

Original Research Article

Self-Reported Illness and Birth Weight in the Philippines: Implications for Hypotheses of Adaptive Fetal Plasticity

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ABSTRACT It has been proposed that prenatal nutrition provides the fetus with a cue allowing it to adjust biological settings in anticipation of postnatal nutrition. To evaluate the reliability of fetal growth rate as a nutritional cue, this study assesses the extent to which a nonnutritional factor—maternal illness symptoms during pregnancy—predicts birth outcomes in a large, population-based sample of Filipino women and their newborns ($n = 2,887$). Self-reported illness symptoms were collected during pregnancy and used to predict weight, length, BMI, and gestational age at birth. Independent of potential confounders, number of reported symptoms predicted a significant dose-response decrease in birth weight and BMI, but not length that reflected a combination of reduced fetal growth rate and reduced duration of gestation. These effects were comparable in male and female offspring, but tended to be stronger when reported closer to term. Among women interviewed at 32 weeks gestation or later, multiple symptoms predicted a 144 g birth weight reduction compared with no symptoms. These findings suggest an acute effect of maternal illness on fetal nutrition late in gestation when growth rate and fat deposition are most rapid. Although modest, the effect was larger than that of most pregnancy macronutrient supplementation trials. These findings using cross-sectional, self-reported illness symptoms highlight a nonnutritional maternal influence on fetal nutrition, which could attenuate its value as a cue of postnatal ecology. *Am. J. Hum. Biol.* 20:538–544, 2008. © 2008 Wiley-Liss, Inc.

Birth weight has long been a focus of public health research owing to its relationship with perinatal morbidity and mortality (Alexander et al., 2003). Interest in birth weight has recently been rekindled by the finding that being born small also predicts elevated risk for a wide range of adult diseases, including diabetes, hypertension, and cardiovascular disease (Gluckman and Hanson, 2006; Osmond and Barker, 2000). Risk of developing these conditions may be especially high if an individual born light experiences rapid weight gain during childhood or becomes overweight or obese as an adult (Hales and Barker, 2001; Ravelli et al., 1998). From a biomedical perspective, some have interpreted these findings as evidence that the fetus has a capacity to predict its future nutrition from prenatal cues, with adult metabolic disease occurring when the cue does not correspond with the adult environment (e.g. Bateson et al., 2004; Gluckman and Hanson, 2005). From a perspective of evolutionary biology, birth weight-related changes in fitness correlates, including postnatal growth rate, maturational timing, and ovarian function, have been taken as evidence for adaptive fine-tuning of life history strategy in response to ecological information conveyed across the placenta (e.g. Jasienska et al., 2006a,b; Kuzawa and Pike, 2005). As one example, Polish women born small have lower ovarian steroid production as adults (Jasienska et al., 2006b), and may use prenatal nutritional cues to adjust the sensitivity of ovarian function to energetic stress (Jasienska et al., 2006a).

Although differing in focus, biomedical and anthropological proposals for adaptive fetal plasticity both require that the fetus has access to a reliable cue of future nutritional ecology (Kuzawa, 2005). Although fetal growth rate is insulin-sensitive (Gluckman and Pinal, 2003), and is thus an index of nutrients crossing the placenta, fetal nutrition is not a simple correlate of the nutrients con-

sumed by the mother (Harding, 2001; Institute of Medicine, 1990). Maternal physiology and metabolism buffer the fetus from both negative (Dufour and Sauter, 2002; Prentice and Goldberg, 2000; Ulijaszek, 2002) and positive changes in maternal intake (Kramer, 1993), with the consequence that the nutrition received by the fetus is often not tightly coupled to fluctuations in her current macronutrient intake (Morton, 2006). Fetal growth rate is often strongly predicted by conditions experienced prior to pregnancy, including prepregnancy nutritional status and the nutritionally-sensitive measures of the mother's growth rate during fetal life, infancy, and early childhood. As a source of information on chronic nutritional trends, it has been argued that this "inertia" in the fetal nutritional signal could provide an integrated and thus more reliable basis for the offspring to use to adjust long-term metabolic strategy (Kuzawa, 2005), or for the mother to calibrate reproductive expenditure (Wells, 2003, 2007).

While these life course and intergenerational influences on maternal–fetal nutrient transfer could render fetal nutrition a more reliable anticipatory cue, a wide range of nonnutritional factors have the potential to modify fetal nutrition and growth, and by implication, long-term metabolic settings and disease risk in offspring. Psychosocial stress, high altitude hypoxia, and smoking are examples of nonnutritional maternal factors that have well-established

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lished negative effects on fetal growth rate (Lampl et al., 2003; Moore et al., 1998). Another potentially important factor is maternal illness, which can adversely impact birth outcomes operating through several pathways. The majority of work on the effects of maternal illness on fetal development has focused on infections of the reproductive tract, which can induce premature delivery or fetal growth restriction (Challis et al., 2005; Romero et al., 2006; Schultz et al., 1991; Svare et al., 2006). Although less well studied, nonreproductive tract infections, which are far more common, could also affect birth size by sapping energy from the growing fetus as a result of symptoms like reduced maternal intake (anorexia), compromised nutrient absorption, and impaired pregnancy weight gain (Mata et al., 1977; McDade, 2003; Siega-Riz and Adair, 1993) or by inducing spontaneous preterm delivery (Munn et al., 1999; Smith et al., 2007). If commonly reported maternal illness symptoms have a substantial influence on fetal nutrition this could diminish the strength and reliability of any nutritional signaling, with implications for hypotheses about adaptive fetal plasticity. As evidence for such an effect, a recent study reports that individuals *in utero* during the 1918 influenza epidemic went on to have compromised adult economic performance, health, and survivorship (Almond, 2006), suggesting that long-term developmental trajectories and biological settings in offspring may in some instances be set in response to transient maternal health status during gestation.

This study aims to explore one potential constraint on the signaling value of fetal growth rate by evaluating whether a woman's self-reported illness symptoms during pregnancy predict offspring birth weight. We examine the association between maternal illness and birth outcomes in a large, population-based birth cohort of Filipino women and their newborns, with an eye to clarifying the nature, timing, and possible pathways of any such effect.

MATERIALS AND METHODS

Study population

This study uses data from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), an ongoing, community-based, prospective study in Cebu City, the second largest metropolitan area in the Philippines. The CLHNS is a 1-year birth cohort that originally enrolled 3,327 women from 33 randomly-selected communities, including densely populated urban and periurban neighborhoods and more isolated rural villages in the mountains or nearby islands (Adair et al., 2001). All pregnant women in the selected communities were invited to participate if they gave birth between May 1, 1983, and April 30, 1984 ($n = 3,327$). The infant sample (3,080 single live births) was thus representative of singletons born in the Cebu metropolitan area during this 1-year interval. Cases lost between the baseline (pregnancy) and birth surveys were due to migration out of the study area, refusal to participate, and fetal loss (Adair and Popkin, 1988). Extensive information on each woman's individual, household and community characteristics were collected during a baseline (pregnancy) survey conducted at a mean of 30 ± 4 weeks gestation (Adair and Popkin, 1988; Adair et al., 2001). These data, along with birth outcomes and gestational age measured within 6 days of birth, form the basis of the present analyses.

Data collection

Data were collected during interviews conducted in the respondents' homes. All data were obtained under conditions of informed consent and with human subjects clearance from the University of North Carolina, Chapel Hill, and the University of San Carlos (see Adair and Popkin, 1988 for details on study design). Information on maternal health, reproductive histories, and pregnancy complications were obtained during the baseline interview. Maternal anthropometrics (height, weight, and triceps skinfold thickness) were measured using standard techniques. Maternal height and weight were used to adjust birth weight for maternal body size. To avoid using a measure of maternal weight that includes the weight of the fetoplacental unit, maternal weight measured after birth was used in analyses.

For infants born in hospitals, birth weight was measured by birth attendants using hospital scales, while for infants born at home, birth weight was measured by birth attendants who had been provided with Salter (London) hanging-type scales and trained in their use. Birth weight data were obtained on 3,080 singleton liveborns. Gestational age at birth was estimated from the mother's report of the date of her last menstrual period. In cases where this date was unknown, when pregnancy complications occurred, or if the infant weighed <2.5 kg at birth, gestational age was determined using the Ballard method (Ballard et al., 1979). Gestational age at the time of the baseline interview was estimated by subtracting the date of the interview from the gestational age at birth determined by either the Ballard method or mother's report of her last menstrual period. Relative weight at birth was assessed by calculating the body mass index (BMI), rather than the ponderal index, because BMI is less related to birth length in this sample (Kuzawa and Adair, 2003).

Prevalence of maternal illness was assessed during the baseline interview, which occurred primarily during the second or third trimester. Women were asked if they had experienced any illness within the last 7 days. If they answered "yes", they were asked to report the symptoms experienced, with more than one symptom reportable. Symptoms and illnesses were coded as cold, cough, fever, diarrhea, tuberculosis, blood in sputum, or other illness. No additional information is available concerning the "other illness" reported.

Statistical analysis

All analyses were performed with version 10 of Stata (Stata Corporation, College Station, TX). Maternal illness was coded as a three level scale from 0 to 2 based on the number of symptoms reported (0 = no symptoms, 1 = 1 symptom, 2 = 2 or more reported symptoms [multiple symptoms]). Birth weight was analyzed as a continuous variable and was also modeled as the dichotomous outcome of low birth weight (LBW; birth weight $\leq 2,500$ g). Gestational age, a possible mechanism for small birth size, was also analyzed as both a continuous variable and as the dichotomous outcome of preterm delivery (PTD; delivery < 37 completed weeks gestation). A series of models were run, beginning with simple relationships between illness and each birth outcome and progressively adding variables that could confound the association, or that might be in the causal pathway, including gestational age

TABLE 1. Characteristics of CLHNS mothers and their newborns^a

	Total sample (<i>n</i> = 2,887)	Range	No symptoms (<i>n</i> = 2,067)	1 symptom (<i>n</i> = 582)	2+ symptoms (<i>n</i> = 238)	<i>P</i> ^b
Household						
Urban (%)	76.7		76.1	78.9	76.1	
Has flush/water-sealed toilet (%)	47.5		48.0	46.1	49.4	
Own refrigerator (%)	6.8		7.1	6.7	4.2	
Own TV (%)	18.4		19.0	19.6	10.0	
Household income (pesos)	283 ± 523	(0.1, 16,887)	288 ± 559	279 ± 272	242 ± 248	
Mother						
Age (years)	26.6 ± 6.0	(14.8, 47.1)	26.5 ± 6.0	26.7 ± 5.9	26.6 ± 6.0	
Height (cm)	150.6 ± 5.1	(130.4, 178.1)	150.6 ± 5.0	150.9 ± 5.4	150.3 ± 4.9	
BMI ^c (kg/m ²)	22.1 ± 2.6	(15.1, 39.7)	22.1 ± 2.5	22.0 ± 2.7	22.1 ± 2.7	
Triceps skinfold (mm)	12.8 ± 4.0	(3.6, 35.7)	12.9 ± 4.0	12.9 ± 4.1	12.5 ± 4.1	
First pregnancy (%)	20.6		21.2	19.2	19.3	
Smoker (%)	12.9		12.2	12.9	18.9	*
Newborn						
Female (%)	47.2		47.6	45.9	47.1	
Birth weight (g)	2993 ± 430	(907, 4,800)	3006 ± 428	2977 ± 426	2919 ± 455	**
Birth length (cm)	49.2 ± 2.2	(40.1, 58.4)	49.3 ± 2.1	49.2 ± 2.2	49.0 ± 2.3	
BMI (kg/m ²)	12.3 ± 1.4	(5.3, 17.8)	12.4 ± 1.4	12.3 ± 1.4	12.1 ± 1.4	*
LBW ^d (%)	13.4		12.4	15.1	17.6	*
Gestational age (wks)	38.8 ± 2.1	(30.0, 42.1)	38.8 ± 2.1	38.8 ± 2.1	38.4 ± 2.2	*
Premature ^e (%)	15.4		14.5	16.5	21.0	*

^aValues are mean ± SD (continuous variables) or % (categorical).

^bTest for statistically significant differences across symptom levels using oneway ANOVA (continuous variables) and chi-square (categorical); **P* < 0.05; ***P* < 0.001.

^cBody mass index.

^dLow birth weight, birth weight < 2,500 g.

^eGestational age at birth < 37 weeks.

at birth, infant sex, maternal triceps skinfold thickness as a measure of energy status, primiparity, stature, smoking status, and household income.

Analyses and models were restricted to the subsample of mothers and infants for whom all variables were available (*n* = 2,887). Mothers excluded from the analyses due to missing data (*n* = 135) did not differ from the analysis subsample with respect to baseline data on reports of illness, age, height, or income, but were more likely to be primiparous (25.2% vs. 20.6%), smokers (18.1% vs. 12.9%), and they had a slightly lower BMI (21.4 vs. 22.1; *P* = 0.01). Newborns excluded from the analyses did not differ in relation to mean birth weight, gestational age, or sex, but were less likely to be LBW (6.1% vs. 13.4%) and more likely to be delivered preterm (19.8% vs. 15.4%).

RESULTS

Characteristics of the infants and mothers included in this study are reported in Table 1. Compared with the US women (McDowell et al., 2005) the Cebu mothers in this sample were shorter (mean: 150.6 cm vs. 162.1 cm in Cebu and US, respectively), thinner (mean BMI: 22.1 kg/m² vs. 28.2 kg/m²), but had a similar prevalence of smoking (12.8% vs. 10.2%) (Martin et al., 2006). Mean birth weight at Cebu was roughly 0.3 kg lower than in the US (2,993 g vs. 3,316 g; NCHS). Compared with the US (Martin et al., 2006; Svare et al., 2006), Cebu infants were more likely to be born premature (15.4% vs. 12.5%) or LBW (13.4% vs. 8.1%).

At baseline, 28.3% of women (*n* = 820) reported having experienced at least one symptom in the past 7 days. Reported symptoms included cold (29.5%), cough (49.9%), tuberculosis (0.12%), blood in sputum (0.61%), diarrhea (2.80%), fever (13.5%), and other illness (42.9%). More than one symptom was reported by 8.2% of all women (*n* = 238) while 20.1% of all women reported a single symptom in the preceding 7 days (*n* = 582).

We evaluated whether maternal illness predicted birth weight using a series of regression models that progressively added variables to evaluate possible sources of confounding and mechanisms of effect (Table 2). A crude relationship between the number of symptoms and birth weight was found in a univariate regression (Model 1) with report of multiple symptoms predicting a significant decrease in birth weight and one symptom associated with a more modest, nonsignificant, birth weight decrement. The magnitude of the symptom-related decrease in birth weight did not differ significantly by sex (males: −46.5 g females: −43.5 g) and as such all models were pooled and adjusted for offspring sex.

Gestational age was next added to clarify whether maternal illness predicts a reduction in birth weight owing to a decreased duration of gestation, reduced fetal growth rate, or both (Model 2). The resultant changes in the coefficients relating illness symptoms with birth weight differed by the number of symptoms reported. Adjusting for gestational age increased slightly the regression coefficient for a single symptom, consistent with a role of reduced fetal growth rate. In contrast, the regression coefficient for multiple symptoms decreased, indicating that the relationship between multiple symptoms and birth weight was partly due to reduced duration of gestation. Consistent with this interpretation, in a logistic regression, the odds ratio of PTD was 1.16 (95% CI: 0.90–1.5; *P* = 0.225) for women reporting one symptom and 1.57 (95% CI: 1.24–2.20; *P* ≤ 0.01) for women reporting two or more symptoms.

Stratifying models by duration of gestation (not reported in table) demonstrated that slower fetal growth rate was also an important contributor to reduced birth weight among offspring of women reporting illness, especially among those born pre-term. When models were limited to the subsample born premature, the effect of a single symptom (β = −74.7 g; *P* = 0.173) and multiple symptoms (β = −193.7 g; *P* = 0.008) on birth weight were both

TABLE 2. Regression models predicting offspring birth weight^a

	Model 1	Model 2	Model 3	Model 4	Model 5
1 Illness symptom	-29.7 ± 20.2	-34.2 ± 19.4	-38.6 ± 19.1*	-39.1 ± 18.3*	-40.2 ± 18.3**
2+ Illness symptoms	-87.6 ± 29.4**	-65.7 ± 28.3*	-69.4 ± 27.9*	-62.3 ± 26.8*	-62.1 ± 26.7**
Gestational age (weeks)		55.5 ± 3.6***	55.1 ± 3.6***	51.8 ± 3.5***	51.6 ± 3.5***
Female			-65.1 ± 15.2***	-59.2 ± 14.6***	-58.7 ± 14.6***
First pregnancy			-169.8 ± 18.7***	-151.8 ± 19.8***	-158.0 ± 20.0***
BMI ^b (log [kg/m ²])				715.0 ± 64.9***	704.4 ± 65.0***
Height (cm)				14.3 ± 1.4***	14.0 ± 1.4***
Smoker				-57.5 ± 22.2**	-55.1 ± 22.2*
Mother age (years)				2.2 ± 1.4	2.3 ± 1.4
Income (log Pesos)					17.2 ± 7.7*
Constant ± SE	3006.3 ± 9.5	854 ± 141.3	936.0 ± 139.3	-3359.1 ± 312.5	-3362.2 ± 312.3
Model R ²	0.003	0.078	0.109	0.182	0.183

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

^a $\beta \pm SE$ (g).

^bBMI, body mass index.

greater than among the full sample, and these associations were independent of gestational age at birth. Thus, maternal illness symptoms not only predicted earlier parturition, but among those born early, illness also had a more sizeable negative association with fetal growth rate as indicated by size adjusted for gestational age.

In the full sample, further adjusting for infant sex and primiparity (Model 3) had minimal effects on either illness coefficient, although the regression coefficient for a single symptom did become statistically significant after this adjustment. Addition of maternal nutritional status variables, age, and smoking in Model 4 had minimal effects on either regression coefficient. Triceps skinfold thickness was found not to predict birth weight independent of other predictors in the model ($P = 0.899$) and therefore is not reported. To adjust for the impact of socioeconomic status, household income was added to the final model (Model 5). Again, neither regression coefficient was substantially affected after further adjustment.

A reduction in birth weight could reflect reduced length, ponderal growth, or both. We therefore investigated similar models predicting birth length and offspring birth-BMI. The full model (comparable with Model 5 in Table 2) explained 9.6% of the variance in birth-BMI and 12.3% of the variance in birth length. Although maternal illness predicted a dose-response decrease in both birth length and birth-BMI, this relationship was only significant for birth-BMI (Fig. 1).

To evaluate the association between illness and the clinical cut point of LBW (birth weight < 2,500 g), Table 3 presents the results of logistic regression models predicting LBW. Report of multiple symptoms at baseline was found to be a significant predictor of LBW, but this relationship was no longer significant after adjusting for gestational age at birth. In contrast, report of one symptom at baseline was found to be a significant predictor of LBW only after adjusting for gestational age at birth.

Finally, we examined whether the association between maternal illness and offspring birth weight varied according to the gestational age at which women were asked about illness symptoms. The negative association between illness symptoms and birth weight was strongest closer to term. Although the interaction was not significant, multiple symptoms vs. no reported symptoms was associated with a 32, 57, and 144 g decrement in mean birth weight in the three tertiles representing gestational timing of the

baseline interview (Fig. 2). One interpretation of the greater association between maternal illness and birth outcome when measured late in gestation is that women who were sick late in pregnancy initiated parturition early. To evaluate this possibility, we ran these models before and after adjusting for duration of gestation, modeled as either a dichotomous (PTD) or continuous variable. After this adjustment, the interaction between gestational timing of interview and number of symptoms was essentially unchanged in models predicting all three birth outcomes.

DISCUSSION

Women reporting illness symptoms in this cohort gave birth to newborns who were lighter and thinner, but not shorter, than offspring born to women reporting no illness symptoms. The predicted decrease in birth outcome was comparable in male and female offspring, and was greater in the offspring of women reporting more than one illness. To the extent that fetal growth rate reflects the intergenerational transfer of nutrients, these findings provide insights into one maternal but nonnutritional influence on the nutrients that the fetus receives in support of growth.

Consistent with previous reports, this study found an increased risk of both PTD (Ludvigsson et al., 2005; Munn et al., 1999; Pitiphat et al., 2005; Svare et al., 2006) and LBW in association with illness symptoms (Bogges et al., 2006; Munn et al., 1999; Schultz et al., 1991; Svare et al., 2006). At Cebu, the regression models suggest that reduction in the duration of gestation and in fetal growth rate both contribute to reduced birth weight in offspring of women reporting illness symptoms during pregnancy. The fact that symptoms remained a significantly negative predictor of birth weight independent of gestational age is consistent with an effect of maternal illness on fetal growth rate. However, adjusting for gestational age at birth had opposite effects on the coefficients for one vs. multiple symptoms, suggesting that the contribution of prematurity vs. fetal growth restriction as a mechanism varies by intensity of illness symptoms. Mothers reporting one symptom had a slightly longer gestational age at delivery. Adjusting for this difference in gestational duration unmasked a significant, negative association between a single reported symptom and fetal growth rate for gesta-

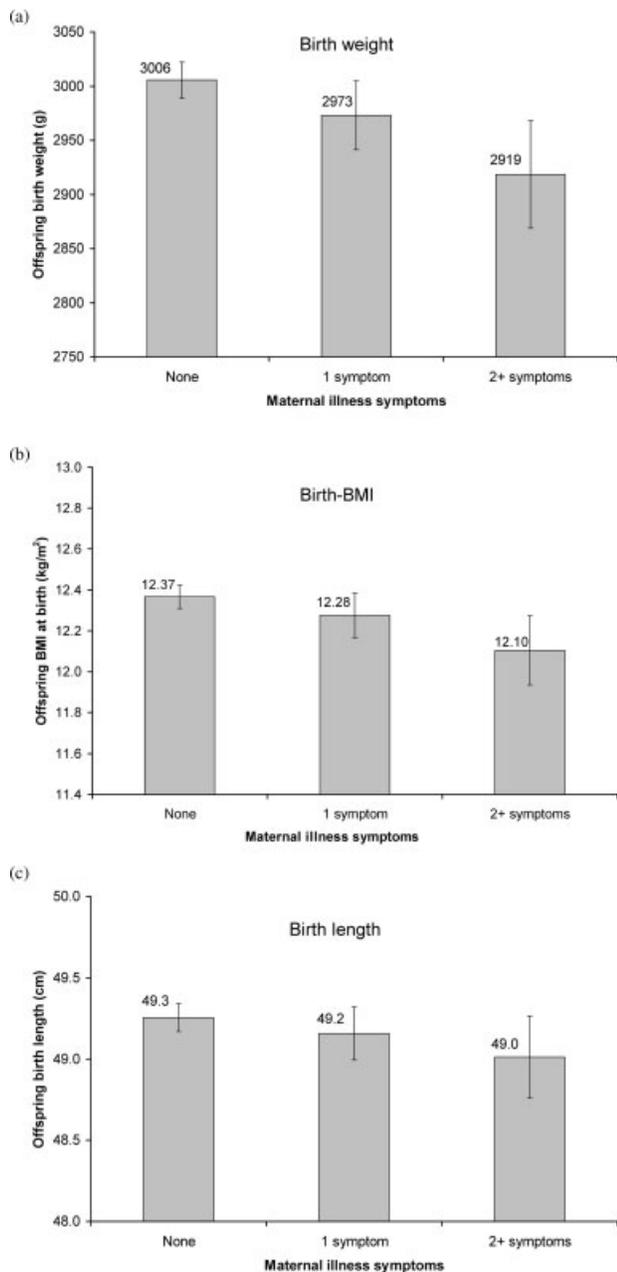


Fig. 1. Association between number of symptoms reported by mother and offspring (a) birth weight, (b) birth-BMI, and (c) birth length. Values = mean ± 95% CI and are adjusted for all variables included in Model 5 (Table 2). In each graph the Y-axis covers ~1 standard deviation of the outcome, allowing visual comparability of relationships across outcomes. The joint *F*-test for the 1 and 2+ symptom coefficients was significant for birth weight ($P < 0.013$) and birth BMI ($P < 0.028$) but not birth length ($P < 0.4$).

tional age, highlighting the likely importance of fetal growth restriction as a pathway to smaller offspring birth size. The larger negative association between multiple symptoms and birth weight was attenuated 25% (from 88 to 66 g birth weight decrement) after adjusting for differences in duration of gestation. This finding is consistent with the significant reduction in gestational age at birth

TABLE 3. Maternal illness symptoms as predictors of giving birth to a low birth weight baby

	Odds ratio (95% CI)
One symptom	
Unadjusted	1.25 (0.96, 1.63)
Adjusted ^a	1.31* (1.00, 1.72)
Multiple symptoms	
Unadjusted	1.51* (1.05, 2.16)
Adjusted ^a	1.40 (0.94, 1.98)

* $P < 0.05$.

^aAdjusted for gestational age at birth.

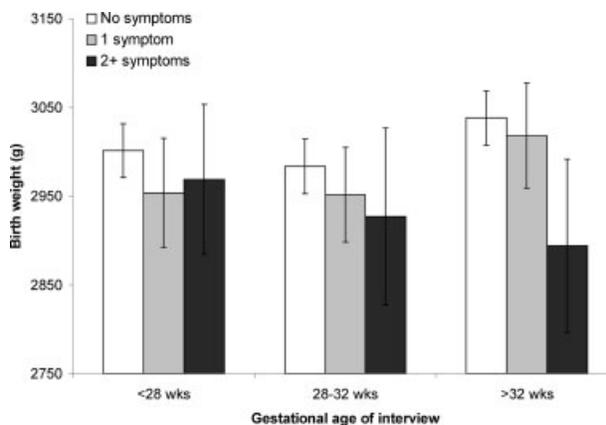


Fig. 2. Association between number of symptoms reported by mother and offspring birth weight stratified by gestational age of interview. Values = mean ± 95% CI and are adjusted for all variables included in Model 5 (Table 2). Model $R^2 = 0.183$. Interaction between number of symptoms and tertiles of gestational age at interview is not significant.

in women reporting multiple symptoms, and their significantly greater odds of a preterm delivery.

That fetal growth restriction also operates in these premature deliveries was demonstrated by the significantly decreased gestational age-adjusted birth weights of preterm newborns whose mothers reported symptoms compared with those preterm newborns whose mothers reported no symptoms. This shows that birth weight is lower in newborns whose mothers reported symptoms not only because they were born earlier, but also because they were smaller at the same gestational age. Thus, fetal growth restriction and prematurity tend to co-occur in offspring of mothers reporting illness symptoms during pregnancy.

Illness symptoms predicted reduced birth weight regardless of the gestational timing of the maternal interview. It is notable, however, that the greatest birth weight decrement was seen in infants whose mothers were interviewed later in gestation (after 32 weeks). One possible explanation for this finding, which is not testable with our cross-sectional data, is that individuals whose mothers reported symptoms late in gestation had less time to recover any growth deficits via compensatory or catch-up growth. If some of the early-exposed offspring did experience catch-up growth later in gestation, this would reduce the apparent effect of earlier maternal symptoms on fetal growth. The greater effect size of illness in later interviews could also trace to differences in gestational dura-

tion. Given the sensitivity of the parturitional cascade closer to term (Challis et al., 2005), infections experienced late in gestation might be more likely to initiate parturition early. Contrary to this expectation, adjusting these models for gestational age at birth did not change the illness coefficients. Although our finding awaits validation in a study using serial illness data, a greater impact of maternal illness on late gestation growth rate is biologically plausible as this is the age of most rapid fetal weight gain, and in particular, of fat deposition, which is a nutritionally sensitive element of newborn size and body composition in humans (Kuzawa, 1998; Ulijaszek, 2002).

The limitations of cross-sectional illness data

The limitations of this study, and in particular the cross-sectional nature of the self-reported illness variable, warrant discussion. Because information on self-reported illness symptoms were collected for each woman during a single pregnancy interview, it was not possible to establish which women were experiencing an acute illness, and which chronically suffered from disease symptoms. Given this, some of the apparent effect of illness during pregnancy may have been a symptom of poor health or chronic illness more generally. However, as noted above, illness symptoms had greatest negative associations with birth weight and birth-BMI when reported during the gestational age of fastest fetal growth and fat deposition, consistent with an acute rather than chronic effect of maternal illness on offspring growth. To the extent that illness had an acute effect on fetal growth rate, the cross-sectional nature of the illness data would tend to underestimate its true effect. A woman who was sick at any point in gestation other than the week of her baseline interview was included in the “not sick” group for this analysis despite the fact that she did experience an illness during pregnancy. This should underestimate the apparent effect of illness on birth weight, because it compares newborns of mothers experiencing illness at the time of their baseline interview to some newborns whose mothers may have experienced an illness at any other time during pregnancy but who were nonetheless coded as healthy. Our ability to detect an association between illness and birth outcomes, despite these limitations, suggests that the true impact of illness during pregnancy could be more substantial. A study including serial measurement of maternal illness symptoms across gestation would be necessary to evaluate this.

Implications for models of intergenerational nutritional signaling

These findings have implications for the concept of maternal–fetal nutritional signaling as a basis for adaptive plasticity, and for the role of fetal nutrition as an influence on adult disease risk. It has been argued that the signaling value of fetal nutrition may trace to a combination of two factors (Kuzawa, 2005): (1) the capacity of maternal metabolism to buffer fetal nutrient flow from transient positive and negative swings in intake and energy balance; and (2) a capacity to anchor or calibrate nutrient flow to chronic experiences of the mother (and to a lesser extent, grandmother) across her lifecourse. A system that ignores short-term variability but manages to cue into more stable, longer-term trends could provide a useful basis for adjusting metabolic and life history strategy in a

long-lived species. The evidence presented here for an acute effect of symptoms on fetal growth rate points to the importance of common illnesses during pregnancy as constraints on the predictive quality of any maternal–fetal nutritional signaling. To the extent that populations are burdened with common low-level communicable disease, as appears to be true in this Filipino cohort, this could elevate future metabolic disease risk in offspring (Kuzawa, 2007).

It could be argued that the illness effect, which is on the order of several ounces of birth weight, would have trivial implications for fetal nutrition and long-term biological settings or risk for disease. It is notable, however, that the magnitude of the association of illness with birth weight reported here was greater than the effect of most pregnancy supplementation trials on birth weight, including those conducted in the setting of developing nations (Kramer, 1993; cf. Ceesay et al., 1997). The birth weight deficit associated with multiple illness symptoms was 144 g when the women reporting symptoms were interviewed after a 32-week gestation, and 193.7 g if the illness effect was evaluated within the subset of these women who also gave birth prior to term. If these associations are causal, illness may have an effect on fetal growth—and presumably future life history strategy and metabolic disease risk—of a similar magnitude to that ascribable to normal variation in maternal macronutrient intake. In addition, given the common reporting of illness symptoms in this sample, any health impacts must be evaluated at the population level, in which they could shift the birth weight distribution. The deficit in birth weight predicted by multiple symptoms reported late in gestation was roughly half the difference in the Cebu and US birth weight means. Additional research employing serial ultrasound and illness assessments will be necessary to evaluate more definitively the role of illness as an influence on fetal nutrition and growth, and any associated impact on long-term health of offspring.

In conclusion, in this Philippine cohort, mothers who reported illness symptoms during pregnancy gave birth to offspring who were lighter and thinner, but not shorter, at birth, than women not reporting symptoms. These findings, which reflect reductions in both durations of gestation and fetal growth rate, illustrate how birth weight is not only a function of a mother’s nutritional status during pregnancy, but also of her health more generally. If maternal illness symptoms do not correlate with nutrition, their impact on fetal nutrition and growth rate should attenuate the value of fetal nutrition as a cue of the external nutritional environment. Despite the limitations in our cross-sectional measure of illness symptoms, the effect size on birth weight exceeded the typical effect of nutritional supplementation trials, especially when the illness was reported close to parturition. The possible long-term effect of maternal illness on offspring health warrants research attention.

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