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Association of Gestational Weight Gain and Maternal Body Mass Index in Early Pregnancy With Risk for Nonaffective Psychosis in Offspring

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IMPORTANCE Prenatal exposure to famine is associated with a 2-fold risk for nonaffective psychoses. Less is known about whether maternal nutrition states during pregnancy modify offspring risk for nonaffective psychoses in offspring in well-fed populations.

OBJECTIVE To determine whether gestational weight gain (GWG) during pregnancy and maternal body mass index (BMI) in early pregnancy are associated with risk for nonaffective psychoses in offspring.

DESIGN, SETTING AND PARTICIPANTS This population-based cohort study used data from Swedish health and population registers to follow up 526 042 individuals born from January 1, 1982, through December 31, 1989, from 13 years of age until December 31, 2011. Cox proportional hazards regression models adjusted for socioeconomic status and potential risk factors were used to examine the risk for developing nonaffective psychoses. Family-based study designs were used to further test causality. Data were analyzed from February 1 to May 14, 2016.

EXPOSURES Gestational weight gain during pregnancy, maternal body mass index at the first antenatal visit, and paternal body mass index at the time of conscription into the Swedish military (at 18 years of age).

MAIN OUTCOMES AND MEASURES Hazard ratios (HRs) for the diagnosis of nonaffective psychoses (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*] codes F20 to F29 and *International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 295, 297 and 298, except 298A and 298B) and narrowly defined schizophrenia (*ICD-9* code 295 and *ICD-10* code F20).

RESULTS The 526 042 individuals in the cohort (48.52% female and 51.47% male; mean [SD] age, 26 [2.3] years) included 2910 persons with nonaffective psychoses at the end of follow-up, of whom 704 had narrowly defined schizophrenia. Among the persons with nonaffective psychosis, 184 (6.32%) had mothers with extremely inadequate GWG (<8 kg for mothers with normal baseline BMI), compared with 23 627 (4.52%) of unaffected individuals. Extremely inadequate GWG was associated with an increased risk for nonaffective psychoses among offspring in adjusted models (HR, 1.32; 95% CI, 1.13-1.54) and in matched-sibling analysis (HR, 1.61; 95% CI, 1.02-2.56). Similar patterns were observed when considering narrowly defined schizophrenia as the outcome. Maternal mild thinness in early pregnancy was weakly associated with an increased risk for nonaffective psychosis in offspring (HR for BMI≥17.0 and <18.5, 1.21; 95% CI, 1.01-1.45), as was paternal severe thinness (HR for BMI<16.0, 2.53; 95% CI, 1.26-5.07) in mutually adjusted models. In matched-sibling analysis, no association was observed between maternal underweight (HR, 1.46; 95% CI, 0.90-2.35), overweight (HR, 1.11; 95% CI, 0.73-1.68), or obesity (HR, 0.56; 95% CI, 0.23-1.38) and risk for nonaffective psychosis in offspring.

CONCLUSIONS AND RELEVANCE Inadequate GWG was associated with an increased risk for nonaffective psychosis in offspring, consistent with historical studies on maternal starvation. These findings support the role of maternal undernutrition in nonaffective psychosis pathogenesis.

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Nonaffective psychoses, or schizophrenia spectrum disorders, are increasingly considered neurodevelopmental disorders.[1-5] Prenatal exposure to famine during the Dutch Hunger Winter (1944-1945) was associated with a 2-fold increase in the risk for nonaffective psychosis in offspring.[6-8] Similarly, exposure to prenatal famine during the Chinese Great Leap Forward (1959-1961) led to a 2-fold increased relative risk for schizophrenia.[9,10] Results from such disparate settings demonstrate that maternal malnutrition during pregnancy may increase the risk for psychosis among offspring.[11,12]

Deficits in maternal nutrition during pregnancy, including micronutrient deficiencies (eg, folate, vitamin D, iron) and protein-caloric malnutrition, have been associated with abnormalities in offspring neurodevelopment.[11,13] Obesity, paradoxically, has been associated with deficiencies in nutrients vital to neurodevelopment, such as vitamin A, folate, vitamin D, and essential fatty acids,[14,15] and offspring risk for neural tube defects.[16] A range of maternal nutritional states during pregnancy may contribute to the risk for psychoses in offspring. Khandaker et al[17] reviewed several studies that used maternal body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) as a proxy for maternal nutrition, but these produced conflicting results hampered by low numbers of cases.

This study's aim was to investigate the association among maternal baseline BMI, gestational weight gain (GWG), and offspring risk for nonaffective psychosis in the largest cohort studied to date. We hypothesize that extremes in baseline maternal BMI or GWG, signifying suboptimal prenatal nutrition, would contribute to an increased risk for nonaffective psychosis in offspring. We posit that extremely low GWG is analogous to early gestational exposure to starvation seen in the famine studies. We used 2 family-based study designs—paternal-offspring comparisons and matched-sibling comparisons[18-20]—to evaluate the weight of evidence for any observed associations.

Key Points

Question Are gestational weight gain during pregnancy and maternal body mass index in early pregnancy associated with a risk for nonaffective psychosis in offspring?

Findings In this population-based cohort study of 526 042 individuals born in Sweden from 1982 through 1989, extremely inadequate gestational weight gain was associated with a significantly increased risk for nonaffective psychosis in offspring in adjusted and sibling comparison models. A weak, U-shaped association was found between maternal body mass index at the beginning of pregnancy and risk for nonaffective psychosis in offspring in adjusted models.

Meaning Insufficient weight gain during pregnancy may increase the risk for nonaffective disorders in offspring, even in an affluent and well-nourished population.

Methods

Study Design

This national, population-based cohort study used data from Psychiatry Sweden, a linkage of Swedish health and population registers.[21] Ethical approval was granted by the Regional Ethical Committee of Stockholm. No informed consent was required for the analysis of anonymized register data.

Study Population

The study population included all nonadopted individuals born in Sweden from January 1, 1982, through December 31, 1989 (n = 798 934), who were followed up from 13 years of age until December 31, 2011, for diagnoses of nonaffective psychoses.[21] Children were excluded who died or emigrated before their 13th birthday (2.7%), had incomplete Medical Birth Register data (0.4%), were missing information on their biological father (0.5%), or were part of multiple births (1.9%) (eFigure 1 in the Supplement). In addition, 30.2% of eligible mother-child pairs lacked maternal BMI or GWG data. Those individuals excluded from the final study population were demographically similar to those included (eTable 1 in the Supplement).

Variables

Diagnoses of Nonaffective Psychoses

Data on psychiatric history were taken from the National Patient Register, which has been collecting diagnoses for inpatient care since 1973 and psychiatric outpatient care since 2001. Nonaffective psychosis status was defined as receipt of 1 of the following diagnoses from *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*), or *International Classification of Diseases, Ninth Revision* (*ICD-9*): *ICD-10* codes F20 to F29 and *ICD-9* codes 295, 297, and 298 (except 298A and 298B) (eTable 2 in the Supplement) before December 31, 2011.[21] Narrowly defined schizophrenia (*ICD-9* code 295 and *ICD-10* code F20) was also considered as an outcome.

Exposure: Maternal BMI and GWG

Maternal weight and height at the first antenatal visit were used to approximate baseline maternal BMI. Such data were recorded by midwives in the Medical Birth Register beginning in 1982. The timing of the first antenatal visit was unavailable. However, first trimester weight gain was on average low, and 90% of initial antenatal visits in Sweden occurred before 12 weeks' gestation.[22,23] Weights of less than 40 kg or greater than 140 kg were censored as unrealistic or indicating an existing medical condition, as were heights of less than 140 cm or greater than 210 cm. Maternal baseline BMI values were categorized according to World Health Organization guidelines[24] into standard and extended BMI classifications.

Maternal weight was also recorded before delivery. Gestational weight gain was calculated as the difference in maternal weight between the first antenatal visit and delivery. Based on Institute of Medicine guidelines,[25] GWG was categorized as ideal, inadequate, or excessive according to the maternal baseline BMI categories of underweight (12.5-18.0 kg), normal weight (11.5-16.0 kg), overweight (7.0-11.5 kg), and

obese (5.0-9.0 kg). The GWG categories of inadequate and excessive were divided at their respective medians (by BMI category) to create the following 5 extended GWG categories (eTable 3 in the Supplement): ideal, extremely inadequate, inadequate, excessive, and extremely excessive.

Exposure: Paternal BMI

Paternal BMI was calculated from Swedish conscription register data, collected since 1969. Weight and height were measured objectively at the time of conscription into the Swedish military (at 18 years of age). Measurements were censored and categorized as with maternal BMI. Of the offspring with maternal BMI data, 64.74% also had paternal BMI data and are considered as the paternal BMI subcohort (eFigure 1 in the Supplement).

Covariates

Covariates were considered as potential confounders based on current literature. The following covariates were included in the study and classified as in Blomström et al[21]: birth year, offspring sex,[3] household income at birth (in quintiles, with highest quintile as the reference category),[26] highest level of parental education achieved, single-parent household status,[26] urban birth (child born in a municipality with ≥200 000 inhabitants in 1980),[27] parental immigration status (categorized as 0-2 parents born outside Sweden),[28] parent older than 35 years at the time of birth (0-2 parents),[29] parental nonaffective psychosis diagnosis (0-2 parents), and parental history of psychiatric care (0-2 parents).[30]

Statistical Analysis

BMI and Nonaffective Psychoses

Data were analyzed from February 1 to May 14, 2016. Statistical analyses were performed using STATA/IC software (version 14.1; StataCorp). We analyzed BMI as a categorical variable, then a continuous variable, using Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% CIs for nonaffective psychosis (or schizophrenia) in offspring with robust SEs to account for clustering of observations with mothers. Offspring were followed up from 13 years of age until the diagnosis of nonaffective psychosis, emigration, death, or December 31, 2011, whichever came first. Basic HRs were adjusted for birth year and sex of offspring. The final model for BMI was adjusted for birth year, offspring sex, family income quintile, parent older than 35 years, parental history of nonaffective psychosis, and parent born outside Sweden. Parental educational level was not included in the model owing to colinearity with income quintile. Normal BMI was the reference category in categorical analyses. Categorical analyses were repeated with extended BMI categories.

For continuous analyses, we fit Cox proportional hazards regression models using restricted cubic splines with 5 knots. Restricted cubic spline models allow for the flexible fitting of nonmonotonic associations between variables.[31] Postestimation xbrcspline[31] was used, with the reference category set as BMI of 21.0, denoting minimal risk.[22]

GWG and Nonaffective Psychoses

Similar to BMI, GWG was also analyzed as a categorical (reference category, ideal GWG) and continuous (reference category, 11 kg) variable. Models were adjusted as described above for BMI. Additional models considered maternal baseline BMI and gestational age as covariates. Continuous analysis was repeated with stratification by maternal BMI category.

Sibling Analyses

Matched-sibling analyses comparing affected individuals with their unaffected full siblings were performed to investigate whether observed associations among maternal BMI and GWG and offspring nonaffective psychosis could be the result of confounding by shared familial factors. Narrowly defined schizophrenia was not considered as an outcome in sibling analyses owing to lack of power. Cox proportional hazards regression, stratified by family identity, was performed for matched full siblings, discordant on outcome, adjusted for birth order and sex. We considered BMI and GWG as categorical and continuous exposures as above.

Sensitivity Analyses

Analyses of maternal and paternal BMI were repeated among those individuals with a paternal BMI observation (paternal BMI subcohort) and were analyzed individually as above and in a mutually adjusted model. Finally, the main analyses were repeated stratified by sex.

Results

Study Cohorts

The 526 042 individuals in the study cohort (48.52% female and 51.47% male; mean [SD] age, 26 [2.3] years) included 2910 cases of nonaffective psychoses at the end of follow-up. As expected, offspring who developed nonaffective psychosis or narrowly defined schizophrenia were more likely to be male and to be born in an urban center or to a single parent, an immigrant, or a parent with a history of psychiatric care compared with unaffected offspring (**Table 1** and eTable 4 in the Supplement). In the paternal BMI subcohort, offspring were less likely to have a foreign-born parent compared with the full cohort and were less likely to have a parent 35 years or older, because the conscription register began in 1969 (eTable 1 in the Supplement). Covariates by maternal BMI and GWG categories are presented in eTables 5 and 6 in the Supplement.

Maternal BMI and Nonaffective Psychosis Risk

In the categorical analysis (**Table 2**), offspring of underweight mothers displayed a somewhat increased risk for nonaffective psychosis (adjusted HR, 1.14; 95% CI, 1.00-1.30). In the analysis of extended BMI categories, offspring of mothers with mild thinness (BMI≥17.0 and <18.5) had an increased risk for nonaffective psychosis (adjusted HR, 1.21; 95% CI, 1.06-1.39), as did offspring of mothers with class 2 obesity (BMI≥35.0 and <40.0; adjusted HR, 1.93; 95% CI, 1.00-3.71).

Similarly, in continuous analysis of maternal BMI (**Figure 1**), we observed a U-shaped association between maternal BMI and

Table 1. Characteristics of Psychiatry Sweden Cohort and Each Subcohort

Characteristic	Study Cohort, No. (%)					
	Full		Paternal BMI		Matched-Sibling	
	No Diagnosis of Nonaffective Psychosis	Diagnosis of Nonaffective Psychosis	No Diagnosis of Nonaffective Psychosis	Diagnosis of Nonaffective Psychosis	No Diagnosis of Nonaffective Psychosis	Diagnosis of Nonaffective Psychosis
All	523 132 (99.45)	2910 (0.55)	338 942 (99.52)	1632 (0.48)	1193 (53.28)	1046 (46.72)
Sex						
Female	254 093 (48.57)	1167 (40.10)	164 539 (48.54)	663 (40.62)	549 (46.02)	410 (39.20)
Male	269 039 (51.43)	1743 (59.90)	174 403 (51.46)	969 (59.38)	644 (53.98)	636 (60.80)
Income quintile						
First (lowest)	102 433 (19.58)	661 (22.71)	64 674 (19.08)	376 (23.04)	392 (32.86)	315 (30.11)
Second	104 609 (20.00)	605 (20.79)	71 822 (21.19)	355 (21.75)	292 (24.48)	254 (24.28)
Third	105 284 (20.12)	585 (20.10)	71 649 (21.14)	337 (20.65)	223 (18.69)	213 (20.36)
Fourth	105 969 (20.26)	545 (18.73)	68 996 (20.36)	301 (18.44)	166 (13.91)	130 (12.43)
Fifth (highest)	104 837 (20.04)	514 (17.66)	61 801 (18.23)	263 (16.12)	120 (10.06)	134 (12.81)
Highest level of education achieved, either parent						
Doctorate	7318 (1.40)	38 (1.31)	3716 (1.10)	18 (1.10)	16 (1.34)	13 (1.24)
Master's degree	172 301 (32.94)	926 (31.82)	107 215 (31.63)	519 (31.80)	413 (34.62)	370 (35.37)
University degree	31 056 (5.94)	156 (5.36)	22 662 (6.69)	98 (6.00)	57 (4.78)	50 (4.78)
10-12 y	260 126 (49.72)	1390 (47.77)	176 585 (52.10)	806 (49.39)	559 (46.86)	492 (47.04)
9 y	44 032 (8.42)	319 (10.96)	27332 (8.06)	179 (10.97)	130 (10.90)	102 (9.75)
<9 y	8299 (1.59)	81 (2.78)	1432 (0.42)	12 (0.74)	18 (1.51)	19 (1.82)
Birthplace						
Urban	80 303 (15.35)	525 (18.04)	47 109 (13.90)	263 (16.12)	200 (16.76)	186 (17.78)
Nonurban	442829 (84.65)	2385 (81.96)	291833 (86.10)	1369 (83.88)	993 (83.24)	860 (82.22)
Maternal partner status at time of birth						
Single	50 349 (9.62)	518 (17.80)	29 805 (8.79)	272 (16.67)	129 (10.81)	109 (10.42)
Partner	472 783 (90.38)	2392 (82.20)	309 137 (91.21)	1360 (83.33)	1064 (89.19)	937 (89.58)
Parent born outside Sweden						
Mother	52 310 (10.00)	461 (15.84)	18 357 (5.42)	129 (7.90)	146 (12.24)	126 (12.04)
Father	55 643 (10.64)	524 (18.01)	10 533 (3.11)	83 (5.09)	176 (14.75)	151 (14.44)
Parent age >35 y at time of birth						
Mother	55 772 (10.66)	380 (13.06)	12 971 (3.83)	70 (4.29)	137 (11.48)	96 (9.18)
Father	135 935 (25.98)	860 (29.55)	27 425 (8.09)	107 (6.56)	348 (29.17)	256 (24.47)
Parental psychosis diagnosis						
Mother	4369 (0.84)	132 (4.54)	2349 (0.69)	65 (3.98)	38 (3.19)	38 (3.63)
Father	3599 (0.69)	98 (3.37)	1976 (0.58)	46 (2.82)	36 (3.02)	33 (3.15)
Parental inpatient history of psychiatric care						
Mother	43 587 (8.33)	596 (20.48)	26 037 (7.68)	323 (19.79)	216 (18.11)	187 (17.88)
Father	48 085 (9.19)	577 (19.83)	27 801 (8.20)	310 (19.00)	221 (18.52)	198 (18.93)

nonaffective psychosis among offspring in crude or adjusted models, although with wide CIs. Maternal underweight was usually associated with schizophrenia; no association was apparent between elevated maternal BMI and schizophrenia risk (Figure 1). In matched-sibling analyses, we found little apparent association between maternal BMI and offspring nonaffective psychosis in categorical (Table 2) or continuous analysis (Figure 1).

GWG and Nonaffective Psychosis Risk

Normal-weight and underweight mothers were more likely to gain weight within their recommended ranges (44.59% and 56.52%, respectively), compared with overweight (26.91%) and obese (34.20%) mothers (eTable 7 in the Supplement). Broad GWG categories were not associated with offspring nonaffective psychosis (**Table 3**). For extended GWG categories, the offspring of mothers with extremely inadequate weight gain had

Table 2. Associations Between Nonaffective Psychosis and Maternal BMI in Full and Matched-Sibling Cohorts

	Full Cohort			Matched-Sibling Cohort	
BMI Category	No. of Noncases/Cases With Nonaffective Psychosis	HR (95% CI)[a]	Adjusted HR (95% CI)[b]	No. of Noncases/Cases With Nonaffective Psychosis	HR (95% CI)[c]
Simple maternal BMI					
Normal (≥18.5 to <25.0)					
Nonaffective psychosis	405 675/2199	1 [Reference]	NA	932/810	NA
Schizophrenia	405 675/535	1 [Reference]	NA	NA	NA
Underweight (<18.5)					
Nonaffective psychosis	40 715/258	1.17 (1.02-1.33)	1.14 (1.00-1.30)	87/89	1.46 (0.90-2.35)
Schizophrenia	40 715/64	1.19 (0.92-1.54)	1.17 (0.90-1.51)	NA	NA
Overweight (≥25.0 to <30.0)					
Nonaffective psychosis	64 587/371	1.07 (0.95-1.20)	1.03 (0.91-1.15)	141/129	1.11 (0.73-1.68)
Schizophrenia	64 587/89	1.07 (0.85-1.34)	1.02 (0.81-1.27)	NA	NA
Obese (≥30.0)					
Nonaffective psychosis	12 155/82	1.25 (1.00-1.56)	1.16 (0.93-1.44)	33/18	0.56 (0.23-1.38)
Schizophrenia	12 155/16	1.02 (0.62-1.68)	0.91 (0.55-1.50)	NA	NA
Extended maternal BMI					
Normal (≥18.5 to <25.0)					
Nonaffective psychosis	405 675/2199	1 [Reference]	NA	932/810	NA
Schizophrenia	405 675/535	1 [Reference]	NA	NA	NA
Severe thinness (<16.0)					
Nonaffective psychosis	2395/15	1.14 (0.69-1.89)	1.13 (0.68-1.87)	10/4	0.32 (0.07-1.59)
Schizophrenia	2395/3	0.92 (0.30-2.87)	0.92 (0.30-2.87)	NA	NA
Moderate thinness (≥16.0 to <17.0)					
Nonaffective psychosis	5509/23	0.77 (0.51-1.16)	0.73 (0.49-1.11)	10/12	2.19 (0.68-7.10)
Schizophrenia	5509/6	0.82 (0.37-1.84)	0.79 (0.35-1.77)	NA	NA
Mild thinness (≥17.0 to <18.5)					
Nonaffective psychosis	32 811/220	1.24 (1.08-1.42)	1.21 (1.06-1.39)	67/73	1.64 (0.97-2.77)
Schizophrenia	32 811/55	1.27 (0.96-1.68)	1.25 (0.97-1.65)	NA	NA
Overweight (≥25.0 to <27.5)					
Nonaffective psychosis	45 558/248	1.10 (0.89-1.16)	0.98 (0.86-1.11)	105/82	0.98 (0.64-1.51)
Schizophrenia	45 558/61	1.04 (0.80-1.35)	0.99 (0.76-1.29)	NA	NA
Preobese (≥27.5 to <30.0)					
Nonaffective psychosis	19 029/123	1.20 (1.00-1.44)	1.14 (0.95-1.38)	36/47	1.79 (0.90-3.55)
Schizophrenia	19 029/28	1.14 (0.78-1.67)	1.07 (0.73-1.57)	NA	NA
Obese class 1 (≥30.0 to <35.0)					
Nonaffective psychosis	11 249/71	1.18 (0.93-1.49)	1.09 (0.86-1.38)	32/17	0.71 (0.28-1.85)
Schizophrenia	11 249/15	1.04 (0.62-1.73)	0.93 (0.56-1.56)	NA	NA
Obese class 2 (≥35.0 to <40.0)					
Nonaffective psychosis	779/9	2.15 (1.12-4.14)	1.93 (1.00-3.71)	1/1	NA
Schizophrenia	779/1	0.98 (0.14-7.00)	0.86 (0.12-6.11)	NA	NA
Obese class 3 (≥40.0)					
Nonaffective psychosis	127/2	2.57 (0.64-10.28)	2.57 (0.64-10.28)	NA	NA
Schizophrenia	127/0	NA	NA	NA	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HR, hazard ratio; NA, not applicable.

[a] Adjusted for birth year and sex.

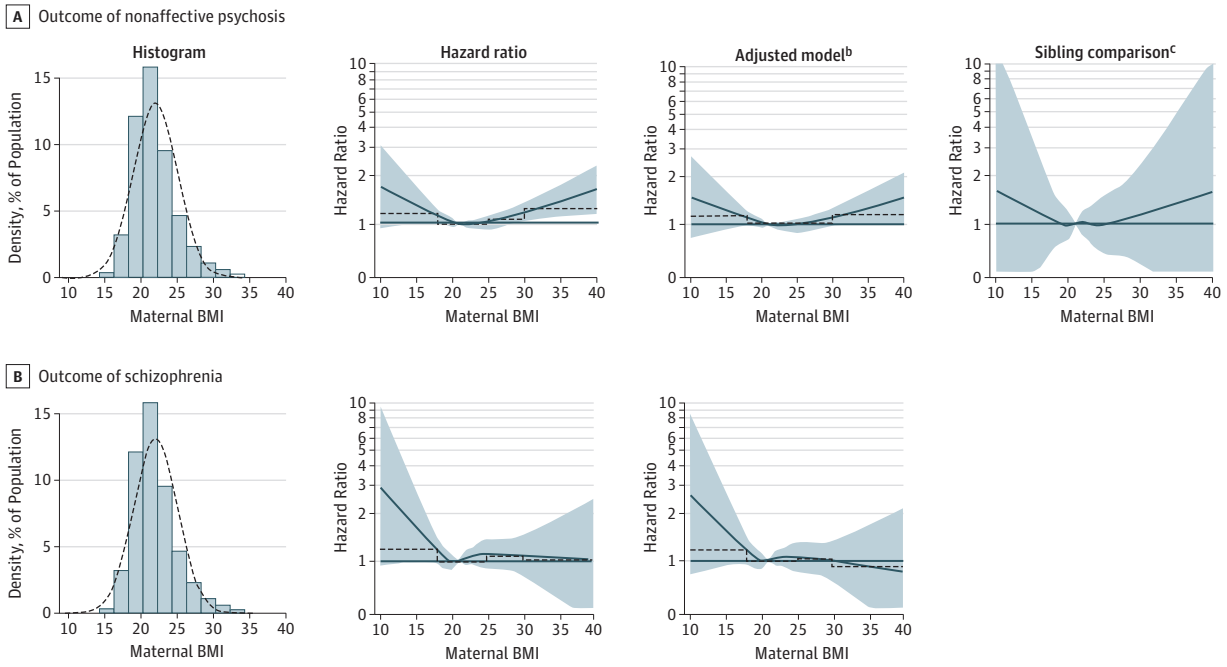
[b] Adjusted for birth year and sex, family income, parent older than 35 years, parent born outside Sweden, and parental history of psychosis.

[c] Adjusted for birth order and sex.

an increased risk for nonaffective psychosis (adjusted HR, 1.36; 95% CI, 1.16-1.58), even after accounting for gestational age and maternal BMI (Table 3).

In continuous analysis, nonaffective psychosis risk in offspring was associated with a low GWG (<11 kg) in unadjusted (**Figure 2**) and adjusted (eFigure 2 in the Supplement) models. Similar patterns were observed for narrowly defined schizophrenia (Figure 2 and eFigure 3 in the Supplement). When stratified by baseline maternal BMI category, the association of low GWG and the risk for nonaffective psychosis remained

Figure 1. Risk for Nonaffective Psychosis and Schizophrenia in Association With Maternal Baseline Body Mass Index (BMI)



Histograms illustrate the distribution of maternal BMI (calculated as weight in kilograms divided by height in meters squared) for those included in each analysis. Basic and adjusted estimates are shown for nonaffective psychosis and schizophrenia. Sibling comparison is shown for only nonaffective psychosis. The curved solid black line represents the hazard ratio (HR) calculated through restricted cubic splines models with 5 knots, with BMI of 21.0 as the reference category. The blue bands represent the 95% CI. The black dotted line represents HR estimates from the categorical model of maternal BMI (see Table 2) and is shown here for comparison. A reference line is included for an HR of 1.00.

[a] Adjusted for birth year and sex.

[b] Adjusted for birth year, sex, family income, parent older than 35 years, parent born outside Sweden, and parental history of psychosis.

[c] Adjusted for birth order and sex.

for the normal-weight and overweight or obese groups (BMI≥25.0), but not for the underweight group.

In the matched-sibling analysis, the risk for nonaffected psychosis increased for offspring born to mothers with extremely inadequate GWG (HR, 1.61; 95% CI, 1.02-2.56) (Table 3). In continuous analysis, a similar finding was observed, although the CIs were wide and included 1 (Figure 2).

Sensitivity Analyses

In the analysis of paternal BMI, we observed an increased risk for nonaffective psychosis among the offspring of severely thin fathers (BMI<16.0; adjusted HR, 2.52; 95% CI, 1.26-5.04) (eTable 8 in the Supplement) and a weak, U-shaped association between paternal BMI and nonaffective psychosis in offspring in continuous analysis, a pattern comparable with that of maternal BMI (eFigure 4 in the Supplement). The association between maternal obesity and the risk for nonaffective psychosis in offspring was strengthened by adjusting for paternal BMI, although the CIs remained wide (eFigure 4 and eTable 8 in the Supplement). In mutually adjusted models, maternal mild thinness in early pregnancy was weakly associated with an increased risk for nonaffective psychosis in offspring (HR for BMI≥17.0 and <18.5, 1.21; 95% CI, 1.01-1.45), as was paternal severe thinness (HR for BMI<16.0, 2.53; 95% CI, 1.26-5.07).

After stratification by sex (eTables 9 and 10 in the Supplement), maternal mild thinness was associated with nonaffective psychosis in male (HR, 1.30; 95% CI, 1.10-1.55) but not female (HR, 1.14; 95% CI, 0.91-1.43) offspring. Extremely inadequate GWG was associated with risk for psychosis in male (HR, 1.32; 95% CI, 1.07-1.63) and female (HR, 1.60; 95% CI, 1.27-2.01) offspring but was more pronounced in the latter.

Discussion

Key Results

Extremely inadequate GWG was associated with an increased risk for nonaffective psychosis in offspring in categorical and continuous analyses, even after adjustment for potential confounders. The sibling analysis suggests that this result is unlikely to be attributable to unmeasured familial confounding. Together these results indicate, similarly to the Dutch Hunger Winter and Great Leap Forward studies,[7-9] that inadequate maternal nutrition during pregnancy increases the risk for nonaffective psychosis in offspring, even in the context of an affluent and well-nourished population.

This study also demonstrated a weak U-shaped association between maternal BMI at the beginning of pregnancy and

Table 3. Associations Between Nonaffective Psychosis and GWG

GWG Category	Full Cohort					Matched-Sibling Cohort	
	No. of Noncases/Cases With Nonaffective Psychosis	HR (95% CI)[a]	Adjusted HR (95% CI) Model 1[b]	Adjusted HR (95% CI) Model 2[c]	Adjusted HR (95% CI) Model 3[d]	No. of Noncases/Cases With Nonaffective Psychosis	HR (95% CI)[e]
Simple GWG category							
Ideal[f]							
Nonaffective psychosis	225 466/1222	1 [Reference]	NA	NA	NA	513/456	NA
Schizophrenia	225 466/299	1 [Reference]	NA	NA	NA	NA	NA
Inadequate[g]							
Nonaffective psychosis	132 039/771	1.07 (0.98-1.27)	1.06 (0.97-1.16)	1.04 (0.95-1.14)	1.05 (0.95-1.14)	316/273	1.01 (0.77-1.32)
Schizophrenia	132 039/177	1.00 (0.83-1.20)	0.99 (0.82-1.19)	0.98 (0.81-1.18)	0.98 (0.81-1.18)	NA	NA
Excessive[h]							
Nonaffective psychosis	165 627/917	1.03 (0.95-1.13)	1.02 (0.93-1.10)	1.02 (0.93-1.10)	1.02 (0.93-1.11)	364/317	1.00 (0.76-1.31)
Schizophrenia	165 627/228	1.07 (0.90-1.27)	1.04 (0.88-1.24)	1.04 (0.88-1.24)	1.06 (0.89-1.27)	NA	NA
Extended GWG category							
Ideal[f]							
Nonaffective psychosis	225 466/1222	1 [Reference]	NA	NA	NA	513/456	NA
Schizophrenia	225 466/299	1 [Reference]	NA	NA	NA	NA	NA
Extreme inadequate[i]							
Nonaffective psychosis	23 627/184	1.43 (1.28-1.67)	1.36 (1.16-1.58)	1.31 (1.13-1.54)	1.32 (1.13-1.54)	60/69	1.61 (1.02-2.56)
Schizophrenia	23 627/45	1.42 (1.04-1.95)	1.33 (0.97-1.83)	1.31 (0.96-1.80)	1.32 (0.96-1.81)	NA	NA
Inadequate[j]							
Nonaffective psychosis	108 412/587	0.99 (0.90-1.10)	0.99 (0.90-1.09)	0.98 (0.89-1.08)	0.98 (0.89-1.08)	256/204	0.90 (0.68-1.20)
Schizophrenia	108 412/132	0.91 (0.74-1.11)	0.91 (0.74-1.11)	0.90 (0.73-1.11)	0.90 (0.73-1.11)	NA	NA
Excessive[k]							
Nonaffective psychosis	133 661/739	1.03 (0.94-1.13)	1.01 (0.92-1.11)	1.02 (0.93-1.12)	1.02 (0.93-1.12)	294/267	1.04 (0.79-1.38)
Schizophrenia	133 661/181	1.04 (0.87-1.25)	1.02 (0.85-1.23)	1.03 (0.85-1.23)	1.04 (0.86-1.27)	NA	NA
Extreme excessive[l]							
Nonaffective psychosis	31 966/178	1.05 (0.90-1.23)	1.01 (0.86-1.18)	1.02 (0.87-1.19)	1.02 (0.87-1.19)	70/50	0.67 (0.38-1.15)
Schizophrenia	31 966/47	1.17 (0.86-1.60)	1.11 (0.82-1.51)	1.11 (0.82-1.51)	1.12 (0.82-1.53)	NA	NA

Abbreviations: GWG, gestational weight gain; HR, hazard ratio; NA, not applicable.

[a] Adjusted for birth year and sex.

[b] Adjusted for birth year, sex, family income, parent older than 35 years, parent born outside Sweden, and parental history of psychosis.

[c] Adjusted for covariates from the previous model and World Health Organization gestational age categories (extreme preterm, <28 weeks; very preterm, 28-32 weeks; moderate preterm, 32-37 weeks; full term, 37-41 weeks; and postterm, >41 weeks).

[d] Adjusted for maternal body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) and covariates in the previous model.

[e] Adjusted for birth order and sex.

[f] Defined by baseline BMI of normal (11.5-16.0 kg), underweight (12.5-18.0 kg), overweight (7.0-11.5 kg), and obese (5.0-9.0 kg). BMI definitions are given in Table 2.

[g] Indicates values below ideal.

[h] Indicates values above ideal.

[i] Defined by BMI of normal (<8.0 kg), underweight (<8.0 kg), overweight (<5.0 kg), and obese (<2.0 kg).

[j] Defined by BMI of normal (8.0-11.5 kg), underweight (8.0-12.5 kg), overweight (5.0-7.0 kg), and obese (2.0-5.0 kg).

[k] Defined by BMI of normal (16.0-22.0 kg), underweight (18.0-22.0 kg), overweight (11.5-22.0 kg), and obese (9.0-17.0 kg).

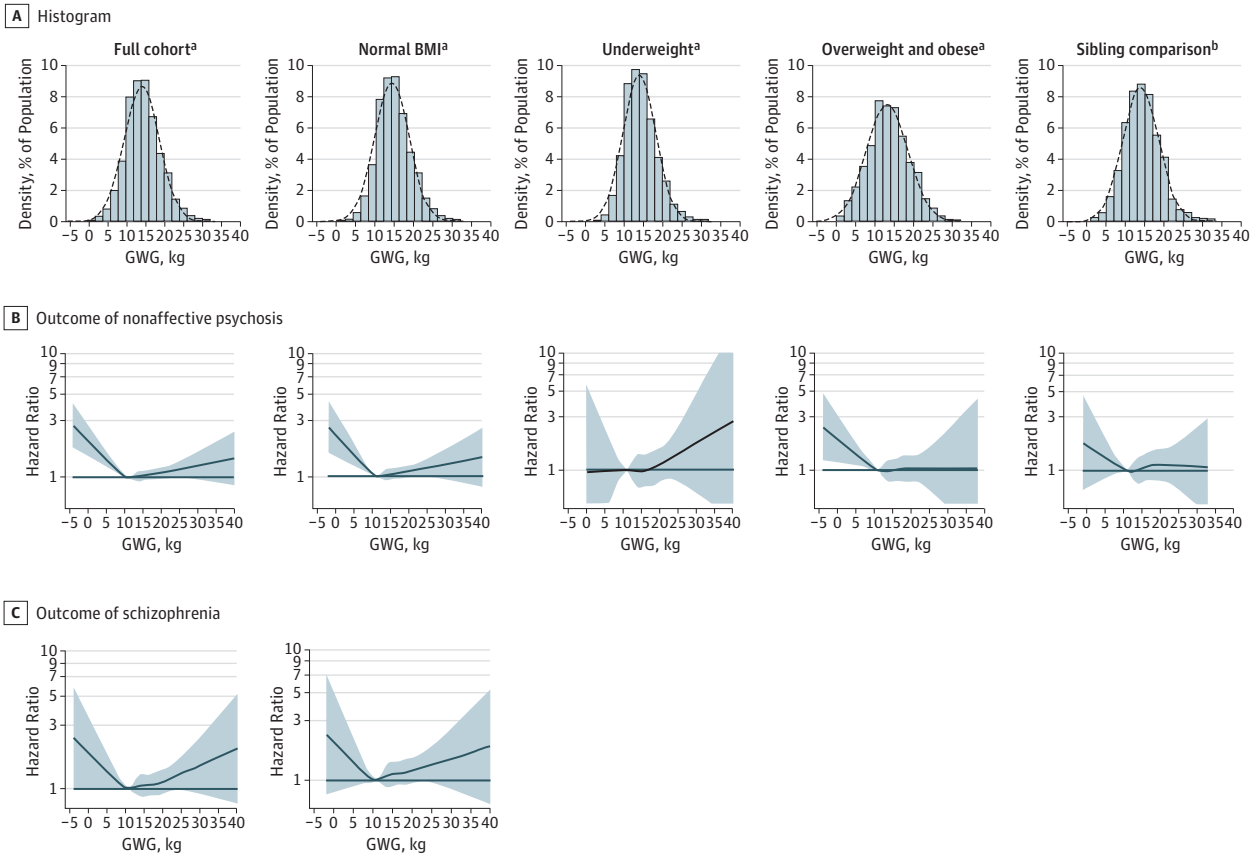
[l] Defined by BMI of normal (>22 kg), underweight (>22 kg), overweight (>22 kg), and obese (>17 kg).

the increased risk for nonaffective psychosis in offspring. However, the results of the paternal comparison indicate that the associations between the risk for nonaffective psychosis in offspring and parental BMI may be partly attributable to genetic or other shared familial factors.

Comparison With Previous Studies

Previous studies have reported contradictory associations between maternal BMI and risk for psychosis in offspring.[17] Low late-pregnancy maternal BMI (≤24.0) was associated with a 3-fold risk for schizophrenia in offspring (reference

Figure 2. Risk for Nonaffective Psychosis and Schizophrenia With Respect to Gestational Weight Gain (GWG) During Pregnancy



The distribution of GWG for each cohort and subcohort is provided in histograms. Results for nonaffective psychosis are presented for the full cohort and stratified by maternal body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) category and the sibling comparison. Results for narrowly defined schizophrenia are presented for the full cohort and restricted to mothers in the normal BMI category. The curved black line represents hazard ratios (HRs) calculated by restricted cubic spline analysis with 5 knots, with GWG of 11 kg as the reference category. The blue bands represent the 95% CIs. A reference line is included for HR of 1.00.

[a] Adjusted for birth year and sex.

[b] Adjusted for birth order and sex.

BMI>30.0).[32] However, late-pregnancy maternal BMI was used as a combined proxy for prepregnancy BMI and GWG, obscuring the contribution of each.

High maternal prepregnancy[33,34] and late pregnancy[35] BMI have also been linked to psychosis in offspring. We observed a 2-fold increased risk associated with maternal obesity (class 2) and an elevated risk for obesity and its subclasses. The results of our family comparison studies indicate that the associations between maternal BMI and the risk for nonaffective psychosis in offspring are at least partly confounded by genetic or other shared familial factors. The only study to date considering a potential correlation between genetic determinants of BMI and the risk for schizophrenia reported an inverse association: evidence of genetic correlation between low BMI and risk for schizophrenia.[36]

We observed a greater effect for female offspring of mothers with extremely inadequate GWG compared with male offspring, but effect estimates overlapped between the sexes. The initial Dutch famine study reported a similar sex effect,[8] but this difference was not apparent in a later, more rigorous analysis.[6] Our result merits cautious interpretation owing to the relative youth of our cohort and the differential age at onset for male and female offspring.[37]

Mechanisms

Although other mechanisms cannot be ruled out based on these observational studies, the association of inadequate GWG with nonaffective psychosis in concert with the findings of the Dutch and Chinese famine studies implicates malnutrition as the effector. Multiple nutrient deficiencies have been demonstrated to affect neurodevelopment and risk for schizophrenia in offspring.[4,11,38] Low GWG during pregnancy may therefore represent an inability to meet the nutrient demands of the placental-fetal unit. Suboptimal nutrient status of mothers with extremely inadequate GWG in our study is evidenced by their lower rates of male births (eTable 10 in the Supplement). Male fetuses place a higher energy demand on mothers during pregnancy,[39] such that states of maternal deprivation lead to fewer male births.[40] Fetal growth restriction, indicated by infants who are small for gestational age, can

result from inadequate GWG, although other factors also contribute. Small size for gestational age has also been linked to an increased risk for nonaffective psychosis.[41,42]

Severely inadequate GWG may otherwise be indicative of an existing maternal medical condition, such as endrocrinologic disorders, malabsorption, anorexia nervosa, bulimia nervosa, or hyperemesis gravidarum. Further research is necessary to understand the association between conditions that lead to insufficient maternal weight gain and the risk for nonaffective psychosis in offspring. Insufficient weight gain can also occur in otherwise healthy individuals owing to insufficient medical guidance or by a drive to conform to societal (but not medical) standards of appropriate weight gain.[43]

Strengths

This study is, to our knowledge, the largest to date to examine the association of maternal BMI and the risk for psychosis in offspring and the first to examine the role of GWG. The large sample size facilitated the use of family-based study designs for more rigorous inference of causation.[20,44] We calculated BMI and GWG from objectively measured, prospectively recorded register data. Swedish registry data on nonaffective diagnoses have high validity.[45]

We were able to adjust GWG for gestational age. Gestational weight gain and gestational age are highly correlated, with inadequate GWG associated with preterm births and low birth weights.[23,46] Accounting for parental psychosis likewise strengthened our results. Nonaffective psychoses are highly heritable,[47,48] and traditional antipsychotics can lead to pronounced weight gain.[49]

Limitations

One issue is the limited follow-up time: ages of offspring at the end of follow-up varied from 22 to 29 years. Nonaffective psychoses manifest typically from the third decade of life onward.[50] As such, our sample is considerably right censored. Although we statistically accounted for this, we may have captured more early-onset, possibly phenotypically distinct cases, which limits generalizability.[17] Future studies will allow for reanalysis as the cohort continues to age. Another limitation is the rate of missing BMI and GWG in the eligible study population, although these data seem to be missing at random from the Medical Birth Register.[22]

Paternal BMI at conscription was used to examine the independence of any observable effect of maternal BMI on nonaffective psychosis among offspring.[18-20] Paternal BMI was unavailable for any later time points. Using paternal BMI at 18 years of age allowed for exploration of the contribution of paternal factors to nonaffective psychosis in offspring while removing the effects of the shared parental environment at the time of pregnancy. Increasing paternal age is related to increased BMI and increased risk for nonaffective psychosis in offspring. By capturing BMI at the same age for all fathers, we avoided potential confounding owing to these associations.[22]

Sibling comparisons were used to test for unmeasured familial confounding. Using sibling analysis in extended categories for a rare outcome reduced power, possibly obscuring true associations. Also, in discordant sibling design, only mothers who varied in BMI or GWG between their 2 index pregnancies contribute to effect estimates; such designs are susceptible to confounding by nonshared factors that might lead to such changes in the same mother.[44]

We improve on the Dutch and Chinese famine studies by using individual measures of parental BMI and GWG as proxies for nutrition in place of population-level measures of starvation. However, BMI and GWG are incomplete representations of metabolic health and nutritional intake and cannot discount other mechanisms of action. We were also limited by the small number of mothers at the extremes of BMI categories.

Last, we recognize the dissonance of applying Institute of Medicine 2009 GWG guidelines to mothers in the 1980s. Using the rationale of Holowko et al,[51] we believe the guidelines represent optimal maternal and child health outcomes, regardless of advice at the time. Our study seemingly validates the 2009 guidelines for mothers with BMI in the normal range, because ideal GWG conferred the lowest risk. However, offspring of overweight and obese women showed an elevated risk for nonaffective psychosis, even at the lower end of the Institute of Medicine ideal GWG range, potentially raising the question of the adequacy of weight gain guidelines for populations outside the normal BMI range, specifically for nonobstetric outcomes.[46,52-54]

Conclusions

Our results corroborate evidence from previous research and indicate that inadequate weight gain during pregnancy contributes to the risk for nonaffective psychosis in offspring. Weight gain outside Institute of Medicine guidelines may have deleterious effects on offspring neurodevelopment.

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Invited Commentary

Prenatal Nutritional Deficiency and Psychosis
Where Do We Go From Here?

Ezra Susser, MD, DrPH; Katherine M. Keyes, PhD

In this issue of *JAMA Psychiatry*, Mackay et al[1] report that extremely inadequate gestational weight gain is linked to nonaffective psychosis in offspring. This result is concordant with several previous studies[2] designed as natural experiments that linked prenatal maternal famine to offspring nonaffective psychosis. The present study, based on Swedish national registries, represents a substantial advance by providing evidence that a similar association is detectable among individuals in a generally well-fed population in more ordinary circumstances. Also notable, the study included strengths of design not possible in the natural experiments, such as rigorous control for parental psychiatric conditions and comparison of affected and unaffected siblings. Thus, it contributes to an increasingly robust body of convergent evidence for a role of prenatal nutritional deficiency in the early origins of psychosis and strengthens the argument for examining prenatal nutritional supplements and dietary patterns as a means of prevention.

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Another strength is that the study highlights puzzling questions that have yet to be resolved. Why was the association with psychosis robust only at the extreme of low weight gain? Why did the investigators find no association of high or low early prenatal body mass index with psychosis, contrary to prevailing views and some prior reports on schizophrenia and other neurodevelopmental disorders?

Inevitably, the study also had limitations. For example, the timing of nutritional deficiency could not be specified using registry data, results were inconclusive at the extremes of body mass index, and the potential role of maternal stress as a cofactor could not be examined. These limitations should be noted but without losing sight of the authors' substantial achievements.

In this commentary, we focus henceforth on how we could build on the convergent evidence to identify mechanisms and preventive interventions for nonaffective psychoses and other neurodevelopmental disorders that fall within the domain of psychiatry. Studies of extreme prenatal exposures remain useful but not sufficient to reach these goals. We propose that the endeavor requires a guiding framework that embraces mutually informative lines of investigation being conducted in tandem. Given limited space, we hope to spark discussion of this framework by focusing on 2 of the central challenges and how they might be overcome.

The first challenge is that translational science is generally presented as a linear progression, with knowledge transferred from basic science to clinical research (step 1), from clinical research to clinical care (step 2), and from clinical care to implementation of public health interventions (step 3). For more than 50 years, however, studies of prenatal nutritional deficiencies and neurodevelopmental disorders have followed a more circuitous route and holistic bridging of disciplines.[2] Studies have been performed in tandem at many levels and have informed one another, including natural experiments based on tragic historical famines, discoveries in basic sciences such as genomics and epigenetics, trials of prenatal micronutrients, clinical research, and epidemiologic studies of risk factors. The interplay has generated hypotheses about mechanisms, such as epigenetic effects and de novo mutations, and supported studies of preventive effects of micronutrients. At present, evidence is being sought for preventive effects of periconceptional folic acid, prenatal choline supplementation, and prenatal vitamin D, and all these efforts are grounded in basic science, animal studies, epidemiologic studies, and clinical research. We propose that translational science as a linear progression is not an appropriate framework for research on prenatal nutrition and neurodevelopmental disorders. Instead, this field should adhere to a conceptual framework that explicitly promotes multiple levels of inquiry proceeding in parallel and not in isolation from one another. We should also encourage cross-level research, exemplified by an investigation by Roffman et al[3] that compares neuroimaging data for children and adolescents born before, during, and after the rollout of folate fortification of food in the United States. Such multileveled and cross-disciplinary efforts fit conceptual frameworks of ecoepidemiology and population health science,[4,5] in which there is an interplay between macro and