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Maternal pre-pregnancy diet and prenatal depression: the mediating role of pre-pregnancy weight status and prenatal inflammation

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Abstract

Depression is a common prenatal psychological complication. We aimed to investigate if maternal pre-pregnancy diet can impact prenatal depressive symptoms and the mediating role of pre-pregnancy BMI and inflammation. We used data (*N* 1141) from the Alberta Pregnancy Outcomes and Nutrition cohort study. We calculated Mediterranean diet adherence (MED) and dietary inflammatory index (DII) scores using data from pre-pregnancy FFQ. In the third-trimester, we assessed depressive symptoms using Edinburgh Postpartum Depression Scale (EPDS) and inflammation through serum C-reactive protein (CRP) levels. BMI was calculated from self-reported pre-pregnancy weight. Race-stratified analyses (white and people of colour) were run. We observed no association between MED or DII tertiles and depressive symptoms. However, white participants in the MED tertile-3 had lower risk of depression (EPDS < 10) compared with tertile-1 (OR = 0·56, 95 % CI, 0·33, 0·95). White individuals in MED tertile-3 had lower BMI (MD = −1·08; 95 % CI, −1·77, −0·39) and CRP (MD = −0·53; 95 % CI, −0·95, −0·11) than tertile-1, and those in DII tertile-2 (MD = 0·44; 95 % CI, 0·03, 0·84) and tertile-3 (MD = 0·42; 95 % CI, 0·01, 0·83) had higher CRP than tertile-1. Among people of colour, neither MED nor DII was associated with BMI or CRP, but BMI was negatively associated with depressive symptoms (β = −0·25, 95 % CI, −0·43, −0·06). We found no association between diet and depressive symptoms through BMI or CRP, in either race. Pre-pregnancy diet might affect the risk of prenatal depression in a race-specific way. Further research is required to explore the racial differences in the association between maternal diet and prenatal depressive symptoms/depression risk.

Keywords: **Mediterranean diet: Dietary inflammatory index: Prenatal depression: BMI: C-reactive protein**

Depression is one of the most common prenatal complications and impacts about 8·5–11·0 % of pregnant individuals[1]. Prenatal depression can increase the risk of pregnancy complications, operative delivery and postpartum depression[2]. It also has negative implications for the offspring including birth outcomes (e.g. preterm birth, small for gestational age, stillbirth and low birth weight) and child development and mental health[2–4]. Prenatal depression is usually left untreated or undertreated because the anti-depressants commonly used may not be as effective[5], and risks associated with these medications[6,7] may discourage physicians and mothers from using them during this sensitive developmental window. Given the high prevalence of prenatal depression and its adverse effects on both mothers and their children, it is crucial to understand the risk factors, as well as the probable pathological pathways involved, to help identify prevention strategies that could target those factors and pathways.

There is growing evidence that a healthy diet can improve mental health[8], and reduce depressive symptoms in those struggling with depression[9,10]. Specifically, adherence to Mediterranean-style diet (MED) and dietary inflammatory index (DII) has been studied in association with depression. Mediterranean diet is a well-known anti-inflammatory diet, which includes plenty of plant-based foods (i.e. whole grain

Abbreviations: APrON, Alberta Pregnancy Outcomes and Nutrition; CRP, C-reactive protein; DII, dietary inflammatory index; EPDS, Edinburgh postpartum depression scale; MED, Mediterranean-style diet; SES, socio-economic status.

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cereals, legumes, fruits and vegetables, nuts and herbs), moderate intake of seafood, dairy and poultry and limited amounts of red meat, sweets and red wine[11]. Greater adherence to MED has been associated with lower depressive symptoms in various non-pregnant populations[12–15]. DII is a literature-based dietary score that measures the potential effect of diet on one's inflammatory status, with high and low scores reflecting pro-inflammatory and anti-inflammatory potential of diet, respectively[16]. Higher DII scores have been associated with greater depressive symptoms in non-pregnant populations particularly in women[17,18]. Recent research suggests that these two dietary indices are also linked with prenatal depression. Greater adherence to MED during pregnancy has been linked with reduced prenatal depressive symptoms[19]. Little is known about the link between maternal DII and prenatal depression, but the following diets with lower inflammatory potential in mid-pregnancy have been associated with fewer prenatal depressive symptoms[20]. The link between these dietary indices and depressive symptoms might be partially mediated through altered BMI[21] or circulating levels of inflammatory markers[22].

Higher adherence to MED is associated with lower risk of overweight and obesity[23] and higher DII scores are associated with increased risk of obesity in adults[24]. Also, both adherence to MED and DII scores are associated with inflammatory biomarkers in the body. Adherence to MED apparently has the most prominent effect in reducing circulating inflammatory biomarkers including C-reactive protein (CRP), compared with other healthy dietary patterns[25]. In pregnant individuals, circulating levels of inflammatory markers in the 3rd trimester were lower in those who had higher adherence to MED during gestation[26]. DII has been positively associated with inflammatory biomarkers including CRP in non-pregnant populations[27–29], and directly associated with serum CRP levels in the 2nd trimester of pregnancy[30]. Although limited and not sufficiently replicated, pre-pregnancy weight status and prenatal inflammation might also affect the risk for prenatal depression[31–34]. Taken together, the evidence linking MED adherence and DII scores to maternal BMI and prenatal inflammation, combined with the probable contribution of maternal BMI and inflammation to prenatal depression, suggests that maternal BMI and inflammation might mediate the association between maternal MED adherence and DII scores and parental depressive symptoms.

Research in non-pregnant individuals has shown that the obesity-depression association is race-specific, and higher BMI is positively associated with depressive symptoms in white women but not among other races[35]. Interestingly, Black women with obesity tend to have lower odds of depression compared with normal weight[35]. Also, while inflammatory profiles are generally similar amongst races, the trajectories of inflammatory markers might differ between racial groups throughout a healthy pregnancy[36]. The higher prevalence of prenatal depression among racialised women[37], and the racial differences in the diet-prenatal depression association[19], obesity-depression association, and prenatal inflammatory trajectories underscores the importance of race-stratified analysis when exploring the association between maternal diet and prenatal depression mediated through maternal BMI and inflammation.

There is scant research on the association between pre-pregnancy diet and prenatal depressive symptoms, and race-stratified analyses are scarce. Furthermore, the probable mediating role of pre-pregnancy BMI and prenatal inflammation in the association between dietary inflammatory indices and prenatal depressive symptoms has been understudied. To address these gaps, the current study had two aims: (1) investigate the association between pre-pregnancy diet (exposure) and prenatal depression (outcome); (2) test whether this association is mediated through pre-pregnancy BMI or late pregnancy inflammation (mediators). We hypothesised that higher adherence to Mediterranean-style diet and lower inflammatory potential of consumed diet during pre-pregnancy is associated with lower depressive symptoms in late pregnancy through decreasing maternal pre-pregnancy BMI and prenatal systemic inflammation (Fig. 1).

Methods

Study overview and participants

We used data from the Alberta Pregnancy Outcomes and Nutrition (APrON) study which is an ongoing longitudinal community cohort study that recruited pregnant individuals in their early- or mid-gestation between 2009 and 2012[38,39]. Pregnant individuals < 27 weeks gestation and aged ≥ 16 years residing in/around Calgary or Edmonton, able to speak and read in English and willing to come for clinic visits were included in this cohort study (n 2189). Stationing research staff in high-volume maternity care and ultrasound clinics (specific to Calgary), distributing information across the city's clinics (specific to Edmonton), posters in public areas (grocery stores, community centres, family physician offices), investigators talking about the study on local television/radio shows, newspapers, banners along roads, prenatal education classes, pregnancy and baby fairs, and word of mouth were methods used to recruit participants to the APrON study[38]. The participants and their children have been followed since then through contacting them via phone or email. For the current study, we excluded participants with CRP greater than 19 mg/l (n 8), as this CRP level might be suggestive of acute infection/inflammation in pregnancy[39], and those with unlikely daily calorie intakes of < 600 kcal or > 3500 kcal (n 53)[40].

Data collection

Pre-Pregnancy dietary assessment. A Food Frequency Questionnaire (FFQ) was used to collect data on pre-pregnancy diet. This 154-item semiquantitative FFQ was based on the National Cancer Institute's Diet History Questionnaire for Canadians[41] and has been validated for assessing pre-pregnancy diet[42]. The participants completed the FFQ during their first study visit to reduce recall bias. Details on this FFQ and how the dietary information collected were converted to frequency of consumption of the food items, and calories and nutrients have been previously published[43]. Briefly, participants were asked to report their average frequency of consumption and portion sizes of foods and drinks during the

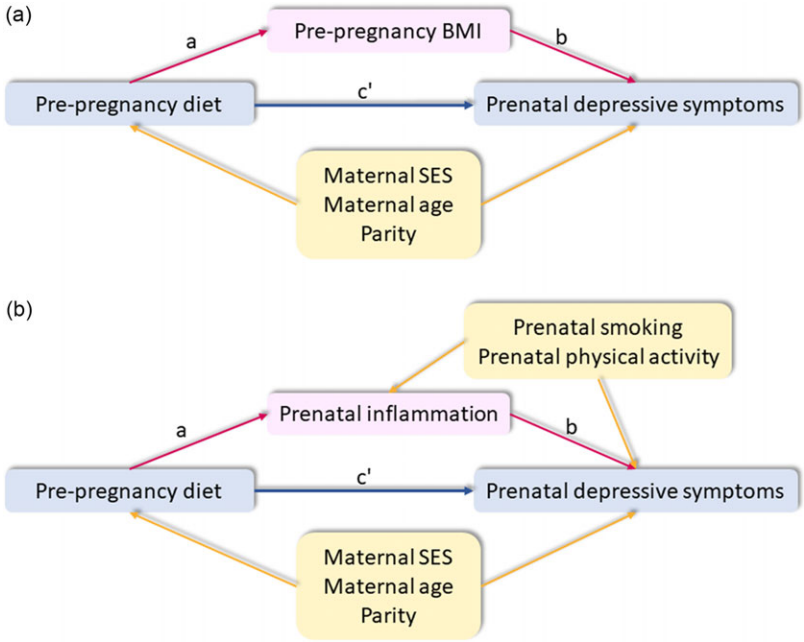

Fig. 1. The study directed acyclic graph (DAG). SES, socio-economic status.

12 months prior to becoming pregnant. The frequency of consumption data was transformed into daily frequencies. Daily intake of calories and nutrients were derived using the FoodProcessor version 10·14[44], which linked data from the questionnaire to the Canadian Nutrient File. The calories and nutrient from all the items were summed to obtain the total daily intake[43]. We used this data to calculate MED adherence and DII scores (study exposures) as outlined below.

Mediterranean diet (MED) adherence. To calculate the MED adherence (referred to as MED from hereafter) score, we followed the protocol by Trichopoulou *et al.*[45,46] and incorporated the modifications suggested by Fung *et al.*, which were based on dietary patterns and eating behaviours that have been constantly linked with lower risks of chronic disease[47]. We considered the intake of the following 9 items in the calculation of MED score: vegetables (excluding potato products), legumes, fruits, nuts, whole grains, red and processed meat, fish, alcohol, and the monounsaturated: saturated fat ratio. For all the items except meats and alcohol, the participants with intake above the median intake received 1 point; otherwise, they received 0 points. For red and processed meats, the scoring was reverse (i.e. those with intake below the median received 1 point; otherwise, they received 0 points). We assigned 1 point for alcohol intake between 5 and 15 g/d. The MED scores could range between 0 and 9, with higher scores indicating higher adherence to the Mediterranean diet. We grouped the participants into tertiles based on their MED scores.

Dietary inflammatory index. DII assesses the inflammatory potential of diet one takes, based on 45 food parameters[16]. We had data on 29 of these food parameters from the APrON participants (online Supplementary Table 1). The APrON study pre-pregnancy FFQ did not capture data on the following DII components: Eugenol (mg), Garlic (g), Ginger (g), Onion (g), Saffron (g), Turmeric (mg), Green/black tea (g), Flavan-3-ol (mg), Flavones (mg), Flavonols (mg), Flavonones (mg), Anthocyanidins (mg), Isoflavones (mg), Pepper (g), Thyme/oregano (mg), Rosemary (mg). We followed the procedures described by Shivappa *et al.*[16] to calculate the DII scores for each participant. Briefly, we used each participants' intake data to calculate a z-score for each one of the food parameters based on the world average and standard deviation and converted the z-scores to percentile scores. We centered the percentile scores by doubling and subtracting 1 and multiplied the centered scores for each food parameter by the respective 'overall food parameter-specific inflammatory effect score' to obtain the 'food parameter-specific DII score'. We summed all the 'food parameter-specific DII scores' to create the 'overall DII score' for each participant. Negative scores are indicative of anti-inflammatory diet whereas positive scores indicate pro-inflammatory diet. We grouped the participants into tertiles based on their overall DII scores.

Pre-Pregnancy BMI. Pre-pregnancy BMI (potential mediator in this study) was calculated as pre-pregnancy self-reported weight (kg) at first study visit (to reduce recall bias) divided by height squared (m^2). Height was measured to the nearest 0·1 cm (Charder HM200P Portstad Portable Stadiometer, USA) at a prenatal study visit and by trained staff. Also, based on the pre-pregnancy BMI, we classified the participants as having underweight (< 18·5 kg/m^2), normal weight (18·5–24·9 kg/m^2) and overweight/obesity (≥ 25·0 kg/m^2)[48].

Maternal C-reactive protein. CRP concentrations (potential mediator in this study) were measured in the third trimester blood samples that were collected by a phlebotomist at a mean of 32·5 weeks gestation (range: 27·0–39·0 weeks). Because any acute illness can increase CRP levels, participants were asked to

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report any symptoms of illness and were rescheduled as necessary. Blood samples were processed into serum and stored at −80°C until assays. Sandwich ELISA (R&D Systems®, Minneapolis, MN, USA) were used to measure serum concentrations of CRP (detection range: 15·6–2000 pg/ml). To ensure the resulting concentrations fell within the detection range, maternal serum samples were diluted 1 in 10 000 prior to their addition to plates. All samples were run in duplicate to determine CV where a CV of ≥ 10 required a re-analysis. If the concentration was above the reference range we diluted more, and if it was below the reference range, we diluted less (compared with the original dilution of 1:10 000) before repeating the assays.

Maternal depression. At the third trimester, participants reported depressive symptoms (study outcome) within the past 7 d on a scale of 0–3 using the ten-item Edinburgh Postpartum Depression Scale (EPDS). EPDS is the most extensively used instrument to screen prenatal and postpartum depression and has satisfactory validity, moderate to good reliability and a good to moderate correlation with other depression measures[49,50]. The overall score range on this scale is 0–30, with higher scores indicating a higher severity of depressive symptoms. We used the cut-off of 10 to identify individuals at risk of prenatal depression[51].

Covariates

Age. Women of advanced age may have significantly higher rates of depression than younger women[52]. Moreover, older women of reproductive age have better diet quality than their younger peers in many aspects including fat and salt intake[53], and younger age has been associated with lower prenatal diet quality[54]. Therefore, maternal age might confound the link between pre-pregnancy diet and prenatal depressive symptoms. Age was self-reported by the participants in our study.

SES. Socio-economic status (SES) can confound the association between maternal diet and prenatal depressive symptoms because low educational level and poor economic status may decrease diet quality in females[54] and increase the risk of prenatal depression[55]. We averaged the z-scores of self-reported family annual income and maternal education and created a composite SES variable. SES scores with higher values represented lower socio-demographic risk (i.e. higher annual income and higher education).

Parity. Parity might affect maternal diet quality[54] and the risk for developing prenatal depression[56]. We included self-reported parity as a dichotomous variable in our analyses, 0 indicating primiparity (first-time mother) and 1 indicating multiparity.

Smoking. Prenatal smoking has been associated with antenatal depressive symptoms[57]. Individuals smoking during gestation have also shown lower levels of anti-inflammatory biomarkers compared with non-smokers[58]. Therefore, smoking was considered as a confounding factor in the association between maternal diet and prenatal depressive symptoms, mediated through inflammation (Fig. 1(b)).

Physical activity. Higher prenatal physical activity during pregnancy is associated with lower incidence and severity of depressive symptoms[59]. Also, light physical activity is associated with lower CRP concentrations in late pregnancy[60]. Hence, we considered physical activity as a confounding factor in the association between maternal diet and prenatal depressive symptoms, mediated through inflammation (Fig. 1(b)). In the APrON study, prenatal physical activity was assessed using the Baecke questionnaire[38], which has been previously used to assess physical activity during pregnancy[61]. The questionnaire assesses work, sport and leisure time activities excluding sport. Questions on work and leisure time are scored using a five-point Likert scale, while sports score is calculated based on the intensity and duration (time spent per week and the proportion of year spent playing) of sports. Scores for work, sport and leisure were calculated and added up to compute a total score[62].

Statistical analysis

Based on the study inclusion criteria and the data available for the participants at different timepoints, a sample of n 1141 were included in our study. We used SPSS version 26.0 (IBM Corp.) to analyse the data. We checked q-q and p-p plots and the skewness and kurtosis for study variables to assess the normality of distribution. We categorised the MED and DII scores into tertiles in our analyses (as opposed to treating them as continuous variables), because categorising dietary indices as categorical variables in nutritional research can enhance interpretability, capture non-linear relationships and reduce measurement error[63]. We conducted two sets of analyses: (1) stratified all our analyses by race (self-identified as white *v.* people of colour) and (2) ran pooled sample analyses and included race as an additional covariate. To test the association between pre-pregnancy MED and DII tertiles and prenatal depressive symptoms, we conducted analysis of covariance test. We also ran multivariable logistic regression using EPDS ≥ 10 as cut-off point to assess the association between diet and the risk of depression (covariates: maternal age, SES and parity). Before running the mediation analyses, we checked the associations between the exposure (pre-pregnancy diet) and the mediators (pre-pregnancy BMI and prenatal inflammation; path (a), and the associations between the mediators and the outcome (prenatal depressive symptoms; path (b)). Since the independent variable in our study (MED/DII tertiles) was categorical, these additional analyses allowed for better understanding of the between-tertile differences. To test the association between pre-pregnancy MED and DII tertiles and pre-pregnancy BMI or prenatal inflammation, we conducted analysis of covariance (covariates: maternal age and SES). We also conducted multinomial logistic regression (covariates: maternal age and SES) to test the association between pre-pregnancy MED and DII tertiles and BMI category (underweight, normal weight and overweight/obesity; normal weight set as reference group). We tested the association between pre-pregnancy BMI or prenatal inflammation and late-pregnancy depression using multivariable linear regression; maternal age and SES were included as covariates in both models and smoking and physical activity were additional covariates in the model testing the link between inflammation and depressive symptoms.

Moreover, we ran ANCOVA (covariates: maternal age, SES, parity) to test the association between pre-pregnancy BMI categories and prenatal depressive symptoms. We conducted mediation analysis using Process Macro in SPSS to test if maternal pre-pregnancy BMI or prenatal inflammation mediated the association between pre-pregnancy diet and prenatal depression (independent variable: prenatal MED/DII tertiles; dependent variable: prenatal depressive symptoms, mediator: BMI or inflammation; Fig. 1). Maternal age, SES and parity were included as covariates in both models, and smoking and physical activity were additional covariates in the models testing the mediating role of inflammation in the association between maternal diet and depressive symptoms. $P < 0{\cdot}05$ was considered statistically significant.

Results

All the reported results are based on the models adjusted for covariates indicated in "Statistical Analysis" section. We had different sample sizes for different aims because we included in each set of the analyses all those with valid data to sustain the maximum power possible. Table 1 summarises the characteristics of the participants included in the current study stratified by self-identified race. Participants who were self-identified as white (referred to as 'white' from hereafter) had significantly higher household annual income ($P < 0{\cdot}001$), pre-pregnancy BMI ($P = 0{\cdot}003$) and pre-pregnancy MED scores ($P = 0{\cdot}01$) compared with those self-identified as 'people of colour'. Please see online Supplementary Table 2 for the comparison of the characteristics of the APrON study participants included in the current study (n 1141) to those not included (n 1048).

Higher pre-pregnancy MED scores were significantly correlated with lower pre-pregnancy DII scores ($r(1141) = -0{\cdot}59$, $P < 0{\cdot}001$). The tertiles of the pre-pregnancy MED and DII scores were also negatively correlated (χ^2 (4, n 1141) = 391·37, $P < 0{\cdot}001$).

Pre-Pregnancy diet and prenatal depression

We found no overall or pairwise associations (Fig. 2(a), (c), (f)) between MED tertiles and prenatal depressive symptoms neither in white individuals (F (2, 904) = 1·18, $P = 0{\cdot}308$) nor in people of colour (F (2, 154) = 1·73, $P = 0{\cdot}181$), or pooled sample (F (2, 1063) = 0·73, $P = 0{\cdot}480$). Likewise, we found no overall or pairwise associations (Fig. 2(b), (d), (e)) between DII tertiles and prenatal depressive symptoms in white (F (2, 904) = 0·19, $P = 0{\cdot}825$), people of colour (F (2, 154) = 2·00, $P = 0{\cdot}138$) or the pooled sample (F (2, 1063) = 0·31, $P = 0{\cdot}730$). However, when we tested the association between pre-pregnancy diet and the *risk* of depression (defined as EPDS scores 10 or above) through multivariable logistic regression analysis, white participants in the third MED tertile had 44 % decreased risk of late pregnancy depression compared with those in the first tertile (OR = 0·56, 95 % CI, 0·33, 0·95; Fig. 3(a)); no such association was observed for DII tertiles in white participants (Fig. 3(b)). We found no significant association between MED or DII tertiles and risk of prenatal depression in people of colour (Fig. 3). In the pooled analyses with race as a covariate, the association between pre-pregnancy diet and risk of prenatal depression did not reach statistical significance for MED tertiles (OR = 0·81, 95 % CI, 0·64, 1·02; Fig. 3(a)) and remained non-significant for DII tertiles (OR = 0·94, 95 % CI, 0·75, 1·17; Fig. 3(b)). The percentage of individuals at risk for prenatal depression, within each MED and DII tertile are presented in online Supplementary Fig. 1.

Pre-Pregnancy diet and prenatal depression: mediation through pre-pregnancy BMI

Pre-pregnancy diet and BMI. There was a significant association between MED tertiles and pre-pregnancy BMI in white individuals (F (2, 938) = 4·76, $P = 0{\cdot}009$), and those in the first tertile had significantly greater BMI compared with the third tertile (MD = 1·08; 95 % CI, 0·39, 1·77, Fig. 4(a)). There was no overall or pairwise associations between DII tertiles and pre-pregnancy BMI in white participants (F (2, 938) = 0·16, $P = 0{\cdot}849$; Fig. 4(b)). Also, there was no overall or pairwise associations between MED (F (2, 164) = 0·99, $P = 0{\cdot}374$) or DII (F (2, 164) = 0·80, $P = 0{\cdot}452$) tertiles and pre-pregnancy BMI in people of colour (Fig. 4(c) and (d)). In the pooled sample, there was a significant association between MED tertiles and pre-pregnancy BMI (F (2, 1101) = 5·24, $P = 0{\cdot}005$), and those in the first tertile had significantly greater BMI compared with those in the third tertile (MD = 1·03; 95 % CI, 0·40, 1·66, Fig. 4(e)). We observed no overall or pairwise associations between DII tertiles and pre-pregnancy BMI in the pooled sample (F (2, 1101) = 0·18, $P = 0{\cdot}836$; Fig. 4(f)). Analyses with BMI as a categorical variable yielded similar results (please see online Supplementary material for details).

Pre-pregnancy BMI and prenatal depressive symptoms. Among white participants, pre-pregnancy BMI was not associated with prenatal depressive symptoms ($\beta = 0{\cdot}03$, 95 % CI, −0·03, 0·09). Among people of colour, higher pre-pregnancy BMI was significantly associated with lower depressive symptoms in late pregnancy ($\beta = -0{\cdot}25$, 95 % CI, −0·43, −0·06). In the pooled analyses, pre-pregnancy BMI was not associated with third prenatal depressive symptoms ($\beta = -0{\cdot}004$, 95 % CI, −0·06, 0·05). Analyses with BMI as a categorical variable produced comparable results (please see online Supplementary material for details).

BMI as a mediator linking pre-pregnancy diet to prenatal depressive symptoms. We observed no significant indirect associations between maternal diet and prenatal depressive symptoms through pre-pregnancy BMI, in race-stratified or pooled sample analyses (Table 2). Due to the similarity of the findings with BMI as a continuous or categorical variable, and since mediation analysis in Process Macro would not allow for including a mediator as a categorical variable, we did not run the mediation analyses with BMI as a categorical variable.

Pre-Pregnancy diet and prenatal depression: mediation through prenatal inflammation

Pre-pregnancy diet and prenatal inflammation. There was a significant association between MED tertiles and CRP concentrations in white individuals (F (2, 944) = 3·24, $P = 0{\cdot}040$), and those in the third tertile had significantly lower concentrations of CRP compared with those in the first tertile (MD = −0·53; 95 % CI, −0·95, −0·11; Fig. 5(a)). But we observed no overall (F (2, 164) = 0·02, $P = 0{\cdot}976$) or pairwise association between

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Table 1. Study participants' characteristics by self-identified race

Variables	White			People of colour		
	n	Results		*n*	Results	
Age, years						
Mean	949	31·34		169	31·83	
SD, range		4·00, 18–44			4·58, 20–44	
Education, *n* (%)	965			170		
Less than high school		10	1·0		2	1·2
Completed high school diploma		64	6·6		16	9·4
Completed trade, technical diploma		179	18·5		25	14·7
Completed university degree		478	49·5		88	51·8
Completed postgraduate degree		234	24·2		39	22·9
Income, *n* (%)	959			172		
< $20 000		10	1·0		6	3·5
$20 000–$39 999		25	2·6		14	8·1
$40 000–$69 999		114	11·9		38	22·1
$70 000–$99 999		236	24·6		28	16·3
≥ $100 000		574	59·9		86	50·0
Parity, no siblings	959	537	56·0	173	100	57·8
Gestational diabetes, *n* (%)	856	29	3·0	156	9	5·1 %
Pre-eclampsia, *n* (%)	856	2	0·2	156	0	0·0
Smoking during pregnancy, *n* (%)	927	9	0·9	165	2	1·1
		Mean	SD, range		Mean	SD, range
Gestational age at recruitment	966	17·09	4·99, 5·00–26·86	175	17·97	4·92, 6·43, 26·86
Physical activity	929	7·49	1·29, 3·66–12·39	166	6·70	1·23, 4·07–10·59
Pre-pregnancy BMI, kg/m^2	960	23·80	4·29, 15·31–46·47	175	22·76	3·83, 15·62–40·90
Pre-pregnancy MED score	966	4·25	1·91, 0–9	175	3·87	1·73, 1–8
Pre-pregnancy DII score	966	−2·06	2·11, −5·48–4·16	175	−1·73	2·31, −5·65, 3·80
Serum CRP at the third trimester, mg/l	966	2·97	2·60, 0·00–17·34	175	2·85	2·49, 0·09, 12·40
EPDS score at the third trimester	928	5·07	3·77, 0–20	166	5·46	4·38, 0, 22
Third trimester depression risk*						
n	928	116		166	26	
%		12·5			15·7	

MED, Mediterranean diet adherence; DII, dietary inflammatory index; CRP, C-reactive protein; EPDS, Edinburgh postpartum depression scale.
* EPDS score ≥ 10.

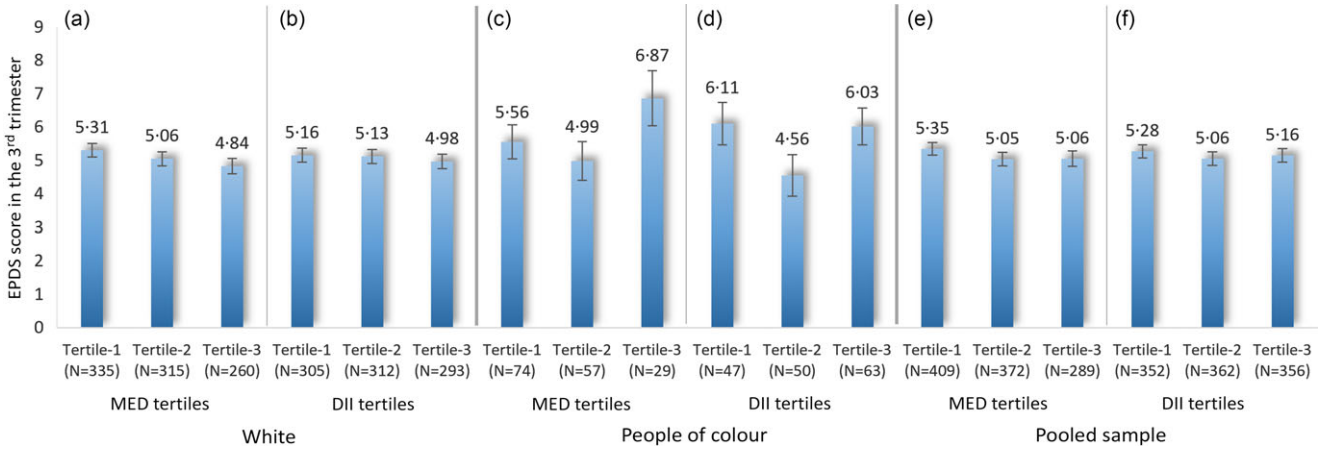

Fig. 2. Pre-pregnancy diet and third trimester EPDS score by self-identified race and pooled sample. Note: Results are based on analysis of covariance (ANCOVA) test (covariates: maternal age, SES, and parity; in the pooled sample analysis, race was included as an additional covariate). The data are presented as estimated marginal means and se. EPDS, Edinburgh postpartum depression scale; MED, Mediterranean diet adherence; DII, dietary inflammatory index; SES, socio-economic status. * $P < 0·05$.

MED tertiles and CRP concentrations in people of colour (Fig. 5(c)). There was no significant association between DII tertiles and CRP levels either in white participants ($F(2, 944) = 2·85$, $P = 0·059$), but those with DII scores in the second and third tertiles had significantly higher concentrations of CRP compared with those in the first tertile (MD = 0·44; 95 % CI, 0·03, 0·84; and MD = 0·42; 95 % CI, 0·01, 0·83, respectively; Fig. 5(b)). There were no significant overall ($F(2, 164) = 1·31$, $P = 0·273$) or pairwise associations between DII tertiles for CRP concentrations in people of colour (Fig. 5(d)).

In the pooled sample analysis, there was no significant overall association between MED tertiles and prenatal CRP levels ($F(2, 1107) = 2·60$, $P = 0·075$), but those in the first tertile had significantly greater CRP concentrations compared with those in

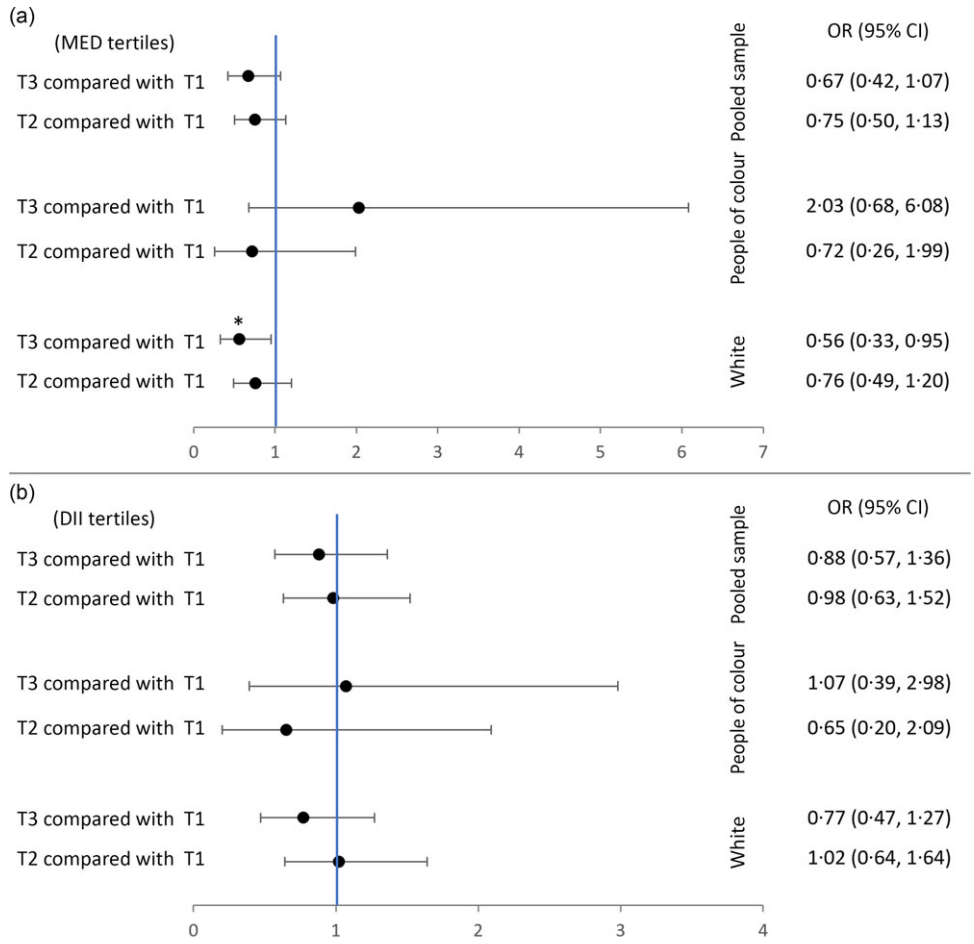

Fig. 3. Pre-pregnancy diet and third trimester risk of depression (EPDS score ≥ 10) by self-identified race and pooled sample. Note: Results are based on multivariable logistic regression tests (covariates: maternal age, SES and parity; in the pooled sample analysis, race was included as an additional covariate). The data are presented as OR and 95 % CI. EPDS, Edinburgh postpartum depression scale; MED, Mediterranean diet adherence; DII, dietary inflammatory index; SES, socio-economic status. * $P < 0{\cdot}05$.

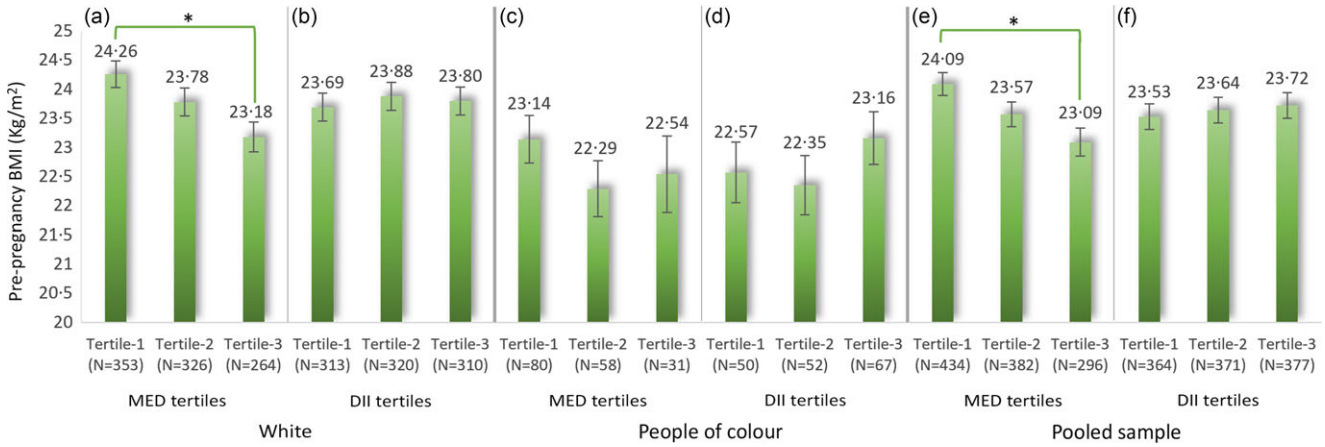

Fig. 4. Pre-pregnancy diet and pre-pregnancy BMI by self-identified race and pooled sample. Note: Results are based on analysis of covariance (ANCOVA) test (covariates: maternal age, SES and parity; in the pooled sample analysis, race was included as an additional covariate). The data are presented as estimated marginal means and se. MED, Mediterranean diet adherence; DII, dietary inflammatory index; SES, socio-economic status. * $P < 0{\cdot}05$.

Table 2. The association between maternal pre-pregnancy diet and prenatal depression: mediation through pre-pregnancy BMI

		Total effect†			Direct effect†			Indirect effect†		
White (*n* 910)										
	Compared with T1	*β*	95 % CI	*P*	*β*	95 % CI	*P*	*β*	95 % CI	*P**
MED	T2	−0·26	−0·84, 0·31	0·37	−0·25	−0·83, 0·33	0·39	−0·01	−0·06, 0·02	–
	T3	−0·46	−1·08, 0·15	0·14	−0·44	−1·05, 0·18	0·16	−0·02	−0·09, 0·04	–
DII	T2	−0·07	−0·66, 0·52	0·82	−0·07	−0·67, 0·52	0·81	0·01	−0·02, 0·04	–
	T3	−0·22	−0·82, 0·39	0·48	−0·22	−083, 0·38	0·47	0·004	−0·02, 0·04	–
People of colour (*n* 160)										
	Compared with T1	*β*	95 % CI	*P*	*β*	95 % CI	*P*	*β*	95 % CI	*P*
MED	T2	−0·57	−2·08, 0·95	0·46	−0·85	−2·35, 0·64	0·26	0·29	−0·03, 0·75	–
	T3	1·31	−0·61, 3·23	0·18	1·10	−0·78, 2·99	0·25	0·21	−0·17, 0·70	–
DII	T2	−1·55	−3·33, 0·23	0·09	−1·56	−3·30, 0·18	0·08	0·005	−0·40, 0·47	–
	T3	−0·09	−1·77, 1·60	0·92	0·14	−1·52, 1·80	0·87	−0·22	−0·72, 0·23	–
Pooled sample (*n* 1070)										
	Compared with T1	*β*	95 % CI	*P*	*β*	95 % CI	*P*	*β*	95 % CI	*P*
MED	T2	−0·31	−0·85, 0·23	0·27	−0·31	−0·85, 0·23	0·26	0·004	−0·03, 0·05	–
	T3	0·03	−0·56, 0·63	0·91	0·03	−0·57, 0·62	0·92	0·003	−0·03, 0·04	–
DII	T2	−0·26	−0·82, 0·30	0·36	−0·26	−0·82, 0·30	0·37	−0·001	−0·02, 0·02	–
	T3	0·10	−0·46, 0·67	0·73	0·10	−0·46, 0·67	0·73	<−0·001	−0·02, 0·02	–

T, tertile; MED, Mediterranean diet adherence; DII, dietary inflammatory index; SES, socio-economic status.
* *P* values are not provided by Process Macro (SPSS) for indirect effects.
† Results based on mediation analysis with categorical independent variable (Process Macro, SPSS). Models adjusted for maternal age, SES and parity. In the pooled sample analysis, race was included as an additional covariate.

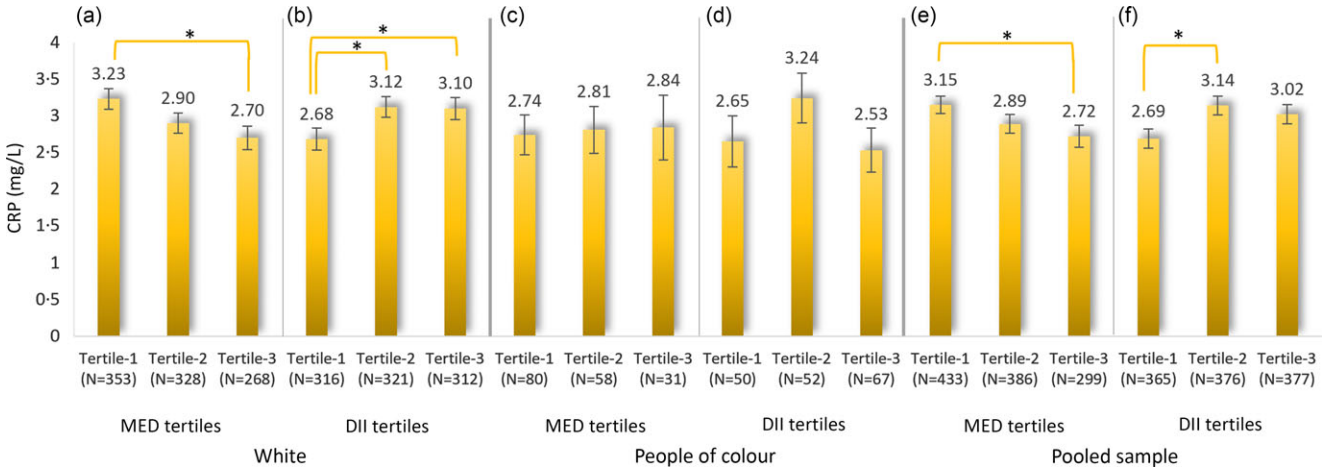

Fig. 5. Pre-pregnancy diet and third trimester CRP by self-identified race and pooled sample. Note: Results are based on analysis of covariance (ANCOVA) test (covariates: maternal age and SES; in the pooled sample analysis, race was included as an additional covariate). The data are presented as estimated marginal means and se. CRP, C-reactive protein; MED, Mediterranean diet adherence; DII, dietary inflammatory index; SES, socio-economic status. * $P < 0{\cdot}05$.

the third tertile (MD = 0·44; 95 % CI, 0·05, 0·82; Fig. 5(e)). We found a significant overall association between DII tertiles and prenatal CRP levels (F (2, 1107) = 3·03, $P = 0{\cdot}049$) and a significant difference between those in the first and second tertiles (MD = −0·45; 95 % CI, −0·82, −0·08; Fig. 5(f)).

Prenatal inflammation and depressive symptoms. We observed no significant association between prenatal CRP concentrations and late-pregnancy depressive symptoms in white individuals ($\beta = 0{\cdot}05$, 95 % CI, −0·04, 0·15), people of colour ($\beta = -0{\cdot}21$, 95 % CI, −0·48, 0·06) or pooled sample ($\beta = 0{\cdot}01$, 95 % CI, −0·08, 0·10).

Inflammation as a mediator linking pre-pregnancy diet to prenatal depressive symptoms. There was a significant difference in depressive symptoms between the first and second DII tertiles among people of colour ($\beta = -1{\cdot}90$, 95 % CI, −3·64, −0·17). However, there were no significant associations between MED and DII tertiles and prenatal depressive symptoms through prenatal CRP, in neither racial group nor pooled sample (Table 3).

Discussion

Maternal diet and prenatal depression

Based on our findings in this study, higher MED was not significantly associated with depressive symptoms in late pregnancy, but decreased the *risk* of prenatal depression (defined as EPDS ≥ 10) in white individuals. Other than a

Table 3. The association between maternal pre-pregnancy diet and prenatal depression: mediation through CRP concentrations

		Total effect†			Direct effect†			Indirect effect†		
White (*n* 906)										
	Compared with T1	*β*	95 % CI	*P*	*β*	95 % CI	*P*	*β*	95 % CI	*P**
MED	T2	−0·27	−0·86, 0·30	0·35	−0·27	−0·85, 0·31	0·37	−0·01	−0·05, 0·02	–
	T3	−0·52	−1·14, 0·09	0·10	−0·51	−1·13, 0·11	0·11	−0·01	−0·06, 0·02	–
DII	T2	−0·02	−0·61, 0·57	0·95	−0·04	−0·63, 0·55	0·90	0·02	−0·02, 0·07	–
	T3	−0·13	−0·75, 0·48	0·67	−0·14	−0·76, 0·48	0·65	0·01	−0·02, 0·05	–
People of colour (*n* 158)										
	Compared with T1	*β*	95 % CI	*P*	*β*	95 % CI	*P*	*β*	95 % CI	*P*
MED	T2	−0·33	−1·83, 1·18	0·67	−0·31	−1·81, 1·19	0·68	−0·02	−0·27, 0·20	–
	T3	1·42	−0·48, 3·32	0·14	1·47	−0·42, 3·36	0·13	−0·05	−0·39, 0·26	–
DII	T2	−1·90	−3·64, −0·17	0·03	−1·81	−3·55, −0·07	0·04	−0·09	−0·42, 0·08	–
	T3	−0·43	−2·08, 1·22	0·61	−0·48	−2·13, 1·17	0·56	0·05	−0·15, 0·27	–
Pooled sample (*n* 1064)										
	Compared with T1	*β*	95 % CI	*P*	*β*	95 % CI	*P*	*β*	95 % CI	*P*
MED	T2	−0·29	−0·83, 0·25	0·29	−0·29	−0·83, 0·25	0·29	−0·001	−0·03, 0·02	–
	T3	−0·31	−0·90, 0·27	0·29	−0·31	−0·90, 0·28	0·30	−0·003	−0·03, 0·03	–
DII	T2	−0·25	−0·81, 0·31	0·38	−0·26	−0·82, 0·30	0·37	0·01	−0·04, 0·05	–
	T3	−0·14	−0·72, 0·44	0·64	−0·14	−0·72, 0·44	0·63	0·001	−0·02, 0·02	–

CRP, C-reactive protein; T, tertile; MED, Mediterranean diet adherence; DII, dietary inflammatory index; SES, socio-economic status.
* *P* values are not provided by Process Macro (SPSS) for indirect effects.
† Results based on mediation analysis with categorical independent variable (Process Macro, SPSS). Models adjusted for maternal age, SES, parity, smoking during pregnancy and physical activity in the third trimester. In the pooled sample analysis, race was included as an additional covariate.

significant difference of depressive symptoms between the first and second DII tertiles among people of colour, we did not find a significant association between DII tertiles and prenatal depressive symptoms or risk of depression, in either racial group or pooled sample.

Many of the studies on the role of maternal diet in prenatal mental health have assessed maternal diet *during* pregnancy. The only study that investigated *pre-pregnancy* dietary patterns in association with prenatal depression found that merely the healthy dietary pattern and not the unhealthy dietary patterns were associated with depressive symptoms[64]. Similarly, a systematic review of observational studies concluded that a healthy dietary pattern prior to or during pregnancy was inversely associated with prenatal depressive symptoms, but the association between an unhealthy dietary pattern and depression was not definitive[65]. Like these findings, we also observed that the healthy diet index (MED) and not the unhealthy diet index (high DII) in pre-pregnancy was linked with the risk of prenatal depression.

Only a few studies have addressed the association between MED and prenatal depression with none using pre-pregnancy MED. A longitudinal study observed no significant association between mid-pregnancy MED and either mid- or late-pregnancy depressive symptoms[66]. Similarly, using data from a USA cohort study, Oddo *et al.* revealed that MED was not associated with decreased depressive symptoms[67]. However, the latter study showed that MED decreased the odds of high depressive symptoms defined as scores 10 and above on the Patient Health Questionnaire-9[67]. Similar to the Oddo *et al.* study[67], we found that MED decreased the odds of depression (EPDS ≥ 10) but did not decrease depressive symptoms. Another cohort study, which is probably the only study that ran race-stratified analyses, showed that MED during early pregnancy was associated with lower likelihood of depressive mood in the first trimester particularly among Hispanic women[19]. Unlike the latter study, we observed that MED was associated with lower risk of prenatal depression only in white participants. It is noteworthy that we grouped all the races other than white into one category in our study (people of colour), which is a different classification of racial groups compared with the previous race-stratified study which included Hispanics and Black African Americans as two separate groups. Also, part of the discrepancy between findings of these studies might be explained by the notion that the socio-cultural settings in which the Mediterranean diet is consumed, and not just the diet itself, might be responsible for the beneficial health effects of MED[68].

While little is known about the link between DII and prenatal depression, studies in non-pregnant populations have found that higher DII is associated with increased incidence of depression and more depressive symptoms, particularly among women[69,70]. Interestingly, we found that among people of colour, those in the second DII tertile had lower depressive symptoms compared with the first tertile, when the model included maternal age, SES, parity, physical activity and smoking as covariates.

Maternal diet and prenatal depression: mediation through pre-pregnancy BMI

In our study, higher MED was associated with lower BMI in white participants, and higher maternal BMI was associated with lower depressive symptoms in people of colour; pre-pregnancy BMI did not mediate the association between maternal pre-pregnancy diet and prenatal depression.

Few studies have directly assessed the mediating role of BMI in the association between diet and depression. A cohort study including adolescents found that a healthy dietary pattern could protect against depression partially through reduced BMI[71]. Also, a study among elderly people showed that higher DII scores were associated with a higher risk of depression, and the association was in part mediated by increased BMI[21]. However,

results from other studies that considered the probable effect of BMI in the association between diet and depression by adjusting for BMI or testing it as an effect modifier indicated that BMI might not account for the link[72,73].

There is some evidence in the literature linking MED and DII to BMI and pre-pregnancy BMI to prenatal depression, suggesting a mediation role of BMI in the association between maternal diet and depression. Meta-analyses of randomised controlled trials and cohort studies have demonstrated that MED leads to a greater reduction of body weight in comparison with other diets[74] and decreased risk of obesity[23]. Our results were in accord with these findings, as we also found that white women in the third tertile of MED had significantly lower pre-pregnancy BMI compared with those in the first tertile. Nonetheless, we did not observe a similar result among people of colour. This finding was in agreement with some prior research that showed MED was particularly helpful in reducing weight among white people, apparently because a non-adapted MED might not capture the traditional foods consumed by different races, and therefore would not provide an accurate picture of the association between MED and obesity in them[75]. Studies that have investigated the association between DII and body weight have come up with conflicting results. Among non-pregnant populations, some studies have found that those consuming a diet with high inflammatory potential have higher BMI compared with those with lower DII scores[76], while others have shown that higher DII scores are not necessarily associated with higher BMI[77–79]. In a study among pregnant individuals, higher DII scores in the first trimester were associated with higher BMI[80]. It is probable that the method of dietary assessment attributed to the discrepant results, as studies that used dietary recalls or food diaries, which are more accurate methods of dietary intake assessment compared with FFQ, found a significant association between DII and BMI[76,80], while those that used FFQ did not. The dietary assessment method in our study was FFQ, probably explaining the null results in terms of the association between DII and BMI.

Obesity has been shown to be associated with increased odds of prenatal depression[33]. In a large birth cohort study by Sominsky *et al.*, pre-pregnancy obesity was associated with increased EPDS scores in mid-gestation[81]. However, a prospective study in China found no significant correlation between pre-pregnancy BMI and prenatal depressive symptoms[34], and a comparison of white and south Asian women in a British pregnancy cohort observed no significant association between BMI categories and depression, in neither racial group[82]. Conversely, a cohort study of Hispanic women found that overweight was associated with *lower* depressive symptoms across pregnancy[83]. Generally, it seems that the positive association between obesity and depression exists only among white women[35]. These racial differences in obesity–depression association might stem from the impact of social and cultural factors on body image and weight satisfaction among women[84]. Unlike the previous studies, we observed no significant association between obesity and depressive symptoms in white participants either. This might be explained by the different impact of obesity on distinct symptom domains of depression, as Chu *et al.* reported that overweight and obesity were associated with increased somatic symptoms but not cognitive-affective or overall depressive symptoms[85]. Which adds to the complexity of the association between pre-pregnancy BMI and prenatal depression is the probable mechanisms involved. A common pathway from obesity to depression is believed to be increased adiposity-derived inflammation in the body[86], and Chu *et al.* study found that the association between obesity and somatic symptoms of depression was partially mediated through increased CRP[85]. However, like our study (data not shown), the Sominsky *et al.* study found no mediating role for inflammatory biomarkers in the association between pre-pregnancy obesity and prenatal depressive symptoms[81].

Maternal diet and prenatal depression: mediation through prenatal inflammation

We found that higher MED was associated with lower inflammation, and higher DII was associated with higher inflammation in the third trimester in white individuals. However, the prenatal CRP levels were not associated with prenatal depressive symptoms and did not mediate the association between maternal diet and prenatal depressive symptoms.

MED has been studied extensively in association with inflammatory biomarkers. In a study among elderly subjects, MED was associated with lower CRP levels, but no association was observed between MED and other inflammatory biomarkers like IL-6[87]. Similarly, among adolescents and adults, higher MED was associated with lower concentrations of CRP, but not other inflammatory biomarkers[88]. Contrarywise, a study by Flor-Alemany *et al.* among pregnant individuals revealed that MED in mid-gestation was associated with lower levels of the pro-inflammatory biomarker TNF-α but not CRP or IL-6 levels in late pregnancy[89]. Interestingly, in a study that conducted race-stratified analyses, higher MED significantly *increased* the pro-inflammatory biomarker IL-17A in Black African-American women[19].

Regarding the association between DII and inflammation, our findings agreed with recent evidence that DII was associated with elevated CRP levels in non-pregnant populations[90,91]. However, DII scores calculated based on dietary data from both pre-pregnancy and prenatal periods (weighted means) were not associated with early-pregnancy inflammatory biomarkers in an ethnically diverse cohort[92]. In another pregnancy study, there was a significant difference in the second trimester CRP levels between those with low *vs.* high DII (based on the median scores) only among individuals with complicated pregnancy; there were no significant differences in the other trimesters, for other inflammatory cytokines or in non-complicated pregnancy[93]. A study among Chinese pregnant women found a U shape association between DII scores and pro-inflammatory biomarkers in the third trimester, with circulating inflammatory cytokines first decreasing and then increasing with the increasing DII scores[94]. These inconsistent findings might be due to the different dietary assessment methods, different ways of DII calculation (point *v.* weighted mean), different study populations and the fact that the inflammatory status fluctuates during pregnancy, and there might be a buffering system to change the prenatal inflammatory status in response to external effectors like diet, to ensure a normal pregnancy[94].

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While a large body of evidence exists regarding the role of inflammation in the pathogenesis of depression, little is known if inflammation is also implicated in prenatal depression. A recent meta-analysis of prospective studies found that IL-6 had a stronger association than CRP with future depression[95]. Similarly, the only inflammatory biomarker associated with depressive symptoms at week 28 of gestation was IL-6, and CRP did not have a significant association with the EPDS scores[81]. Our study also found no association between CRP and prenatal depression, possibly indicating that only specific inflammatory biomarkers are implicated in prenatal depression pathophysiology. That we only assessed CRP in our study and both our dietary indices, especially MED, have shown more significant effect on reducing CRP levels than other inflammatory cytokines in different population (see above), while IL-6 seems to be the inflammatory biomarker implicated in depression might have been the main reason that we found no mediating role for inflammation in the association between maternal diet and prenatal depression. Moreover, many other factors should be taken into account when interpreting the association between inflammation and *prenatal* depression, including pregnancy complications, current or past stressors, social support, depression diagnosis prior to pregnancy and pharmacotherapies like antidepressants[96]. In addition, some previous research suggests that central and not peripheral inflammation might be more strongly linked with depression, as higher levels of inflammatory cytokines in the cerebrospinal fluid, and not the plasma levels, were associated with augmented odds of prenatal depression[97].

Strengths and limitations

Our study was among the first to investigate the mediating role of maternal BMI and inflammation in the association between maternal diet and prenatal depression. The race-stratified analyses were a main strength of the current study, as racial differences in this area of research are emerging. Moreover, by studying the pre-pregnancy diet, we were privileged to investigate the long-term and habitual diet of the participants in association with their risk of developing depressive symptoms in pregnancy because dietary intake is usually altered during pregnancy especially in early gestation. Also, the longitudinal assessment of the link between diet and depression allowed us to interpret the results from a causality point of view. A lot of the prior research has been cross-sectional, which limits understanding the direction of the association, as depression can also affect diet quality during pregnancy[98,99].

As for any study, our work had some limitations. Although pre-pregnancy FFQ is the most commonly used method to assess dietary intake prior to pregnancy[100], the recall bias associated with its use might limit the ability to definitively distinguish between pre-pregnancy and prenatal diet. Also, the pre-pregnancy FFQ that we used in the APrON study did not capture data on many items that contribute to the final DII score. Although it is common practice to use data on as many DII components as you have in your study and calculate the DII score based on that data[16], lacking data on DII components that play a major role in people's overall dietary inflammation might be a potential drawback. For instance, flavonoids have an important role in controlling inflammation in the body[101], and not having data on them might have affected how accurately we have captured the link between diet and inflammation in our study. Especially that there are racial differences in contribution of dietary components to inflammatory potential of diet[102]. Another limitation of our study was that we had data only on serum CRP levels as a measure of prenatal inflammation in our main cohort, and CRP might not be very well linked to prenatal depression. Moreover, CRP data were only available from the third trimester, which further limits the ability to obtain a clear understanding of its probable role in the association between pre-pregnancy diet and prenatal depression. Another important disadvantage of our study was that the sample size was much smaller for the 'people of colour' group, which might have been responsible for most of the non-significant results for this racial group. A greater portion of the APrON participants had high income and education compared with Canada[39], which reduces the generalisability of our results to the community. Residual confounding is also a limitation in our study, as we could not control for all the factors that might have affected the results, including history of depression diagnosis and antidepressants use.

Conclusion

In conclusion, pre-pregnancy diet might impact the odds of developing depression in late pregnancy. We observed this effect only in white individuals, but cannot suggest that pre-pregnancy diet would not impact depression risk in people of colour because the sample size was much smaller for this group in our cohort. Moreover, the dietary indices we used in our study and the data we had available on DII might not fully capture the inflammatory potential of the diet that different racial groups consume. Given the high prevalence of prenatal depression in all racial groups and its many adverse effects on mothers and their children and the resultant economic burden on the governments, it is suggested that further research explores the potential benefits of healthy dietary patterns in relation to prenatal mental health. Only then would healthcare systems be able to take steps in providing meaningful nutrition support to women before and during pregnancy and consider racial differences in their strategies. Although we did not find a significant mediating role for obesity and inflammation in this study, our findings do not rule out the possible mediating role of these factors. Future studies are encouraged to use more comprehensive assessment of inflammatory status in the body, FFQ that obtain data on all the DII components and adaptive MED (with components adapted to the study populations) to better reflect the adherence of people residing in non-Mediterranean countries to the healthy Mediterranean style diet.

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The authors declare none.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the University of Calgary Health Research Ethics Board (REB14-1702) and University of Alberta Health Research Ethics Biomedical Panel (Pro00002954). Written informed consent was obtained from all subjects.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114524001028

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