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Impact of consuming a Mediterranean-style diet during pregnancy on neurodevelopmental disabilities in offspring: results from the Boston Birth Cohort

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Background: While consuming a Mediterranean-style diet (MSD) among pregnant women is expected to affect offspring neurodevelopment, the current evidence is limited. This prospective birth cohort study aimed to explore the association of maternal MSD with neurodevelopmental disabilities (NDD) in offspring, especially among children born to mothers with overweight or obesity (OWO) and/or diabetes mellitus (DM) since they have a higher risk for oxidative stress and immune/metabolic disturbances.

Methods: We analyzed data from a subgroup of mother–child dyads enrolled in the Boston Birth Cohort. Maternal dietary information (*via* food frequency questionnaires, Food frequency questionnaires [FFQ]) and sociodemographic information were obtained *via* in-person interviews within 24 to 72 hours postpartum. Maternal clinical information and child diagnosis of NDD including autism, attention-deficit/hyperactivity disorder (ADHD), and other developmental disabilities (DD) were extracted from medical records. A Mediterranean-style diet score (MSDS) was calculated using the FFQ. The association of maternal MSDS with NDD, autism, ADHD, and other DD was evaluated using multivariable logistic regression models adjusted for pertinent covariates.

Results: This study included 3153 mother–child pairs, from which we identified diagnoses of 1362 (43.2%) NDD, including 123 (3.9%) case of autism, 445 (14.1%) ADHD, and 794 (25.2%) other DD. In the overall sample, women with a higher maternal MSDS (per standard deviation increase) were less likely to have offspring with NDD (adjusted odds ratio [OR]: 0.904, 95% confidence interval [CI]: 0.817–1.000; *P* value: 0.049). Using MSDS quintile 1 as the reference, being in the combined group of quintiles 3–5 was associated with a 26% lower likelihood of NDD (adjusted OR: 0.738, 95% CI: 0.572–0.951; *P* value: 0.019). When stratified by mothers with OWO/DM *vs.* without OWO/DM, the association between maternal MSDS and offspring NDD was greater in children born to mothers with OWO/DM.

Conclusions: In this prospective birth cohort, a higher maternal MSDS was associated with a lower likelihood of NDD in the offspring. Furthermore, this association of maternal MSDS with offspring NDD was greater in children born to women with OWO/DM. More studies are needed to replicate the findings and further analyze NDD subgroups and explore underlying molecular pathways.

Keywords: Diet, Neurodevelopmental disabilities, Autism, Attention-deficit/hyperactivity disorder, Pregnancy, Clinical nutrition

Introduction

Maternal nutrition during pregnancy is a critical factor in the neurodevelopment of the offspring. Fetal brain development is rapid and requires high levels of energy, protein, essential fatty acids, and key micronutrients.[1] A maternal diet that is deficient in essential nutrients or severely imbalanced may affect fetal genetic programming and expression and lead to an inflammatory response that can affect brain development.[2] Evidence based on animal, epidemiological, and genetic studies suggests that immune dysregulation affects brain development and is associated with many neurodevelopmental disabilities (NDD) such as autism and attention-deficit/hyperactivity disorder (ADHD).[3,4] In addition to maternal nutritional status, evidence

The data, data dictionary, and analytical programs used in this study are not currently available to the public. However, they can be made available upon reasonable request and after the review and approval of the Institutional Review Boards. The source code to replicate the results will be provided upon request.

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also showed that maternal overweight/obesity (OWO) and diabetes mellitus (DM) may increase the likelihood of NDD among offspring through immune and metabolic dysregulation.[5–8]

There are two acknowledged models for how society views disabilities, including the medical model and the social model. Traditionally, the medical model views disability as a defect within the individual and that these defects should be cured, fixed, and/or eliminated, while the social model values the collective richness and diversity that disabilities bring and calls for an end to discrimination and oppression against disabled people through education, accommodation, and universal design.[9] Efforts to shift from the traditional medical model to the social model helps bring attention to the unconscious bias of the medical model and awareness of the need to advocate for full inclusion and equality of all people within society.

In recognition of the valid and unique experience of each disabled person, there is no universal language to describe disabilities. In this study, we used the term neurodevelopmental disabilities to describe individuals with diagnoses of autism, ADHD, and other neurodevelopmental disabilities and to emphasize the potential barriers they face as identified in the social model of disability.

The prevalence of NDD in children is over 15% worldwide.[10] Results from the National Health Interview Survey (NHIS) indicated that from 2015 to 2017, the prevalence of NDD among US children aged 3 to 17 years was 17.8%.[11] About 1 in 44 US children aged 8 years were autistic in 2018[12]; and approximately 6 million US children (9.8%) aged 3 to 17 years were diagnosed with ADHD from 2016 to 2019.[13] The underlying reasons for the rising diagnoses of NDD are not completely understood, while increased awareness of NDD and more screening efforts may have contributed to the increase.

A Mediterranean-style diet (MSD), which is characterized by a moderate daily intake of grains, vegetables, fruits, low-fat dairy products, olive oil, nuts, and wine, weekly intake of fish and legumes, and limited meat intake, is considered to be a healthy dietary pattern that has long been considered to have various positive health outcomes.[14–19] Adherence to a MSD has been associated with methylation changes in inflammation-related genes[20] and the generation of antioxidant and anti-inflammatory effects.[21] A MSD has also been associated with improved cognition in adults,[22] reductions in cardiovascular/chronic heart disease mortality and morbidity,[23] improvement of components of metabolic syndrome,[24] and decreased incidence of DM.[25] A multicenter randomized trial showed that a simple, individualized MSD during pregnancy has the potential to reduce gestational weight gain and the risk of gestational diabetes.[26] Many studies have explored the association of maternal dietary patterns with birth outcomes.[27] However, despite the potential of a MSD to improve maternal inflammatory status and to affect the neurodevelopment of the offspring, studies of the effects of maternal MSD on NDD have been limited. Most previous studies have only focused on the effects of the consumption of specific food groups or micronutrients on offspring neurodevelopment, though a broader understanding of maternal dietary patterns could provide a more accurate assessment of offspring nutritional status. In this study, we used a prospective birth cohort to explore the association of maternal MSD with NDD in offspring, especially in groups of women at high risk of metabolic disorders including OWO and/or DM, to better understand the potential association of maternal dietary patterns with offspring neurological development.

Methods

Study population

This study included 3153 mother–child pairs, a subset of the Boston Birth Cohort (BBC) recruited at birth at Boston Medical Center (BMC) from 1998 to 2018, who had at least one postnatal follow-up. The BBC was initially designed as a molecular epidemiologic study of the determinants of low birthweight (LBW) and preterm birth (PTB).[28] The BBC enrolled mothers who delivered a singleton live birth. For every PTB and/or LBW infant, two term and appropriate for gestation age (AGA) birthweight infants were enrolled. Exclusion criteria for enrollment included multiple-gestation pregnancy, pregnancies resulting from *in vitro* fertilization, PTB due to maternal trauma, and newborns with major birth defects.

Mothers provided written informed consent within 24 to 72 hours of delivery and were interviewed by trained research staff using a standardized questionnaire. Clinical information and birth outcomes were abstracted from electronic medical records (EMRs). Children who continued to seek postnatal care at BMC were followed. The study was approved by the Institutional Review Boards of Johns Hopkins Bloomberg School of Public Health and Boston Medical Center.

Diagnosis of neurodevelopmental disabilities

We defined five NDD groups based on physician diagnoses as documented in EMRs. The EMRs for BBC participants consist of all primary care and subspecialty visits at BMC since January 2004. Both International Classification of Diseases-9 (ICD-9) codes (before October 1, 2015) and ICD-10 codes (after October 1, 2015) were used to document the primary and secondary diagnoses at each visit. Cases were defined as follows: children ever diagnosed with autism (ICD-9: 299.0-299.91; ICD-10: F84.0-F84.9) constituted the autism group; children ever diagnosed with ADHD (ICD-9: 314.0-314.9; ICD-10: F90.0-F90.9) but without autism constituted the ADHD group; children ever diagnosed with dyslexia, dyscalculia, dyspraxia, or developmental delays (ICD-9: 315.0-315.9; ICD-10: F80.0-F81.89, F88-F89, R48.0, H93.25) but without autism and ADHD constituted the other developmental disabilities (other DD) group; children ever diagnosed with autism, ADHD, or other DD constituted the NDD group; and children without any of the aforementioned diagnoses in their EMRs were assigned to the typically developing (TD) group.

Definition of Mediterranean-style diet score

Among the 3165 mother–child pairs, dietary data were available for 3153 mothers. Food frequency questionnaires (FFQ) [Supplementary Table S1, http://links.lww.com/PN9/A27] administered at the postpartum interview included questions about the mother's weekly intake of multiple foods during pregnancy. The foods ultimately selected for analysis were green vegetables, orange vegetables, fruits, meat, fish, eggs, beans, rice, dairy, and wheat (pasta, bread, and cereal). Questions regarding other foods including shellfish, soy, seeds, peanuts, nuts, and juice consumption were added as an update to the FFQ and therefore were not considered during the analysis. The detailed method

for calculating the Mediterranean-style diet score (MSDS) has been described previously.[23] Briefly, there are different frequencies for every selected food group consumed weekly, including 6 to 7 days, 3 to 5 days, 1 to 2 days, and none. To calculate the MSDS, we assigned a score to each selected food group based on days per week that the selected food groups were consumed (0 = none; 1 = <1 day; 2 = 1–2 days; 3 = 3–5 days; 4 = 6–7 days). Based on a MSD characterized by little to no meat intake, all selected food groups were positively scored except for meat.[29] For data analysis, in addition to analyzing the MSDS as a continuous variable, we identified and compared quintiles of the MSDS with the first quintile (ie, lowest MSDS) as the reference.

Definition of covariates

This study carefully considered and controlled for prenatal and perinatal factors that are known or suspected to affect the likelihood of offspring NDD. Covariates used for adjustment in the model included race and ethnicity,[30] education,[31] marital status,[32] maternal age,[33] alcohol use,[34] ever smoking,[7] DM,[5] preeclampsia,[35] pre-pregnancy body mass index (BMI),[5] parity,[36] plasma folate and vitamin B12 levels,[37] child sex,[38] PTB,[33] and LBW.[33] Since sugar intake (from added sugars *vs.* naturally occurring sugars (ie, fruits)) is also an important component of dietary assessment, we also included soft drink consumption as a covariate.

The self-identified race and ethnicity of the study groups was categorized into four groups: non-Hispanic Black (African American and Haitian), non-Hispanic White, Hispanic, and Other (Cape Verdean, Asian, Pacific Islander, More than one race, and Other race). Education was categorized into three groups: lower than high school, high school, and higher than high school. Marital status was categorized into two groups: married and other (divorced, separated, single, and widowed). Parity (number of prior live births) was categorized into 0 and >0. Maternal age in years was used as a continuous variable. Alcohol consumption was defined as a binary variable categorized as ever or never used alcohol anytime from 6 months before pregnancy to delivery. Smoking status during pregnancy was defined as a binary variable categorized as ever or never smoked anytime from 6 months before pregnancy to delivery. Soft drink consumption was categorized into ≤1 cup per month and >1 cup per month during pregnancy. Pre-pregnancy BMI was categorized into overweight/obesity (BMI ≥25 kg/m^2) and normal weight/underweight (BMI <25 kg/m^2). DM was categorized into no DM and preexisting DM/gestational DM. Preeclampsia was categorized into no preeclampsia, mild preeclampsia, and severe preeclampsia. Child sex was defined as sex assigned at birth (male, female). PTB was defined as delivery at less than 37 completed weeks of gestation. LBW was defined as a birthweight under 2500 g. Plasma folate (nmol/L) was measured using chemiluminescent immunoassay with diagnostic kits (Shenzhen New Industries Biomedical Engineering Co., Ltd., Shenzhen, China) and plasma B12 (pmol/L) was measured using the Beckman Coulter ACCESS Immunoassay System (Beckman-Coulter Canada, Mississauga, Canada) using a MAGLUMI 2000 Analyzer.

We performed simple imputation for covariates with missing values with proportions not exceeding 5.5% of the total sample size. For categorical variables, we imputed the missing values to the group with the highest frequency; and for continuous variables, such as BMI, we imputed missing values based on race-specific mean values. Although annual household income is also a potentially relevant factor in the development of NDD, it was not considered in this study due to the proportion of missing values higher than 10.0%.

Statistical analysis

Descriptive statistics were performed for comparisons of the covariates across quintiles of MSDS. The normality assumption of continuous variables was tested using histograms and the Shapiro–Wilk test (rejected null hypothesis of normality if $P < 0.05$). Normally distributed continuous variables were reported as means and standard deviation (SD). Nonnormally distributed continuous variables were reported as medians and interquartile ranges (IQRs). Categorical variables were reported as numbers and percentages. The Kruskal-Wallis test was performed to compare continuous variables. Pearson's chi-squared test/Fisher's exact test was used to compare categorical variables. The maternal and child characteristics of the study children by the five groups (NDD, autism, ADHD, other DD, and TD) were also compared using Pearson's chi-squared test/Fisher's exact test and the Kruskal-Wallis test for categorical and continuous variables, respectively.

The maternal MSDSs included a small number of outliers [Supplementary Figure S1, http://links.lww.com/PN9/A27]. Considering that data from women with very low or high MSDSs may be informative, a MSDS at the 0.5% level (MSDS = 12) was assigned to individuals with MSDSs below 12 and a MSDS at the 99.5% level (MSDS = 35) was assigned to individuals with MSDSs above 35. Following this process, we analyzed maternal MSDS first as a categorical variable based on quintiles (ie, quintile 1: ≤21, 2: 21–24, 3: 24–26, 4: 26–28, 5: >28) using the lowest quintile as the reference, and second as a continuous variable to test for a linear trend. Due to fluctuations in the data, we also combined quintile groups 3 through 5 for additional analysis. In the overall sample, unadjusted and adjusted logistic regression models were performed to explore the association of maternal MSDS with offspring NDD, autism, ADHD, and other DD. For adjusted logistic regression analyses, two stages of adjustment were used. In model A, we adjusted for MSDS (continuous or categorical), race and ethnicity, education, maternal age, parity, marriage status, pre-pregnancy BMI, DM, preeclampsia, smoking, alcohol consumption, soft drink consumption, child sex, LBW, and PTB. In model B, we additionally adjusted for plasma folate and vitamin B12 levels. We removed individuals from the analyses if they were missing data for any covariate included in the regression model.

Since consumption of a MSD is considered to generate antioxidant and anti-inflammatory effects, we might expect any beneficial effects on child neurodevelopment to be greatest among offspring of mothers with OWO/DM, since they are at higher risk for oxidative stress and immune or metabolic disturbances.[5,6,8] Due to the proven combined effects of OWO and DM on offspring NDD,[5] we combined maternal OWO and DM into a binary variable (without OWO or DM *vs.* with OWO and/or DM) for further analyses. We stratified the analyses of OWO/DM status (dichotomized) to explore the potential effect modification of maternal OWO/DM on the association between MSDS and offspring NDD. Among women with OWO/DM, we further analyzed the association of MSDS with the NDD

subgroups (autism, ADHD, and other DD). To avoid potential bias due to the MSDS outliers, we performed sensitivity analysis after removing women with MSDSs lower than 12 and higher than 35. We also performed sensitivity analyses stratified by maternal smoking, PTB, and LBW. All statistical analyses were performed using R (version 4.2.1).

Results

Population characteristics

A total of 3153 mother–child pairs were included for analyses. The baseline characteristics of mothers (n = 3153) were compared between the MSDS quintiles (**Table 1**). Mothers in quintile 1 (lowest MSDS; n = 637) were more likely to be younger, non-Hispanic White, unmarried (divorced, separated, widowed, and single), and to have fewer years of educational attainment, to have consumed >1 cup of soft drinks per month during pregnancy, and to have lower plasma folate levels overall compared to those in any other quintile. These mothers were also more likely to have smoked or consumed alcohol anytime from 6 months before pregnancy to delivery. The frequency of the mothers' food group intake stratified by MSDS quintiles is shown in Supplementary Table S2, http://links.lww.com/PN9/A27.

Of the 3153 children, we identified 1362 (43.2%) children with NDD, including 123 (3.9%) autistic children, 445 (14.1%) children with ADHD, 794 (25.2%) children with other DD, and 1791 (56.8%) children without any aforementioned NDD diagnoses in their EMRs who were defined as TD. The characteristics of each NDD group are shown in Supplementary Table S3, http://links.lww.com/PN9/A27. Compared with children defined as TD, children with NDD were more likely to be boys, have low birthweight, and to be born preterm; and their mothers were more likely to self-report as non-Hispanic Black, have a lower MSDS, have pre-pregnancy OWO, and smoked cigarettes anytime from 6 months before pregnancy to delivery. Similarly, compared with children defined as TD, autistic children and children with ADHD or other DD were also more

Table 1

Baseline characteristics of mothers in a subset of the Boston Birth Cohort, stratified by MSDS quintiles.

	N (%)	MSDS quintiles				
Baseline characteristics	Total	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
No.	3153	637	760	696	529	531
Maternal age (years)*	28 (23–33)	27 (22–32)	28 (23–33)	28 (23–33)	29 (24–33)	30 (25–35)
Race and ethnicity*						
Non-Hispanic Black†	1849 (58.6)	376 (59.0)	437 (57.5)	408 (58.6)	310 (58.6)	318 (59.9)
Non-Hispanic White	229 (7.3)	73 (11.5)	56 (7.4)	45 (6.5)	31 (5.9)	24 (4.5)
Hispanic	702 (22.3)	129 (20.3)	176 (23.2)	171 (24.6)	123 (23.3)	103 (19.4)
Other‡	373 (11.8)	59 (9.3)	91 (12.0)	72 (10.3)	65 (12.3)	86 (16.2)
Education§						
Less than HS	133 (4.2)	27 (4.2)	27 (3.6)	39 (5.6)	16 (3.0)	24 (4.5)
HS or equivalent	1904 (60.4)	415 (65.1)	474 (62.4)	407 (58.5)	317 (59.9)	291 (54.8)
Greater than HS	1116 (35.4)	195 (30.6)	259 (34.1)	250 (35.9)	196 (37.1)	216 (40.7)
Marriage status*						
Married	1029 (32.6)	149 (23.4)	202 (26.6)	248 (35.6)	201 (38.0)	229 (43.1)
Other	2124 (67.4)	488 (76.6)	558 (73.4)	448 (64.4)	328 (62.0)	302 (56.9)
Pre-pregnancy BMI						
<25 kg/m^2	1438 (45.6)	277 (43.5)	365 (48.0)	313 (45.0)	237 (44.8)	246 (46.3)
≥25 kg/m^2	1715 (54.4)	360 (56.5)	395 (52.0)	383 (55.0)	292 (55.2)	285 (53.7)
Parity						
0	1350 (42.8)	285 (44.7)	325 (46.3)	310 (44.5)	221 (41.8)	209 (39.4)
>0	1803 (57.2)	352 (55.3)	435 (53.7)	386 (55.5)	308 (58.2)	322 (60.6)
Diabetes						
Yes	344 (10.9)	81 (12.7)	79 (10.4)	75 (10.8)	53 (10.0)	56 (10.5)
No	2809 (89.1)	556 (87.3)	681 (89.6)	621 (89.2)	476 (90.0)	475 (89.5)
Preeclampsia						
Mild	128 (4.1)	21 (3.3)	28 (3.7)	31 (4.5)	32 (6.0)	16 (3.0)
Severe	225 (7.1)	52 (8.2)	52 (6.8)	45 (6.5)	33 (6.2)	43 (8.1)
No	2800 (88.8)	564 (88.5)	680 (89.5)	620 (89.1)	464 (87.7)	472 (88.9)
Ever smoking*						
Yes	580 (18.4)	197 (30.9)	146 (19.2)	113 (16.2)	70 (13.2)	54 (10.2)
No	2573 (81.6)	440 (69.1)	614 (80.8)	583 (83.8)	459 (86.8)	477 (89.8)
Alcohol use§						
Yes	251 (8.0)	62 (9.7)	76 (10.0)	37 (5.3)	33 (6.2)	43 (8.1)
No	2902 (92.0)	575 (90.3)	684 (90.0)	659 (94.7)	496 (93.8)	488 (91.9)
Soft drink consumption*						
≤1 cup per month	1390 (44.1)	223 (35.0)	351 (46.2)	324 (46.6)	234 (44.2)	258 (48.6)
>1 cup per month	1763 (55.9)	414 (65.0)	409 (53.8)	372 (53.4)	295 (55.8)	273 (51.4)
Folate (nmol/L)§‖	31 (20–44)	28 (19–41)	32 (22–46)	31 (20–43)	31 (20–45)	32 (21–49)
Vitamin B12 (pmol/L)‖	263 (214–323)	262 (219–318)	269 (213–329)	257 (210–323)	265 (221–311)	261 (208–336)

p values derived using the χ^2 test or Kruskal-Wallis test. Percentages may not add up to 100% due to rounding.

*p value <0.001.

†Includes those who self-identified as African American and Haitian.

‡Includes those who self-identified as non-Hispanic Asian, Cape Verdean, Pacific Islander, more than one race, and other race.

§p value ≤0.05.

‖Included 2068 mothers. BMI, body mass index; HS, high school; MSDS, Mediterranean-style diet score.

likely to be boys, have low birthweight, and be born preterm. The mothers of autistic children were more likely to be older and to have DM. The mothers of children with ADHD were more likely to have lower education, to be unmarried (divorced, separated, widowed, or single), to have pre-pregnancy OWO, to have smoked cigarettes anytime from 6 months before pregnancy to delivery, and to have a lower level of plasma folate. The mothers of children with other DD were more likely to be older, to self-report as non-Hispanic Black, to have pre-pregnancy OWO, and to have experienced mild/severe preeclampsia.

Associations between maternal MSDS and NDD, autism, ADHD, and other DD

Compared to the mothers of children in the TD group, those with children in the NDD, autism, ADHD, and other DD groups were more likely to have lower MSDSs (**Figure 1**). As shown in **Table 2** and **Figure 2**, the unadjusted logistic regression models showed that a high maternal MSDS (per SD increase) was associated with lower odds of offspring NDD (unadjusted odds ratio [OR]: 0.919, 95% confidence interval [CI]: 0.856–0.986; *P* value: 0.019) and other DD (unadjusted OR: 0.916, 95% CI: 0.842–0.996; *P* value:0.040). Using MSDS quintile 1 as the reference, having a maternal MSDS in quintile 3 (unadjusted OR: 0.770, 95% CI: 0.620–0.957; *P* value:0.019), quintile 5 (unadjusted OR: 0.750, 95% CI: 0.594–0.947; *P* value:0.016), or the combined group of quintiles 3 to 5 (unadjusted OR: 0.806, 95% CI: 0.671–0.967; *P* value:0.020) was associated with lower odds of offspring NDD; and having a maternal MSDS in quintile 5 (unadjusted OR: 0.748 95% CI: 0.567–0.984; *P* value:0.039) or the combined group of quintiles 3 to 5 (unadjusted OR: 0.803, 95% CI: 0.649–0.995; *P* value:0.044) was associated with lower odds of offspring other DD. Maternal MSDSs (whether analyzed as a categorical or continuous variable) were not associated with autism or ADHD in the offspring.

After controlling for covariates (model B), a high maternal MSDS (per SD increase) was still associated with lower odds of offspring NDD (adjusted OR: 0.907, 95% CI: 0.824–0.998; *P* value: 0.045). Using maternal MSDS quintile 1 as the reference, in model B, having a maternal MSDS in quintile 3 (adjusted OR: 0.739, 95% CI: 0.556–0.982; *P* value: 0.037), quintile 5 (adjusted OR: 0.720, 95% CI: 0.527–0.983; *P* value: 0.039) or in the combined group of quintiles 3 to 5 (adjusted OR: 0.769, 95% CI: 0.602–0.983; *P* value: 0.036) was associated with lower odds of offspring NDD; while having a maternal MSDS in quintile 5 (adjusted OR: 0.682, 95% CI: 0.474–0.978; *P* value: 0.038), or in the combined group of quintiles 3 to 5 (adjusted OR: 0.745, 95% CI: 0.562–0.989; *P* value:0.041) was associated with lower odds of offspring other DD. Again, maternal MSDSs (whether analyzed as a categorical or continuous variable) were not associated with autism or ADHD in the offspring.

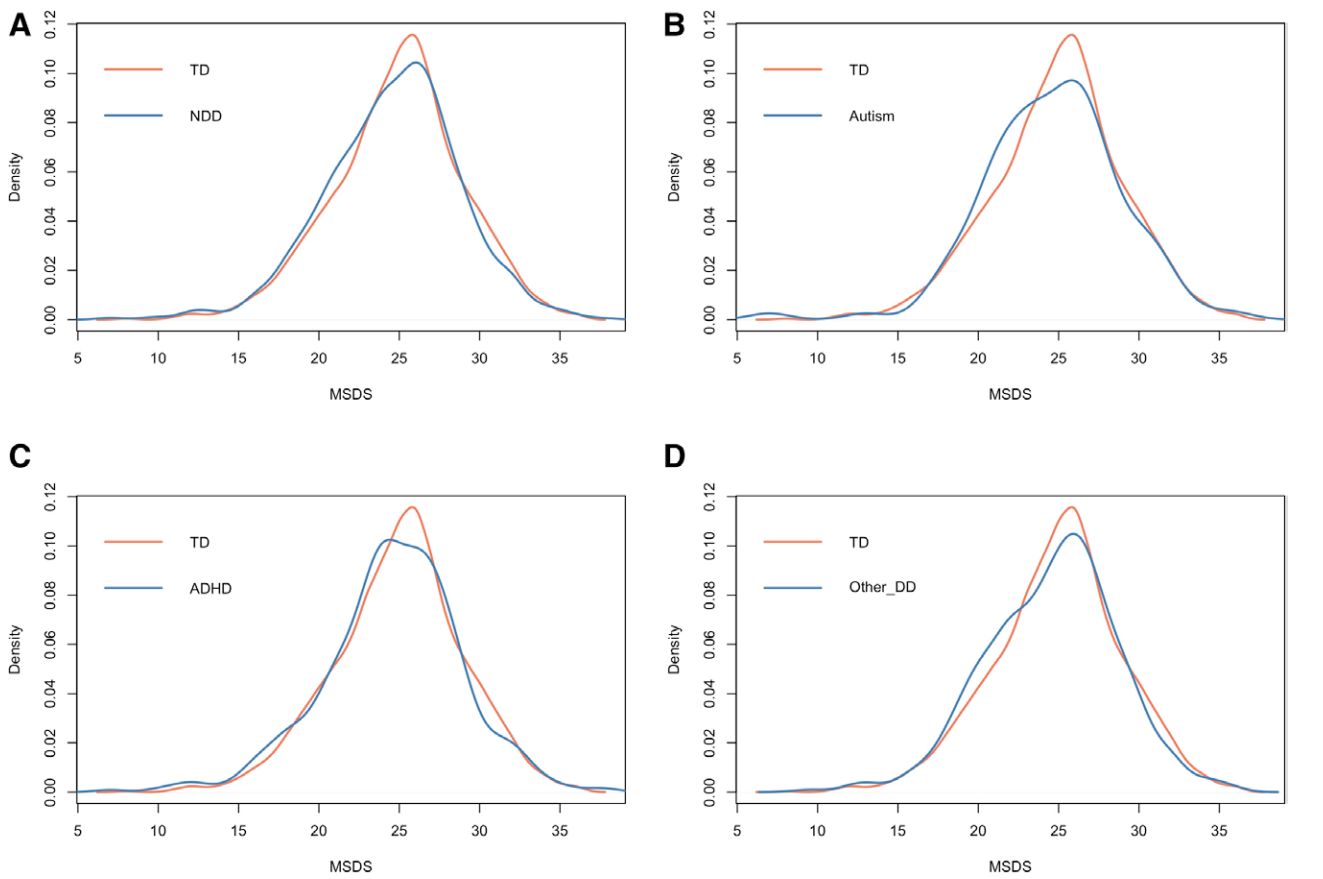

Figure 1: MSDS distribution between participants categorized as TD *vs.* with NDD (A). MSDS distribution between those categorized as TD *vs.* with autism (B). MSDS distribution between those categorized as TD *vs.* with ADHD (C). MSDS distribution between those categorized as TD *vs.* with other DD (D). ADHD, attention-deficit/hyperactivity disorder; DD, developmental disabilities; MSDS, Mediterranean-style diet score; NDD, neurodevelopmental disabilities; TD, typically developing.

Table 2

Unadjusted and adjusted associations of maternal Mediterranean-style diet score with NDD, autism, ADHD, and other DD in offspring.

	TD	NDD			Autism			ADHD			Other DD		
Characteristics	**n**	**n**	**OR (95%CI)**	***P***	**n**	**OR (95%CI)**	***P***	**n**	**OR (95%CI)**	***P***	**n**	**OR (95%CI)**	***P***
MSDS (per 1 SD increase)													
Unadjusted	1791	1362	0.919 (0.856–0.986)	0.019	123	0.933 (0.777–1.122)	0.459	445	0.919 (0.829–1.019)	0.109	794	0.916 (0.842–0.996)	0.040
Model A*	1791	1362	0.939 (0.870–1.012)	0.099	123	0.926 (0.757–1.133)	0.451	445	0.998 (0.892–1.117)	0.969	794	0.918 (0.840–1.003)	0.058
Model B†	1146	922	0.907 (0.824–0.998)	0.045	86	0.874 (0.679–1.128)	0.299	300	0.950 (0.823–1.097)	0.483	536	0.896 (0.801–1.001)	0.053
MSDS quintiles													
Unadjusted													
Q1	339	298	Ref		28	Ref		93	Ref		177	Ref	
Q2	424	336	0.901 (0.730–1.113)	0.336	31	0.885 (0.520–1.512)	0.652	119	1.023 (0.754–1.392)	0.884	186	0.840 (0.654–1.070)	0.173
Q3	415	281	0.770 (0.620–0.957)	0.019	25	0.729 (0.415–1.275)	0.268	86	0.755 (0.545–1.047)	0.092	170	0.785 (0.608–1.012)	0.062
Q4	293	236	0.916 (0.727–1.155)	0.459	20	0.826 (0.450–1.491)	0.530	80	0.995 (0.709–1.394)	0.978	136	0.889 (0.676–1.167)	0.398
Q5	320	211	0.750 (0.594–0.947)	0.016	19	0.719 (0.389–1.304)	0.283	67	0.763 (0.537–1.080)	0.129	125	0.748 (0.567–0.984)	0.039
Q3–Q5‡	1028	728	0.806 (0.671–0.967)	0.020	64	0.754 (0.480–1.211)	0.229	233	0.826 (0.632–1.086)	0.166	431	0.803 (0.649–0.995)	0.044
Model A*													
Q1	339	298	Ref		28	Ref		93	Ref		177	Ref	
Q2	424	336	0.952 (0.763–1.188)	0.664	31	0.842 (0.480–1.482)	0.547	119	1.156 (0.836–1.601)	0.382	186	0.859 (0.663–1.113)	0.249
Q3	415	281	0.799 (0.636–1.004)	0.054	25	0.650 (0.358–1.172)	0.152	86	0.842 (0.596–1.190)	0.330	170	0.776 (0.595–1.011)	0.061
Q4	293	236	0.995 (0.779–1.271)	0.969	20	0.892 (0.469–1.671)	0.722	80	1.232 (0.858–1.769)	0.258	136	0.934 (0.703–1.240)	0.637
Q5	320	211	0.818 (0.638–1.048)	0.112	19	0.724 (0.374–1.375)	0.327	67	1.022 (0.701–1.487)	0.909	125	0.765 (0.572–1.021)	0.070
Q3–Q5‡	1028	728	0.860 (0.708–1.044)	0.127	64	0.734 (0.451–1.220)	0.221	233	1.000 (0.750–1.341)	0.999	431	0.817 (0.653–1.025)	0.079
Model B†													
Q1	195	194	Ref		17	Ref		62	Ref		115	Ref	
Q2	272	230	0.894 (0.676–1.181)	0.430	25	0.961 (0.488–1.932)	0.910	81	1.012 (0.676–1.520)	0.953	124	0.795 (0.574–1.102)	0.168
Q3	272	202	0.739 (0.556–0.982)	0.037	21	0.702 (0.344–1.446)	0.331	60	0.690 (0.449–1.057)	0.088	121	0.721 (0.518–1.003)	0.052
Q4	201	159	0.863 (0.636–1.170)	0.343	12	0.668 (0.289–1.500)	0.333	53	1.038 (0.661–1.629)	0.872	94	0.842 (0.592–1.195)	0.336
Q5	206	137	0.720 (0.527–0.983)	0.039	11	0.608 (0.255–1.398)	0.247	44	0.856 (0.534–1.364)	0.514	82	0.682 (0.474–0.978)	0.038
Q3–Q5‡	679	498	0.769 (0.602–0.983)	0.036	44	0.668 (0.361–1.280)	0.209	157	0.828 (0.578–1.194)	0.306	297	0.745 (0.562–0.989)	0.041

*Controlled for MSDS (continuous or categorical), race and ethnicity, education, maternal age, parity, marriage status, pre-pregnancy BMI, DM, preeclampsia, smoking and alcohol consumption anytime from 6 months before pregnancy to delivery, soft drinks consumption, child sex, low birthweight, and preterm birth.

†Additionally controlled for plasma folate and vitamin B12 levels.

‡Combined group includes those in quintiles 3, 4, and 5. ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; CI, confidence interval; DD, developmental disabilities; DM, diabetes mellitus; MSDS, Mediterranean-style diet score; NDD, neurodevelopmental disabilities; OR, odds ratio; other DD, other developmental disabilities; TD, typically developing.

Associations of maternal MSDS with NDD stratified by maternal OWO/DM

We then stratified the analyses of maternal MSDS and offspring NDD by maternal OWO/DM status (**Table 3**). Among women with OWO and/or DM, after controlling for covariates (model B), a high maternal MSDS (per SD increase) was associated with lower odds of offspring NDD (adjusted OR: 0.840, 95% CI: 0.739–0.953; *P* value: 0.007). Using quintile 1 as the reference, having a maternal MSDS in quintile 3 (adjusted OR: 0.604, 95% CI: 0.415–0.877; *P* value: 0.008), quintile 5 (adjusted OR: 0.543, 95% CI: 0.358–0.820; *P* value: 0.004), or the combined group of quintiles 3 to 5 (adjusted OR: 0.643, 95% CI: 0.464—.888; *P* value: 0.008) was associated with lower odds of offspring NDD. Among women with normal or underweight pre-pregnancy BMI who did not have DM, maternal MSDS was not associated with offspring NDD. We performed an interaction analysis to evaluate the effect of maternal OWO/DM on the association between maternal MSDS and offspring NDD. The results showed that among women with MSDSs in quintile 5, the association of maternal MSDS and offspring NDD was modified by maternal OWO/DM status ($P = 0.036$).

Association of maternal MSDS with autism, ADHD, and other DD among women with OWO/DM

We also analyzed the association of maternal MSDS with offspring autism, ADHD, and other DD among women with OWO/DM [Supplementary Table S4, http://links.lww.com/PN9/A27 and **Figure 3**]. After controlling for covariates (model B), a high maternal MSDS (per SD increase) was associated with lower odds of offspring autism (adjusted OR: 0.658, 95% CI: 0.472–0.913; *P* value: 0.013). Using quintile 1 as the reference, having a maternal MSDS in quintile 3 (adjusted OR: 0.314, 95% CI: 0.124–0.773; *P* value: 0.012), quintile 5 (adjusted OR: 0.265, 95% CI: 0.079–0.773; *P* value: 0.020), or in the combined group of quintiles 3–5 (adjusted OR: 0.321, 95% CI: 0.149–0.706; *P* value: 0.004) was associated with decreased odds of offspring autism. Using quintile 1 as the reference, having a maternal MSDS in quintile 3 (adjusted OR: 0.473, 95% CI: 0.269–0.825; *P* value: 0.009) was associated with decreased odds of offspring ADHD. There was no association between maternal MSDS and offspring other DD among women with OWO/DM. We also conducted the same analysis among women without OWO or DM, and no association of maternal MSDS with offspring autism or ADHD was found [Supplementary Table S5, http://links.lww.com/PN9/A27].

Sensitivity analyses

After removing women with MSDSs lower than 12 or higher than 35, the associations of maternal MSDS with offspring NDD, autism, ADHD, and other DD were consistent with the results of the main analyses described above [Supplementary Table S6, http://links.lww.com/PN9/A27]. We also stratified the analyses of maternal MSDS and offspring NDD by maternal cigarette smoking anytime from 6 months before pregnancy to delivery [Supplementary Table S7, http://links.lww.com/PN9/A27], PTB [Supplementary Table S8, http://links.lww.com/PN9/A27], and LBW [Supplementary Table S9, http://links.lww.com/PN9/A27]. The results indicated that

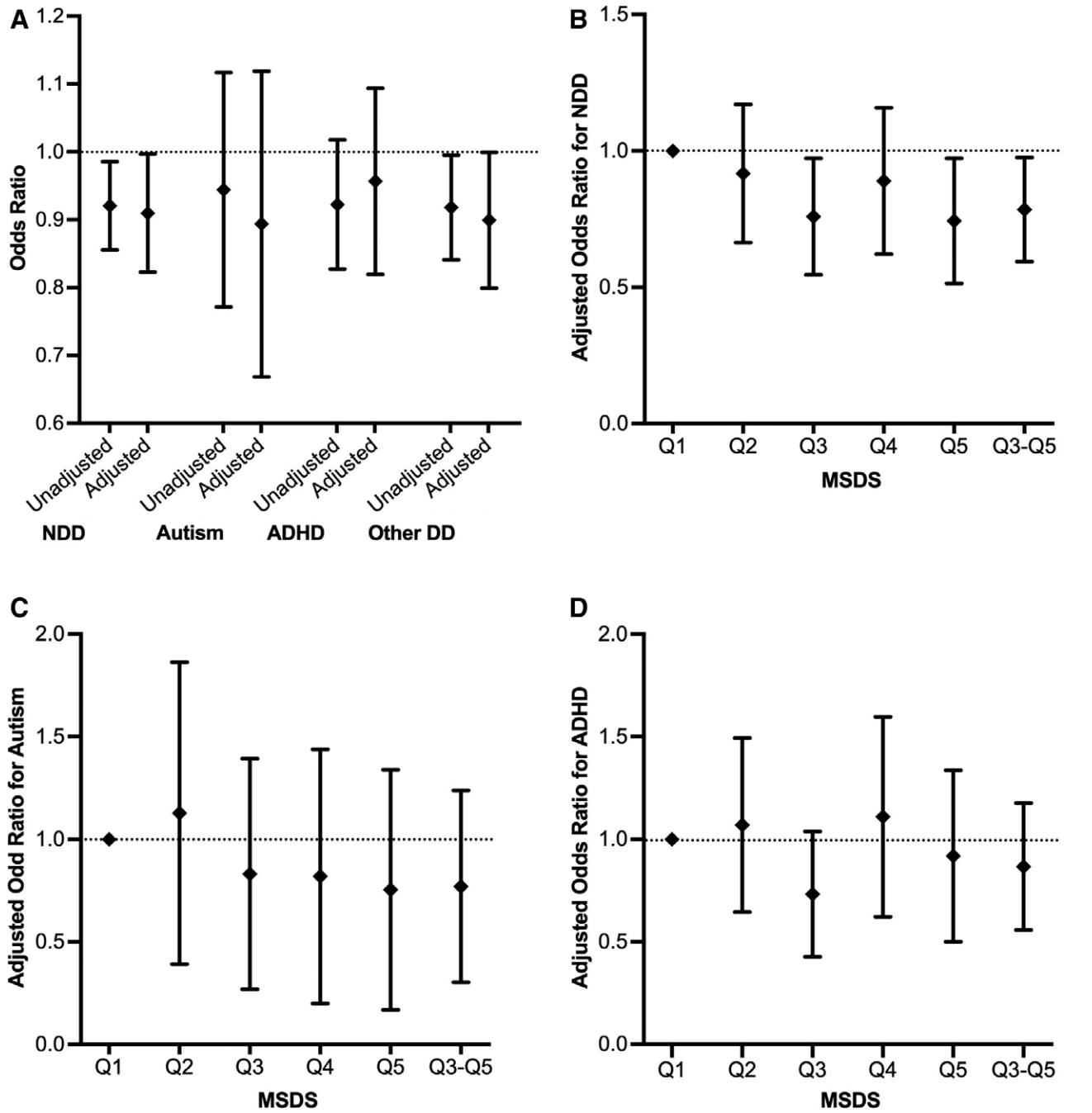

Figure 2: Unadjusted and adjusted ORs for the association of offspring NDD, autism, ADHD, and other DD with MSDSs (A). Adjusted ORs for the association of offspring NDD with MSDSs (B). Adjusted ORs for the association of offspring Autism with MSDSs (C). Adjusted ORs for the association of offspring ADHD with MSDSs (D). ADHD, attention-deficit/hyperactivity disorder; DD, developmental disabilities; MSDS, Mediterranean-style diet score; NDD, neurodevelopmental disabilities; OR, odds ratios.

having higher maternal MSDS was consistently associated with lower odds of offspring NDD among women who reported being nonsmokers, and among women who delivered full-term births and AGA-weight infants. Conversely, possibly due to sample size limitations, we did not identify an association between maternal MSDS and offspring NDD among women who reported being smokers or among women who delivered PTB and LBW infants.

Discussion

In this prospective birth cohort, after controlling for several key potential confounders, a high maternal MSDS showed a lower likelihood of overall NDD and other DD in offspring, while there was no association of maternal MSDS with autism or ADHD in the offspring. In confirmation of our hypothesis, among women with OWO and/or DM, a high maternal MSDS also showed a lower likelihood of NDD in the offspring and this association was greater than that in women without OWO and/or DM. Among women with OWO and/or DM, a high maternal MSDS was also associated with a lower likelihood of autism in the offspring.

Several previous studies have explored the association of maternal dietary patterns with the neurodevelopment of their

Table 3

Adjusted associations between maternal MSDS and NDD in offspring stratified by maternal OWO/DM.

	OWO and/or DM				No OWO or DM				
	Participants	NDD			Participants	NDD			
Characteristics	TD	n	OR (95% CI)	*P*	TD	n	OR (95% CI)	*P*	*P* interaction*
MSDS (per 1 SD increase)									
Model A †	974	818	0.908 (0.823–1.001)	0.053	817	544	0.978 (0.868–1.103)	0.717	0.226
Model B ‡	617	568	0.840 (0.739–0.953)	0.007	529	354	0.983 (0.846–1.143)	0.823	0.065
MSDS quintiles									
Model A†									
Q1	192	186	Ref		147	112	Ref		
Q2	220	195	0.951 (0.710–1.275)	0.738	204	141	0.940 (0.668–1.324)	0.724	0.984
Q3	230	171	0.763 (0.566–1.026)	0.074	185	110	0.827 (0.577–1.185)	0.301	0.664
Q4	156	146	1.025 (0.745–1.411)	0.880	137	90	0.933 (0.635–1.368)	0.722	0.798
Q5	176	120	0.737 (0.531–1.021)	0.067	144	91	0.922 (0.626–1.355)	0.679	0.251
Q3–Q5§	562	437	0.826 (0.642–1.064)	0.138	466	291	0.886 (0.652–1.205)	0.437	0.587
Model B‡									
Q1	99	125	Ref		96	69	Ref		
Q2	140	135	0.780 (0.536–1.132)	0.192	132	95	1.036 (0.674–1.597)	0.871	0.399
Q3	157	127	0.604 (0.415–0.877)	0.008	115	75	0.916 (0.583–1.440)	0.705	0.130
Q4	104	103	0.819 (0.547–1.225)	0.332	97	56	0.839 (0.517–1.358)	0.475	0.880
Q5	117	78	0.543 (0.358–0.820)	0.004	89	59	1.002 (0.616–1.627)	0.993	0.036
Q3–Q5§	378	308	0.643 (0.464–0.888)	0.008	301	190	0.915 (0.622–1.350)	0.652	0.123

*Based on Model B, treating maternal OWO/DM as a binary variable (OWO and/or no OWO or DM) and the MSDS as either a categorical or continuous variable.

†Controlled for MSDS (continuous or categorical), race and ethnicity, education, maternal age, parity, marriage status, preeclampsia, smoking and alcohol consumption anytime from 6 months before pregnancy to delivery, soft drink consumption, child sex, low birthweight, and preterm birth.

‡Additionally controlled for plasma folate and vitamin B12 levels.

§Combined group includes those in quintiles 3, 4, and 5. CI, confidence interval; DM, diabetes mellitus; MSDS, Mediterranean-style diet score; NDD, neurodevelopmental disabilities; OR, odds ratio; OWO, overweight or obesity; TD, typically developing.

offspring.[39–43] A longitudinal study published in 2018 from the United Kingdom showed that pregnant women with a diet rich in fruits and vegetables were more likely to have children (aged 8 years) with higher average IQs.[39] Findings from a birth cohort in China including 1178 mother–child pairs also indicated that high maternal intake of dietary fiber and high-quality protein during mid and late-pregnancy was associated with better gross motor and receptive communication development in offspring aged 1 year.[40] An Australian longitudinal study on women's health including 1554 mother–child dyads indicated that a higher maternal healthy eating index (HEI) in pre-pregnancy was associated with a lower likelihood behavioral disorders in the offspring.[41] Similarly, a French cohort including 1242 mother–child pairs showed that a maternal "low healthy diet" (characterized by low intake of fruits, vegetables, fish, and whole grains) was associated with trajectories of greater ADHD symptomology among the study children.[42] Furthermore, the UK longitudinal study mentioned above showed that a prenatal high-fat and high-sugar diet was positively associated with ADHD symptoms in 83 adolescents with early-onset persistent conduct problems, but not in 81 adolescents with low conduct problems.[43] Although there are differences in maternal dietary measurements, outcome assessment methods, and the results of related studies, a meta-analysis including 18 studies with 63,861 participants showed that better maternal diet quality (fish intake, Omega-6/Omega-3 fatty acid ratio, saturated fat intake, or dietary fiber were used as proxies) during pregnancy had a small association with child neurodevelopment.[44]

Few studies have explored the potential association of maternal MSD with offspring NDD, and the limited available evidence has been inconclusive. Findings from the investigation of another US cohort including 1580 mother–child pairs showed that a higher maternal MSDS was associated with better visual-spatial skills in offspring in early childhood and better intelligence and executive function at mid-childhood.[45] A Dutch cohort study including 3104 child–mother pairs showed that maternal low adherence to a MSD was associated with an increased likelihood of inattention and aggression in their children.[46] In a US neonatal epigenetic study including 325 children, higher perinatal adherence to a MSD was associated with a lower likelihood of autism in the offspring.[47] However, a recent study based on two prospective longitudinal cohorts of more than 800 pregnant women in the US did not find strong evidence that consumption of a MSD among the women was associated with autism in offspring.[48] In our study, a high maternal MSDS was associated with a lower likelihood of overall NDD and other DD in the offspring. Although there was heterogeneity in the NDD and other DD groups, including different categories of neurodevelopmental disabilities, which made the results hard to explain, the results still indicated that a high maternal MSDS might have an influence on neurodevelopment in offspring. The underlying mechanisms should be further explored.

In recent years, there has been increasing evidence of the impact of gene-environment interactions on NDD in offspring.[4] The maternal diet may influence offspring neurodevelopment by affecting epigenetic methylation modifications, microbiome, oxidative stress, and immune response.[49–51] Some essential properties of the MSD have been shown to affect offspring neurodevelopment. For instance, several studies have linked a higher intake of fish (a major dietary source of polyunsaturated fatty acids), which is a characteristic of the MSD, in pregnant women with neurodevelopment in offspring, although recommendations for fish consumption during pregnancy should also consider the potential negative effects of mercury exposure.[52] Polyunsaturated fatty acids may affect the proliferation and differentiation of neural stem cells and the regulation of microglia

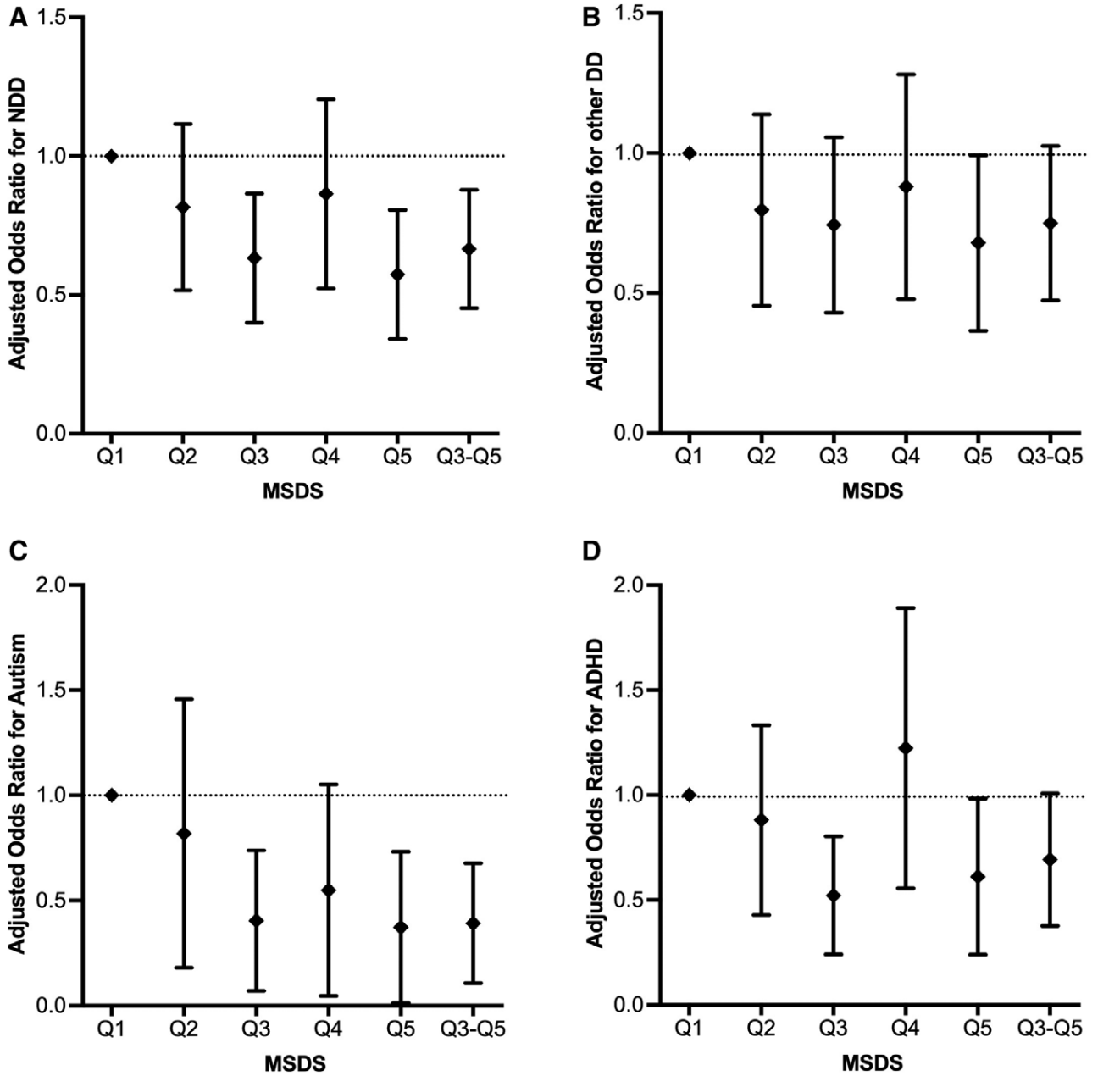

Figure 3: Adjusted ORs for the association of offspring NDD with MSDSs among women with OWO/DM (A). Adjusted ORs for the association of offspring other DD with MSDSs among women with OWO/DM (B). Adjusted ORs for the association of offspring autism with MSDSs among women with OWO/DM (C). Adjusted ORs for the association of offspring ADHD with MSDSs among women with OWO/DM (D). DM, diabetes mellitus; MSDS, Mediterranean-style diet score; NDD, neurodevelopmental disabilities; OR, odds ratios; OWO, overweight/obesity.

and neuroinflammation.[53] Some animal and human studies have also indicated that dietary fiber intake, which is high in the MSD, modulates fetal and early postnatal offspring neurodevelopment by affecting maternal gut microbiome diversity.[54] Fruits and vegetables, which are key food groups of the MSD, are rich in many essential vitamins, including vitamins A, B, and D, which may impact offspring neurodevelopment.[55]

Our results showed that older mothers were more likely to have autistic children or children with other DD, while further analyses did not show interaction effects between maternal age and MSDS on autism and other DD. In the overall sample, after additionally controlling for maternal plasma folate and vitamin B12 levels, a high maternal MSDS was associated with a lower likelihood of NDD among offspring. However, the correlation analysis did not show a significant correlation between maternal MSDS and plasma folate and/or vitamin B12 levels [Supplementary Material, http://links.lww.com/PN9/A27]. We speculate that during pregnancy, women were more likely to use multivitamins or prenatal vitamin supplements regardless of MSD adherence; however, we did not ask them about nutritional guidance from medical providers, including recommendations for consumption of an MSD. Future studies should assess the role of dietary recommendations especially since there is a current lack of clinical nutrition education for physicians.[56,57]

Maternal OWO/DM status has been associated with a higher likelihood of NDD in offspring.[5,58] DNA methylation

modifications of immune genes were found in the cord blood of newborns whose mothers were exposed to OWO/DM, with persistent epigenetic alterations into adulthood.[8] In our study, maternal MSD adherence showed a greater association with NDD in offspring of mothers with OWO/DM compared to mothers without OWO/DM. Among women with the highest MSDSs (quintile 5), the association of MSDS with offspring NDD was modified by maternal OWO/DM status. There was no association of maternal MSDS with autism or ADHD in offspring in the overall sample and in women without OWO or DM, while among women with OWO and/or DM, the results indicated that a high maternal MSDS was associated with a lower likelihood of autism in offspring and having a maternal MSDS in quintile 3 was associated with a lower likelihood of ADHD in the offspring. The underlying mechanisms for how a higher maternal MSDS can impact the effects of OWO/DM on offspring neurodevelopment still require further research; however, due to its associated antioxidant and anti-inflammatory properties, maternal MSD adherence may reduce the likelihood of NDD in offspring by alleviating the inflammatory response and affecting epigenetic methylation modifications in women with OWO/DM.[17,49] Therefore, women with low MSDSs, especially women with OWO/DM, as indicated by our findings, are more likely to have children with NDD. Identifying these women would prompt early screening for NDD in their offspring as well as the provision of needed social supports for both mothers and children. Furthermore, due to the rising prevalence of obesity and diabetes among women of childbearing age, dietary interventions such as the MSD may prove to be a potential protective measure against a range of adverse health outcomes among women.

This study had several strengths. Our study was built on a relatively large sample size and the data collection was conducted by professionally trained research personnel based on standardized protocols. All the study children were delivered and received pediatric care at a single medical center with a uniform EMR system. We identified consistent and significant associations between maternal MSDSs and offspring NDD in the overall sample. We also adjusted for several pertinent sociodemographic variables in the analyses to control for potential confounding.

Our study population, a subset of the BBC, included a high proportion of self-reported non-Hispanic Black women and women with low educational attainment. This is noteworthy in the sense that the findings from this study help to fill in important data gaps for this traditionally understudied population; however, caution is needed to generalize our study's findings to groups with different characteristics.

This study also had some limitations. Information about prenatal maternal diet intake was based on postpartum maternal self-report with possible recall bias and social desirability bias. Diet was assessed according to the frequency of intake of different food groups rather than quantity of consumption; and we did not collect information regarding food quality, preparation methods, and/or access to diverse foods. More information on multiple social and environmental factors that affect women's food choices should be collected in future studies. Food groups and MSD scores were not adjusted for energy intake. However, considering that some women may still have poor dietary habits despite having high MSDSs, we also adjusted for soft drink consumption since it reflects consumption of added sugars in the diet. In addition, this study only considered maternal MSDS and did not adjust for postnatal dietary data for the study children. Maternal MSDSs may be associated with childhood postnatal dietary data, which would affect NDD and thus mediate the observed association between maternal MSDS and NDD in the offspring. We recommend that future studies should collect childhood dietary data to explore potential associations.

Conclusions

In this prospective birth cohort, a higher maternal MSDS was associated with a lower likelihood of NDD in offspring. This association of maternal MSD with offspring NDD was greater in children born to women with OWO/DM. More studies are needed to replicate these findings and further analyze the NDD subgroups, and explore potential underlying molecular pathways. Based on our findings, women of childbearing age should be educated before and during pregnancy about the potential effects of consuming a MSD on the neurodevelopment of their offspring. Consuming a MSD may also reduce maternal OWO and DM, which may affect maternal health. To support this recommendation, we advocate for an increased emphasis on clinical nutrition in medical training, particularly for those who care for women of childbearing age and pregnant women, but also more generally for any medical provider who cares for individuals with OWO and DM. Considering that food choices are affected by multiple individual, social, and environmental factors, it is recommended to increase access to MSD food choices at the community level. We also advocate for identifying women with low MSDSs to prompt early screening of NDD in offspring and to provide early social supports to mothers and children.

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Author Contributions

XC analyzed the data, drafted the initial manuscript, and revised the manuscript. SG and XW conceptualized the study. XW acquired funding. XW, GW, XH, CP, MA supervised field data collection. All the authors critically reviewed and revised the manuscript and approved the final manuscript. XC, SG, and XW agreed to be accountable for all aspects of the work. All authors have read and approved the manuscript.

Conflicts of Interest

The authors report no conflicts of interest.

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