and perinatal adverse outcomes: a prospective multiple events case-control study

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Adverse maternal and offspring reproductive outcomes, such as congenital disabilities, spontaneous pregnancy loss (SPL), preterm birth, gestational diabetes, and gestational hypertension, affect up to 20% of pregnancies [1–3]. Although the evidence remains elusive, a potential link emerged with the inappropriate periconceptional folate status [4]. Folate belongs to one-carbon metabolism (OCM), playing pivotal roles in biological processes during the early development of humans, such as generating methyl groups for use in DNA synthesis, amino acid homeostasis, antioxidant generation, and epigenetic regulation [5,6]. OCM nutrients, such as folate, vitamin B12, B6, and B2, and choline, can be obtained from foods and dietary supplements, and OCM homeostasis can be influenced by imbalanced dietary intake of the micronutrients, genetic variants in regulatory enzymes, and factors related with absorption [7]. Most human studies have focused on preconception supplementation or serum levels of single OCM nutrients, such as folate and vitamin B12; the impact of paternal folate status has received increasing attention, but current supportive evidence is mainly from animal studies [8]. Human studies are lacking in assessing the quantitative relationships between maternal and paternal preconception OCM metabolite homeostasis and the risk of maternal and offspring adverse outcomes in early life.

We hypothesize that the development of congenital heart disease (CHD), spontaneous pregnancy loss (SPL), very and extremely preterm birth (VEPT), maternal gestational diabetes (GDM) and preeclampsia (PE), Kawasaki disease (K_D), and autism spectrum disorder (ASD), share a common etiological pathway: impaired OCM homeostasis in parents before conception. Leveraging an ongoing large prospective cohort, we conducted an exploratory study to quantify the association of preconception maternal and paternal OCM metabolic homeostasis with multiple disease outcomes.

This is a multiple events case-control (MECC) study [9] nested within the ongoing Shanghai Preconception Parent-Child Cohort, including seven disease-case groups (CHD, VEPT, SPL, K_D, ASD, GDM, and PE) and a common control group. Eligible cohort participants were enrolled before conception, delivered by the end of 2023, and had valid blood samples for both parents at enrollment. CHD was confirmed post-birth via cardiac echocardiography, while other conditions were verified using medical records. We planned up to 24 pairs of parents for all case and control groups. CHD and SPL cases were identified by random sampling from all diagnosed cases [4], and the other five case groups included all available identified cases from the defined subcohort. Twenty-four control offspring were randomly selected from those free from any of the selected disease conditions by matching maternal age, hospital, and enrollment date (Fig. S1 online). Written informed consent was obtained from all participants before data collection. The cohort study protocol was approved by the Ethics Committee of the Children's Hospital of Fudan University, Shanghai, China (approval No.: 2016-49; 2018-151; 2021-429).

Preconception 22 serum OCM metabolites were examined in stored serum using ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS, Agilent, USA) at Shanghai Metabolome Institute (Shanghai, China). Details of the assay are described in the Supplementary material.

This study prioritizes hypothesis generation to identify potential associations between preconception OCM metabolites and multiple early-life diseases. Given the exploratory nature and small sample size, analytical strategies prioritized hypothesis generation

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while addressing design complexities, including shared controls, partial matching, and heterogeneous disease outcomes.

To enable direct comparison of biomarker effects across metabolites while preserving biological interpretability, each metabolite was preprocessed in three steps: (1) log-transformation to approximate normality, (2) adjustment for age and batch effects via linear regression, and (3) standardization to *Z*-scores using the mean and standard deviation of the control group. Given the small shared control group and unideal matching with all seven case groups, a weighted multinomial logistic regression with cluster-robust standard errors was conducted as the primary analysis in mothers and fathers separately, with the disease status as the dependent variable and each standardized metabolite as the independent variable [10]. The disease status was treated as a categorical variable, coded as 0 for non-affected (control) and 1 to 7 for the affected status of seven diseases, respectively. Using cluster-robust standard error aimed at minimizing the potential bias due to violation of the independence assumption of covariates in the unconditional "mlogit" analysis and to account for potential intra-pair dependencies within matched case-control sets, which maximumly aligned with the matched design. Adjusted covariates included age and preconception body mass index (BMI) only, hospital and year of recruitment were tried but not included due to convergence issue. In sensitivity analyses, we retained robust standard errors in the weighted multinomial logistic models and restricted these models to biomarkers only without adjusting any covariates to prioritize parsimony and minimize overfitting risks as well as checking the bias of matching variables on the association. Inverse probability weights were applied to account for the sampling design for all the above analyses. Cases were weighted by the inverse of their sampling fraction from the source cohort, and controls were weighted by the inverse of their probability of being selected, adjusted for reuse across multiple disease analyses (Table S1 online).

To balance type II error risks against the exploratory objectives, statistical significance was set at a two-sided $P < 0.1$, requiring both the overall model likelihood ratio test and disease-specific Wald test to meet this threshold. Effect estimates are reported as relative risk ratios (RRR) with 90% confidence intervals. Given the exploratory nature of the current study, no imputation for missing data was conducted, and no adjustments were made for multiplicity. All analyses were conducted using Stata SE16.0 (StataCorp LLC, TX, USA), with code reproducibility ensured through version-controlled scripts (available upon request).

We found 9.94% of 171 mothers were aged 35 years or older, 18.1% had a BMI $\geq$ 28 kg/m^2 before conception, 2.3% were exposed to smoking, and 31.0% were alcohol users; and 10.0%, 24.1%, 35.3%, and 61.3% for 119 fathers, respectively (Table 1). Almost all of the 22 OCM metabolites showed a skewed distribution and varied between parents and among eight groups (Fig. S2 online).

We found significant associations of 13 out of 22 metabolites from the choline metabolism, methionine cycle, folate cycle, and transsulfuration pathway in fathers or mothers with at least one of several disease outcomes (Fig. 1, values in Table S2 online). Significant associations were observed between OCM biomarkers and parental risk of childhood disorders. Specifically, lower maternal choline levels were associated with VEPT, K_D, GDM, and PE (RRRs = 0.59 [90% CI: 0.40, 0.88], 0.49 [90% CI: 0.28, 0.85], 0.60 [90% CI: 0.44, 0.82], and 0.13 [90% CI: 0.07, 0.23]). Fathers of children with CHD or ASD exhibited elevated betaine levels (RRRs = 1.73 [90% CI: 1.15, 2.60] to 2.93 [90% CI: 1.10, 7.77]).

A reduced S-adenosylmethionine/S-adenosylhomocysteine (SAM/SAH) ratio, reflecting impaired methylation capacity, was linked to VEPT in both mothers (RRR = 0.55, 90% CI: 0.39, 0.79) and fathers (RRR = 0.45, 90% CI: 0.22, 0.95), with maternal reductions also associated with PE (RRR = 0.11, 90% CI: 0.05, 0.25). Maternal elevated tHcy was significantly associated with ASD (RRR = 3.46, 90% CI: 1.11, 10.79), K_D (RRR = 3.98, 90% CI: 1.26, 12.53), and PE (RRR = 8.43, 90% CI: 3.48, 20.41), whereas no significant associations were detected in fathers. Additionally, higher maternal methionine correlated with GDM (RRR = 2.70, 90% CI: 1.80, 4.05). MMA, a functional marker of vitamin B12 deficiency, was consistently elevated across parental groups except for mothers with GDM. Significant increases were observed in parents of children with ASD (mothers: RRR = 2.32, 90% CI: 1.37, 3.92; fathers: RRR = 2.06, 90% CI: 1.14, 3.71), mothers with VEPT, PE and of children with K_D (RRRs = 1.53 [90% CI: 1.04, 2.27], 1.81 [90% CI: 1.29, 2.52], and 2.55 [90% CI: 1.71, 3.78]), and fathers of children with CHD (RRR = 1.92, 90% CI: 1.24, 2.97).

In the transsulfuration pathway, reduced maternal oxidized glutathione (GSSG) was associated with VEPT (RRR = 0.49, 90% CI:0.32, 0.76), K_D (RRR = 0.42, 90% CI: 0.24, 0.75), and PE (RRR = 0.17, 90% CI: 0.10, 0.30). Similarly, lower maternal cysteine and cystathionine levels were linked to SPL and VEPT (cysteine: RRRs = 0.64 [90% CI: 0.46, 0.90] and 0.54 [90% CI: 0.38, 0.76]; cystathionine: RRRs = 0.59 [90% CI: 0.37, 0.97] and 0.48 [90% CI: 0.24, 0.96]), while increased maternal taurine correlated with GDM and PE (RRRs = 2.77 [90% CI: 1.60, 4.80] and 8.80 [90% CI: 3.73, 20.84]).

Preconception elevations in glycine and serine were observed in mothers with GDM or PE (RRRs ranged from 1.73 to 2.76) and fathers of children with VEPT (RRR = 2.32). PE demonstrated the broadest metabolic perturbations, involving maternal reductions in choline, SAM/SAH ratio, 5-methyltetrahydrofolate (5-mTHF), and GSSG, alongside increases in tHcy, MMA, glycine, serine, and taurine (Fig. 1, Table S2 online). Sensitivity analyses confirmed the robustness of these associations, with consistent effect directions across all seven case groups despite variations in magnitude and statistical significance (Fig. S3, Table S3 online).

Our MECC study has identified links of impaired preconception homeostasis of OCM in both mothers and fathers with seven maternal and offspring disease outcomes. We discovered 13 metabolites that were linked with at least one disease condition, highlighting biological functions related to the choline metabolism, methionine cycle, folate cycle, and transsulfuration pathway [5]. The detected associations suggest a link between imbalanced parental OCM homeostasis prior to conception and the subsequent development of these adverse outcomes.

Decreased choline levels and/or elevated betaine levels in the case group suggest disrupted choline metabolism, potentially reflecting impaired methylation function or compensatory upregulation of choline-to-betaine conversion. Elevated methionine levels, reduced SAM/SAH ratio, higher MMA levels (indicating functional B12 deficiency), and/or increased homocysteine in the case group suggest dysregulation of the methionine cycle, likely indicating impaired methylation capacity, which may further compromise remethylation/transsulfuration pathways in OCM [5,6]. Lower GSSG and cysteine levels alongside elevated taurine suggest oxidative stress with compensatory upregulation of antioxidant defenses (taurine) and glutathione system depletion (reduced GSSG/cysteine), potentially indicating disrupted redox homeostasis in disease pathogenesis [5,6]. The metabolic aberrations observed in PE cases before conception—including disrupted choline/methionine cycles, oxidative stress, and vitamin B12 functional insufficiency—collectively suggest systemic dysregulation of OCM, impaired methylation capacity, and compensatory antioxidant responses, highlighting their potential role in disease pathogenesis.

The existence of part of these disruptions in parents of the other six diseases before conception indicates potential mechanisms that may be involved in disease pathogenesis. These cross associations of the given metabolites with multiple outcomes indicate that adverse maternal and offspring outcomes during early life may share a common mechanism: the imbalance of OCM homeostasis

Table 1
Preconception characteristics of parents before conception.

Variables	Total	Control	CHD	K_D	ASD	SPL	VEPT	GDM	PE
Mothers									
Number	171	24	24	16	13	24	23	24	23
Age (years), mean (SD)	29.80 (4.00)	29.70 (3.60)	28.90 (4.40)	29.00 (2.90)	30.70 (4.40)	30.40 (4.90)	28.00 (3.20)	31.27 (3.64)	31.00 (3.70)
Age group, *n* (%)									
<35 years	150 (87.72)	22 (91.67)	22 (91.67)	16 (100.00)	12 (92.31)	20 (83.33)	22 (95.65)	20 (83.33)	16 (69.57)
≥35 years	17 (9.94)	2 (8.33)	2 (8.33)	0	1 (7.69)	4 (16.67)	1 (4.35)	4 (16.67)	3 (13.04)
Missing, *n* (%)	4 (2.34)	0	0	0	0	0	0	0	4 (17.39)
Pre-BMI (kg/m^2), mean (SD)	21.70 (2.85)	21.86 (2.23)	20.10 (2.48)	22.51 (3.11)	22.47 (3.02)	21.63 (2.59)	22.13 (3.38)	22.04 (2.93)	21.49 (2.92)
BMI group, *n* (%)									
<24 kg/m^2	134 (78.36)	21 (87.50)	22 (91.67)	9 (56.25)	9 (69.23)	21 (87.50)	19 (82.61)	19 (79.17)	14 (60.87)
≥24 kg/m^2	31 (18.13)	3 (12.50)	2 (8.33)	6 (37.50)	4 (30.77)	3 (12.50)	4 (17.39)	5 (20.83)	4 (17.39)
Missing, *n* (%)	6 (3.51)	0	0	1 (6.25)	0	0	0	0	5 (21.74)
Smoking, *n* (%)[a]	4 (2.34)	1 (4.17)	1 (4.17)	0	0	0	0	2 (8.33)	0
Missing, *n* (%)	11 (6.43)	0	0	1 (6.25)	1 (7.69)	1 (4.17)	3 (13.04)	0	5 (21.74)
Drinking, *n* (%)[b]	53 (30.99)	10 (41.67)	7 (29.17)	4 (25.00)	3 (23.08)	6 (25.00)	7 (30.43)	7 (29.17)	9 (39.13)
Missing, *n* (%)	10 (5.85)	0	0	1 (6.25)	0	1 (4.17)	3 (13.04)	0	5 (21.74)
Fathers									
Number	119	24	24	14	9	24	24	NA	NA
Age (years), mean (SD)	30.34 (4.36)	30.79 (4.05)	29.75 (5.09)	30.09 (2.46)	31.30 (3.71)	31.91 (5.61)	28.66 (2.90)	NA	NA
Age group, *n* (%)								NA	NA
<35 years	104 (87.39)	19 (79.17)	22 (91.67)	14 (100.00)	7 (77.78)	20 (83.33)	22 (91.67)	NA	NA
≥35 years	13 (10.92)	4 (16.67)	2 (8.33)	0	2 (22.22)	4 (16.67)	1 (4.17)	NA	NA
Missing, *n* (%)	2 (1.68)	1 (4.17)	0	0	0	0	1 (4.17)	NA	NA
Pre-BMI (kg/m^2), mean (SD)	24.07 (3.32)	23.52 (3.53)	22.66 (2.49)	24.69 (3.71)	24.69 (3.40)	24.34 (2.60)	25.53 (4.03)	NA	NA
BMI group, *n* (%)								NA	NA
<24 kg/m^2	59 (49.58)	16 (66.67)	16 (66.67)	3 (21.43)	5 (55.56)	11 (45.83)	8 (33.33)	NA	NA
≥24 kg/m^2	46 (38.66)	7 (29.17)	7 (29.17)	6 (42.86)	2 (22.22)	12 (50.00)	12 (50.00)	NA	NA
Missing, *n* (%)	14 (11.76)	1 (4.17)	1 (4.17)	5 (35.71)	2 (22.22)	1 (4.17)	4 (16.67)	NA	NA
Smoking, *n* (%)[a]	42 (35.29)	7 (29.17)	9 (37.50)	2 (14.29)	2 (22.22)	12 (50.00)	10 (41.67)	NA	NA
Missing, *n* (%)	7 (5.88)	1 (4.17)	0	1 (7.14)	1 (11.11)	1 (4.17)	3 (12.50)	NA	NA
Drinking, *n* (%)[b]	73 (61.34)	15 (62.50)	16 (66.67)	4 (28.57)	7 (77.78)	14 (58.33)	17 (70.83)	NA	NA
Missing, *n* (%)	5 (4.20)	1 (4.17)	0	1 (7.14)	0	0	3 (12.50)	NA	NA

ASD: autism spectrum disorder; BMI: body mass index; CHD: congenital heart disease; GDM: gestational diabetes; K_D: Kawasaki disease; NA: not available; PE: preeclampsia; Pre-BMI: preconception body mass index; SPL: spontaneous pregnancy loss; VEPT: very and extremely preterm birth.
[a] Exposed to smoking, defined as self-smoker or exposed to second-hand cigarette smoking (binary variable, yes vs. no) within three months before or during pregnancy.
[b] Alcohol drinking, defined as consuming any alcoholic beverages (binary variable, yes vs. no) during the same period.

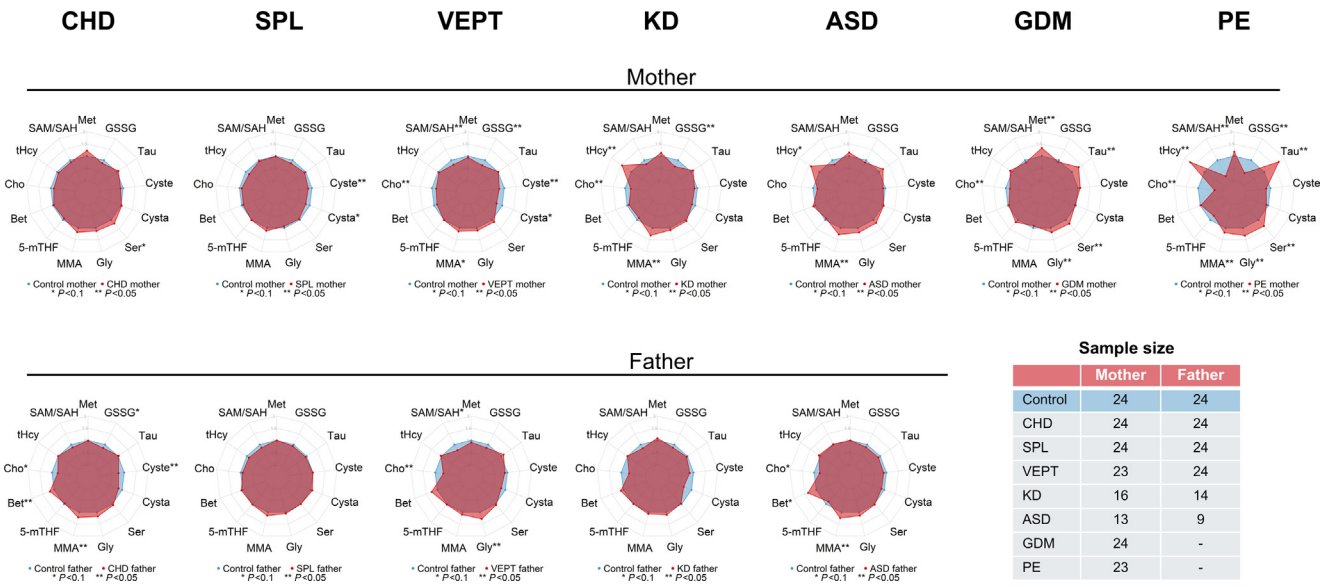

Fig. 1. Associations of OCM metabolites in preconception mothers and fathers with maternal and offspring diseases: weighted multinomial logistic regression analysis with cluster-robust standard error (main analysis). Values are log-scaled odds ratios. Age and preconception body mass index were adjusted as covariates.

in either parent before conception. Moreover, the difference in strength of associations may further explain the plausibility of the same metabolite in the causal link of the diseases. Some of our observations align with existing literature, such as the correlations between maternal lower choline levels and PE and childhood cognitive outcomes [11,12], reduced placental methylation capacity and PE [13], and the association of folic acid supplementation with preterm and PE [14]. The differences in associations of preconceptional metabolites with subsequent disease occurrence reveal that the underlying mechanisms behind the associations may involve effects on early embryonic development processes. For example, the association of higher MMA with CHD, SPL, K_D, ASD, and PE may be due to the impact of biological insufficiency of vitamin B12 on early embryos [7]. The occurrence of CHD, VEPT,

K_D, ASD, GDM, and PE may be associated with the presence of a lower SAM to SAH ratio while increased glycine and serine levels in mothers or fathers before conception, solely or in combination, and related reduced methylation capacity as well as disturbed downstream functions. As downstream pathways of OCM, dysregulations in the redox balance of the transsulfuration pathway may contribute to the risk of all outcomes but ASD, as results from lower GSSG, cysteine, cystathionine but higher taurine in mothers or fathers before conception. Although not statistically significant, we observed some evidence of weaker but consistent associations of the above metabolites and ASD. As one of the most severe gestation complications, PE displayed the most pronounced associations with dysregulated OCM metabolites, aligning with existing knowledge about its complicated pathophysiology. Our study highlights the necessity of paying attention to impaired OCM metabolites and functions in both parents before conception, rather than focusing on single nutrients, during gestation, or only on mothers.

The study's merits include the prospective nature of data and the MECC design. The multinomial logistic regression model simultaneously assesses associations between 22 preconceptional parental OCM biomarkers and 7 disease states and offers distinct advantages over separate binary logistic models: (1) it reduces type I error inflation from multiple testing across 7×22 hypotheses; (2) it preserves statistical power in small-sample analyses by leveraging shared variance across disease categories anchored to the same parental biomarker profiles.

The study's limitations include its exploratory nature, limited sample size, potential selection bias, residual confounding, overfitting of associations, lack of metabolite data from fathers of pregnancies that developed GDM or PE, and the absence of adjustment for multiple comparisons. Especially, potential bias due to violation of the independence assumption for our matched case-control design can not be ruled out. Consistency in the direction and significance of key associations between primary and sensitivity models supports the robustness of our findings despite methodological constraints. Second, given the complex transformations of metabolites before analysis, the exact levels of metabolites and group differences fail to provide clinical indications. Another limitation is inevitable that the covariates adjusted in this study are insufficient; covariates used as matching in selecting controls were not completely adjusted in the "mlogit" analyses to avoid nonconvergence, known factors related to adverse outcomes, such as genetic factors, environmental factors (viral infections, exposure to radiation, etc.), drug intake, and specific occupational exposures, were not available and should be included in future larger confirmatory studies. Therefore, our results are more indicative for the presence of associations between metabolites and diseases but less accurate in magnitude estimation. Future large-scale studies are essential to confirm these associations and disentangle disease-specific versus pleiotropic OCM effects.

Despite these limitations, our findings underscore the importance of investigating periconceptional OCM homeostasis in both parents in etiology studies on maternal and offspring adverse outcomes. The findings advance our understanding of the etiology of these adverse outcomes occurring in early life and reveal potential targets for prevention. Detecting and addressing imbalances in OCM homeostasis before conception may help reduce the risk of adverse outcomes. If confirmed by future studies, the profiles of the metabolites associated with these diseases are hard to interpret or recognize by the naked eyes but are easier to obtain by AI. Moreover, imbalanced OCM function is becoming intervenable via supplementation of nutrients or metabolites such as SAM, cysteine, taurine, etc. [15]. Personalized interventions are becoming possible by identifying high-risk groups of these diseases via comprehensively assessing related key OCM metabolites, dietary intake, and vital genetic variants. Before efforts highlight OCM homeostasis as a potential target for improving preconception health care and prevention of diseases, further validation of the findings by more extensive studies is warranted.

Conflict of interest

The authors declare that they have no conflict of interest.

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Author contributions

Weili Yan and Guoying Huang conceived the idea and designed the study. Yi Zhang, Xiaotian Chen, and Qinyu Yao completed the case-control participants selection and laboratory examinations with the third-part company. Weili Yan drafted the manuscript, and led the statistical analysis. Yuanzhou Peng drew the tables and figures. Wei Sheng, Xiaojing Ma, and the other authors all contributed to interpretation of the results, commented on the manuscript, revised and approved the final version of the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scib.2025.05.043.

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