Eur J Nutr (2005) 44 : 52–59
DOI 10.1007/s00394-004-0491-1

ORIGINAL CONTRIBUTION

Pagona Lagiou
Lorelei Mucci
Rulla Tamimi
Hannah Kuper
Areti Lagiou
Chung-Cheng Hsieh
Dimitrios Trichopoulos

Micronutrient intake during pregnancy in relation to birth size

Received: 10 June 2003
Accepted: 12 January 2004
Published online: 5 March 2004

P. Lagiou · A. Lagiou · D. Trichopoulos
Dept. of Hygiene and Epidemiology
School of Medicine, University of Athens
Athens, Greece

P. Lagiou · L. Mucci · R. Tamimi ·
C.-C. Hsieh · D. Trichopoulos (✉)
Dept. of Epidemiology
Harvard School of Public Health
677 Huntington Avenue
Boston, MA 02115, USA
Tel.: +1-617/432-4560
Fax: +1-617/566-7805
E-Mail: dtrichop@hsph.harvard.edu

H. Kuper
Clinical Research Unit
Dept. of Infectious & Tropical Diseases
London School of Hygiene
& Tropical Medicine
London, UK

A. Lagiou
Faculty of Health Professions
Athens Technological Institute (TEI)
Akadimia Platonos, Greece

C.-C. Hsieh
University of Massachusetts Cancer Center
Worcester, MA, USA

Summary *Background* There exists very little information on possible effects on birth size of micronutrient intakes at levels that are usually encountered among pregnant women in developed countries. *Aim of the study* To examine the relation of the intake of 20 micronutrients with birth weight, placental weight, birth length and head circumference of the offspring. *Methods* In a cohort of 222 Caucasian women with singleton pregnancies in Boston, USA, diet during pregnancy was ascertained at the 27th gestational week through a validated semi-quantitative food frequency questionnaire, covering also intake of dietary supplements. Micronutrient intakes were correlated with birth size parameters after adjustment for confounding variables, including total energy intake. *Results* Pantothenic acid, sodium and vitamin E were positively associated with all four birth size parameters. For pantothenic acid the association was statistically significant with respect to birth length, whereas for sodium with respect to head circumference and for vitamin E with respect to birth weight. In contrast, zinc was inversely associated with all four birth size parameters and the association was statistically significant with respect to head circumference. *Conclusions* In a moderately sized prospective study, we found evidence that pregnancy intake of pantothenic acid, vitamin E and sodium may be positively related with at least one of the studied birth size parameters, whereas an inverse association was found with respect to zinc intake. For the remaining 16 micronutrients, our findings indicate that they are not associated with birth size, at least within the range of intake encountered in this investigation. The results of this exploratory analysis need to be confirmed before pathophysiologic interpretations and generalizations are attempted.

Key words diet – vitamins – minerals – birth size – pregnancy

Introduction

Animal data and human studies in undernourished populations indicate that insufficient intake of several micronutrients, both vitamins and minerals, may have adverse effects on fetal growth, and recommended daily allowances have been formulated [1, 2]. Very little information exists, however, on the fetal growth effects, if any, of micronutrient intakes at levels generally higher than those recommended, that is at levels that are usually encountered in pregnant women under adequate care in developed western countries.

We have examined the relation of the intake of 20 micronutrients (water and lipid soluble vitamins, and minerals) with birth size parameters in a cohort of non-

EJN 491

preeclamptic pregnant Caucasian women under adequate health care who had healthy singleton births after gestation lasting from 37 to 42 weeks, inclusive, in a major university hospital in Boston USA from 1994 to 1995.

Methods

The present investigation was undertaken in the context of an international prospective study on predictors of pregnancy hormones and pregnancy outcomes among women in Boston, USA and Shanghai, China. Descriptive findings from this study have been previously published [3]. Due to lack of an adequate nutrient database for the Chinese diet at this time, we present here data on micronutrients in relation to birth and placental weight, birth length and head circumference of the offspring for the US women only.

Between March 1994 and October 1995, 402 eligible pregnant women were identified at the Beth Israel Hospital in Boston. According to study protocol, women had to be Caucasian, less than 40 years old and have a parity of no more than two. Women were not eligible if they had taken any kind of hormonal medication during the index pregnancy, if they had a prior diagnosis of diabetes mellitus or thyroid disease, or if the fetus had a known major anomaly. A trained health professional met all pregnant women at their first routine prenatal visit to the collaborating maternity clinic, ascertained eligibility for participation, explained to her the objectives of the study and obtained informed consent. The procedures followed were in accordance with the ethical standards for human experimentation established by the Institutional Review Board at the Harvard School of Public Health and Beth Israel Hospital.

Of 402 eligible women, 77 refused to participate, 9 were subsequently excluded because the index pregnancy was terminated through a spontaneous or induced abortion, 2 were excluded because of twin birth and 10 were lost to follow-up after the initial meeting. For the present analysis, we excluded 23 women because they had a pregnancy that lasted less than 37 or more than 42 weeks, 16 women because they had missing data for one or more of the factors evaluated in this analysis and an additional 14 women who developed preeclampsia. Of the remaining 251 pregnant women, 27 had not adequately completed the food frequency questionnaire and 2 had missing data on dietary supplements. Thus, 222 women were included in the present study.

Details on the non-dietary aspects of the questionnaire administered and medical record reviewing have been given in the earlier publication [3]. Birth size parameters, including placental weight, were measured at delivery by study collaborators. For the collection of dietary information we used an extensive semi-quantitative food frequency questionnaire covering also the intake of vitamin and mineral supplements. This questionnaire was identical to the one used and validated in the Nurses' Health Study [4]; information concerning this questionnaire and ways to access it can be found in the internet [5]. The questionnaire was mailed to the women one week prior to their second routine visit to the maternity clinic, which was around the 27th gestational week. It required information on their dietary patterns during the second trimester of pregnancy and was checked for accuracy and completeness by trained interviewers during the women's 2nd visit.

The statistical analyses were conducted using SAS Software version 8.0 (SAS Institute, Cary, NC, USA). Following simple cross-tabulations, the data were modelled through multiple linear regression with dependent variables, alternatively, birth weight, placental weight, birth length and head circumference. Main exposure variables were, alternatively, intake of 20 micronutrients through diet and supplements. Micronutrient intake was calculated using the Nurses' Health Study standard software [6], which in turn relies on standard food composition tables for the United States population [7–9].

In studying the association between micronutrient intake and pregnancy outcomes, we controlled for total energy intake (continuously), as well as for several non-dietary variables with confounding potential. Thus, we controlled, in addition to energy intake, for maternal age (categorically), maternal education (categorically), parity (categorically), maternal height (continuously), pre-pregnancy body mass index (BMI) (continuously), pregravid oral contraceptive (OC) use (categorically), smoking during pregnancy (categorically), exact gestational age at delivery (continuously) and gender of the baby (categorically). Very few women reported alcohol intake at low frequencies and quantities and, thus, alcohol intake was not a possible confounder in these data.

Results

Table 1 shows birth weight, placental weight, birth length and head circumference according to maternal characteristics and gender of offspring. Maternal characteristics were evaluated as possible confounders of the association of micronutrients with birth size characteristics. Positive associations with maternal height, pre-pregnancy BMI and pregravid OC use can be noted, indicating confounding potential. In contrast, no consistent effects were evident with respect to parity, smoking during pregnancy, maternal age and educational level. Because, however, confounding does not depend on statistical significance [10], all these factors were controlled for in the main analyses.

In Table 2, the mean, standard deviation, median and quartiles of intake of the studied micronutrients are presented, together with the respective recommended in-

European Journal of Nutrition (2005) Vol. 44, Number 1

Table 1 Birth weight, placental weight, birth length and head circumference of babies born to 222 non pre-eclamptic Caucasian women with gestation 37 to 42 weeks, inclusive, according to maternal characteristics. Boston, USA 1994–1995

	n	Birth weight (g) Mean (SE)	Placental weight (g) Mean (SE)	Birth length (cm) Mean (SE)	Head circumference (cm) Mean (SE)
Maternal age (years)					
18–24	5	3570 (160)	591 (65)	49.60 (1.54)	34.90 (0.29)
25–29	60	3478 (64)	543 (21)	50.17 (0.30)	34.38 (0.20)
30–34	138	3614 (39)	592 (16)	50.92 (0.20)	34.75 (0.15)
35+	19	3489 (117)	597 (47)	50.15 (0.49)	34.11 (0.33)
Maternal education					
High school graduate	36	3583 (77)	607 (51)	50.30 (0.42)	34.66 (0.24)
College graduate	92	3635 (48)	584 (17)	51.05 (0.24)	34.70 (0.16)
Higher	94	3490 (49)	563 (14)	50.32 (0.23)	34.47 (0.19)
Parity					
1	136	3570 (41)	570 (13)	50.67 (0.20)	34.70 (0.13)
2	86	3558 (50)	590 (22)	50.55 (0.25)	34.44 (0.20)
Height (cm)					
< 159	50	3473 (71)	573 (20)	50.26 (0.31)	34.18 (0.19)
160–164	53	3527 (71)	550 (22)	50.53 (0.28)	34.53 (0.20)
165–169	63	3599 (54)	577 (18)	50.70 (0.33)	34.85 (0.18)
170+	56	3647 (58)	616 (35)	50.94 (0.32)	34.75 (0.30)
Pre-pregnancy BMI (kg/m^2)					
< 18.9	26	3468 (72)	541 (29)	50.30 (0.39)	34.07 (0.24)
19–21.9	107	3530 (45)	580 (21)	50.38 (0.23)	34.50 (0.18)
22–24.9	59	3681 (60)	580 (18)	51.41 (0.30)	35.01 (0.19)
25+	30	3549 (102)	597 (26)	50.19 (0.41)	34.60 (0.27)
Oral contraceptive use prior to index pregnancy					
No	50	3437 (59)	533 (19)	49.98 (0.27)	34.26 (0.21)
Yes	172	3603 (37)	590 (14)	50.81 (0.18)	34.69 (0.13)
Smoking in pregnancy					
No	211	3566 (32)	579 (12)	50.68 (0.15)	34.64 (0.11)
Yes	11	3555 (192)	564 (50)	49.55 (1.12)	33.82 (0.41)
Gender of offspring					
Male	112	3631 (40)	579 (13)	51.15 (0.22)	34.76 (0.17)
Female	110	3498 (48)	578 (20)	50.08 (0.21)	34.42 (0.14)

takes. The large majority (89 %) of pregnant women reported consumption of one or more specified dietary supplements and the indicated micronutrient intakes incorporate both dietary and supplement sources. It is evident that most women consume quantities exceeding the recommended daily intakes.

Tables 3 to 6 present the crude and adjusted mean changes in birth weight, placental weight, birth length and head circumference per standard deviation increase of the studied micronutrients. Adjustment was done for energy intake, the maternal characteristics indicated in Table 1, exact gestational age at delivery, as well as offspring gender. Both crude and adjusted data are presented for all studied micronutrients, to allow comparisons with the results of other investigations. Whenever a micronutrient is significantly ($p < 0.05$) associated with any of the four birth size parameters – which are strongly intercorrelated – data in all four tables are given in bold fonts.

Pantothenic acid and sodium are positively associated with all four birth size parameters. For pantothenic acid the association is significant with respect to birth length and suggestive with respect to birth weight, whereas for sodium the association is significant for head circumference and suggestive for birth weight. Vitamin E is also positively associated with all four birth size parameters, but the association is both substantial and statistically significant only with respect to birth weight. Lastly, zinc is inversely associated with all four birth size parameters and the association is statistically significant with respect to head circumference. None of the associations retains statistical significance when p values are adjusted through the Bonferroni procedure.

Discussion

We did not find strong evidence in support of a positive or inverse association between the studied micronutrients on the one hand and birth weight, placental weight,

Table 2 Recommended Daily Allowances (RDAs) and daily intake of micronutrients, through diet and supplements, among 222 Caucasian non pre-eclamptic women with gestation 37 to 42 weeks, inclusive. Boston, USA 1994–1995

Micronutrient	RDAs*	Mean	Standard error of the mean	Standard deviation	Median	First quartile	Third quartile
Vitamin B1 (mg)	1.5	3.2	0.1	1.6	3.2	2.4	3.8
Vitamin B2 (mg)	1.6	3.9	0.1	1.8	3.7	2.9	4.6
Niacin (mg)	17	37.3	1	14.6	36.8	28.2	44.0
Folate (µg)	400	1056.6	32.2	479.1	1129	743.6	1342.1
Pantothenic acid (mg)	*3–12*	6.6	0.3	4.5	5.6	4	7.5
Vitamin B6 (mg)	2.1	5.6	0.5	7.7	4.1	2.6	5.9
Vitamin B12 (µg)	2.2	12.2	0.4	5.6	12.2	8.4	15.0
Vitamin C (mg)	70	307.5	14.6	217.0	253.6	186.6	377.0
Retinol (IU)	2666.7	6219.4	217.1	3235.3	5886.3	4367.1	8523.1
Vitamin D (IU)	400	616.6	16.7	249.4	636.4	472.2	763.1
Vitamin E (mg)	10	23.7	2.9	42.7	15.6	6.9	34.6
Iron (mg)	30	61.0	2.1	31.7	70.2	32.4	79.7
Calcium (mg)	1200	1298.2	39	581.7	1238.5	884.3	1622.9
Phosphorus (mg)	1200	1512.3	43	640.3	1435.7	1084.5	1888.9
Copper (mg)	*1.1*	1.6	0.1	1	1.4	1	2.0
Magnesium (mg)	*150–500*	354.8	11	163.9	332.7	256.2	423.2
Manganese (mg)	*1–10*	2.2	0.1	1	2	1.5	2.6
Potassium (mg)	*3100*	3191.7	102.6	1528.2	3000.5	2293.6	3873.9
Sodium (mg)	*600–3500*	2303.2	65.7	978.7	2114.6	1653.1	2822.0
Zinc (mg)	15	20.8	0.8	11.5	19.8	11.3	28.9
Energy intake (kJ)	10460	8635.4	226.8	3380.3	8357.5	6399.9	10161.7

* Regular fonts refer to intakes recommended during pregnancy (source: (2) Picciano, 1996) . *Italics* refer to intakes, or range of intakes recommended for adult women, in the absence of specific recommendations for pregnant women (source: Commission of the European Communities. Reports of the Scientific Committee for Foods (Thirty-first series) . Nutrient and energy intakes for the European Commission. Luxembourg, Office for Official Publications of the European Community, 1993)

Table 3 Crude and adjusted* mean change in birth weight per standard deviation increase in micronutrient intake among 222 Caucasian non pre-eclamptic women with gestation 37 to 42 weeks, inclusive, Boston, US 1994–1995. The adjusted associations are indicated in bold fonts when the respective micronutrient has been significantly associated with any of the four birth size parameters

	BIRTH WEIGHT					
	Crude			Adjusted		
	Mean change (g)	(95% CI)	P value	Mean change (g)	(95% CI)	P value
Micronutrient						
Vitamin B1	+48.8	−14.3 to +112.0	0.13	+45.3	−27.4 to +118.0	0.22
Vitamin B2	+38.4	−24.5 to +101.3	0.23	+27.8	−44.6 to +100.2	0.45
Niacin	+53.2	−9.1 to +115.5	0.10	+72.0	−5.9 to +149.8	0.07
Folate	+23.2	−39.6 to +86.0	0.47	+2.3	−59.3 to +63.8	0.94
Pantothenic acid	+84.9	+21.3 to +148.5	0.01	**+65.6**	**−6.7 to +137.9**	**0.08**
Vitamin B6	+6.8	−57.5 to +71.2	0.84	+2.7	−54.4 to +59.7	0.93
Vitamin B12	+14.0	−48.9 to +77.0	0.66	−19.3	−83.1 to +44.5	0.56
Vitamin C	+21.2	−41.5 to +83.9	0.51	−26.8	−95.8 to +42.2	0.45
Retinol	+26.0	−37.3 to +89.2	0.42	+29.3	−27.1 to +85.7	0.31
Vitamin D	+10.4	−52.1 to +72.8	0.75	−10.0	−70.1 to +50.0	0.74
Vitamin E	+38.0	−29.0 to +105.1	0.27	**+64.5**	**+5.9 to +123.0**	**0.03**
Iron	−11.2	−73.8 to +51.4	0.73	−6.7	−63.9 to +50.6	0.82
Calcium	+23.3	−35.5 to +82.2	0.44	+3.4	−70.5 to +77.2	0.93
Phosphorus	+58.1	−2.6 to +118.9	0.06	+78.9	−46.9 to +204.7	0.22
Copper	+5.0	−56.6 to +66.6	0.87	−64.3	−142.6 to +13.9	0.11
Magnesium	+63.4	+2.3 to +124.4	0.04	+88.2	−9.9 to +186.3	0.08
Manganese	+56.9	−5.1 to +118.8	0.07	+51.9	−29.6 to +133.4	0.21
Potassium	+52.0	−8.7 to +112.8	0.10	+11.4	−115.1 to +138.0	0.86
Sodium	+68.4	7.2 to +129.5	0.03	**+117.0**	**−7.8 to +241.9**	**0.07**
Zinc	−19.9	−82.2 to +42.5	0.53	**−48.5**	**−112.2 to +15.3**	**0.14**

* Adjusted for all covariates in Table 1, for exact gestational age at delivery and for total energy intake

Table 4 Crude and adjusted* mean change in placental weight per standard deviation increase in micronutrient intake among 222 Caucasian non pre-eclamptic women with gestation 37 to 42 weeks, inclusive, Boston, US 1994–1995. The adjusted associations are indicated in bold fonts when the respective micronutrient has been significantly associated with any of the four birth size parameters

	PLACENTAL WEIGHT					
	Crude			Adjusted		
	Mean change (g)	(95% CI)	P value	Mean change (g)	(95% CI)	P value
Micronutrient						
Vitamin B1	+2.9	−22.1 to +27.9	0.82	−3.1	−38.5 to +32.4	0.87
Vitamin B2	+7.7	−17.0 to +32.4	0.54	+4.5	−30.2 to +39.1	0.80
Niacin	+4.3	−21.7 to +30.4	0.75	+2.2	−33.2 to +37.6	0.90
Folate	+1.7	−22.3 to +25.8	0.89	−1.3	−28.6 to +26.1	0.93
Pantothenic acid	+20.9	−2.7 to +44.5	0.09	**+20.0**	**−11.4 to +51.5**	**0.21**
Vitamin B6	−1.8	−23.2 to +19.7	0.87	−4.0	−25.1 to +17.1	0.71
Vitamin B12	+5.4	−20.8 to +31.5	0.69	+0.6	−29.9 to +31.0	0.97
Vitamin C	−6.5	−29.1 to +16.2	0.58	−25.6	−56.0 to +4.8	0.10
Retinol	−3.3	−27.7 to +21.2	0.79	−4.3	−28.7 to +20.2	0.73
Vitamin D	+10.5	−14.4 to +35.4	0.41	+5.0	−22.5 to +32.5	0.72
Vitamin E	−4.7	−33.7 to +24.4	0.75	**+1.7**	**−26.4 to +29.9**	**0.90**
Iron	−5.3	−29.7 to +19.1	0.67	−3.3	−28.4 to +21.8	0.80
Calcium	+10.7	−12.3 to +33.6	0.36	+3.3	−32.9 to +39.4	0.86
Phosphorus	+18.3	−5.3 to +41.8	0.13	+39.9	−14.9 to +94.8	0.16
Copper	+3.2	−20.7 to +27.1	0.79	−4.4	−38.4 to +29.6	0.80
Magnesium	+9.1	−13.7 to +32.0	0.44	−0.3	−43.0 to +42.4	0.99
Manganese	+13.1	−9.1 to +35.4	0.25	+13.8	−19.0 to +46.5	0.41
Potassium	+12.1	−10.3 to +34.4	0.29	+12.3	−45.0 to +69.6	0.67
Sodium	+13.6	−9.7 to +36.9	0.25	**+24.7**	**−34.4 to +83.7**	**0.41**
Zinc	+11.5	−13.6 to +36.7	0.37	**+17.7**	**−10.0 to +45.4**	**0.21**

* Adjusted for all covariates in Table 1, for exact gestational age at delivery and for total energy intake

Table 5 Crude and adjusted* mean change in birth length per standard deviation increase in micronutrient intake among 222 Caucasian non pre-eclamptic women with gestation 37 to 42 weeks, inclusive, Boston, US 1994–1995. The adjusted associations are indicated in bold fonts when the respective micronutrient has been significantly associated with any of the four birth size parameters

	BIRTH LENGTH					
	Crude			Adjusted		
	Mean change (cm)	(95% CI)	P value	Mean change (cm)	(95% CI)	P value
Micronutrient						
Vitamin B1	+0.13	−0.18 to +0.45	0.41	+0.07	−0.30 to +0.43	0.72
Vitamin B2	+0.07	−0.24 to +0.39	0.64	−0.03	−0.39 to +0.33	0.89
Niacin	+0.16	−0.15 to +0.47	0.31	+0.23	−0.16 to +0.62	0.24
Folate	+0.02	−0.29 to +0.33	0.88	−0.14	−0.45 to +0.16	0.36
Pantothenic acid	+0.43	+0.12 to +0.75	0.01	**+0.42**	**+0.06 to +0.78**	**0.02**
Vitamin B6	−0.02	−0.33 to +0.30	0.92	−0.04	−0.32 to +0.25	0.79
Vitamin B12	+0.05	−0.26 to +0.36	0.77	−0.13	−0.44 to +0.19	0.44
Vitamin C	+0.15	−0.16 to +0.46	0.36	−0.03	−0.38 to +0.31	0.85
Retinol	+0.02	−0.29 to +0.34	0.88	+0.01	−0.27 to +0.29	0.94
Vitamin D	+0.01	−0.30 to +0.32	0.94	−0.10	−0.40 to +0.20	0.52
Vitamin E	+0.04	−0.30 to +0.37	0.83	**+0.17**	**−0.13 to +0.46**	**0.27**
Iron	−0.13	−0.44 to +0.18	0.40	−0.17	−0.45 to +0.11	0.24
Calcium	+0.05	−0.24 to +0.34	0.72	+0.00	−0.37 to +0.37	0.99
Phosphorus	+0.19	−0.11 to +0.49	0.22	+0.35	−0.27 to +0.98	0.27
Copper	+0.04	−0.26 to +0.35	0.78	−0.17	−0.56 to +0.22	0.40
Magnesium	+0.19	−0.11 to +0.49	0.22	+0.22	−0.27 to +0.71	0.39
Manganese	+0.23	−0.07 to +0.54	0.14	+0.19	−0.21 to +0.60	0.35
Potassium	+0.18	−0.12 to +0.48	0.25	−0.01	−0.64 to +0.62	0.98
Sodium	+0.21	−0.09 to +0.52	0.17	**+0.39**	**−0.23 to +1.01**	**0.22**
Zinc	−0.10	−0.41 to +0.21	0.54	**−0.21**	**−0.53 to +0.10**	**0.19**

* Adjusted for all covariates in Table 1, for exact gestational age at delivery and for total energy intake

Table 6 Crude and adjusted* mean change in head circumference per standard deviation increase in micronutrient intake among 222 Caucasian non pre-eclamptic women with gestation 37 to 42 weeks, inclusive, Boston, US 1994–1995. The adjusted associations are indicated in bold fonts when the respective micronutrient has been significantly associated with any of the four birth size parameters

	HEAD CIRCUMFERENCE					
	Crude			Adjusted		
	Mean change (cm)	(95% CI)	P value	Mean change (cm)	(95% CI)	P value
Micronutrient						
Vitamin B1	+0.22	+0.00 to +0.44	0.06	+0.10	−0.17 to +0.36	0.48
Vitamin B2	+0.17	−0.05 to +0.39	0.14	+0.03	−0.23 to +0.30	0.81
Niacin	+0.22	+0.00 to +0.44	0.05	+0.12	−0.17 to +0.41	0.41
Folate	+0.13	−0.09 to +0.36	0.24	+0.01	−0.21 to +0.24	0.91
Pantothenic acid	+0.26	+0.03 to +0.48	0.03	**+0.07**	**−0.19 to +0.34**	**0.59**
Vitamin B6	+0.01	−0.22 to +0.24	0.94	−0.02	−0.23 to +0.19	0.87
Vitamin B12	+0.21	−0.01 to +0.43	0.06	+0.09	−0.15 to +0.32	0.47
Vitamin C	+0.13	−0.09 to +0.35	0.24	−0.07	−0.32 to +0.18	0.58
Retinol	+0.15	−0.08 to +0.37	0.20	+0.13	−0.08 to +0.34	0.22
Vitamin D	+0.01	−0.21 to +0.23	0.92	−0.10	−0.32 to +0.12	0.38
Vitamin E	+0.04	−0.19 to +0.28	0.73	**+0.10**	**−0.11 to +0.32**	**0.35**
Iron	−0.05	−0.27 to +0.17	0.66	−0.08	−0.29 to +0.13	0.48
Calcium	+0.14	−0.07 to +0.35	0.20	−0.02	−0.29 to +0.26	0.90
Phosphorus	+0.30	+0.09 to +0.51	0.01	+0.28	−0.18 to +0.74	0.24
Copper	+0.11	−0.11 to +0.32	0.33	−0.18	−0.46 to +0.11	0.23
Magnesium	+0.32	+0.10 to +0.53	0.004	+0.28	−0.08 to +0.64	0.13
Manganese	+0.32	+0.10 to +0.54	0.004	+0.25	−0.04 to +0.55	0.10
Potassium	+0.25	+0.03 to +0.46	0.03	−0.16	−0.62 to +0.30	0.51
Sodium	+0.36	+0.15 to +0.57	0.001	**+0.48**	**+0.02 to +0.93**	**0.04**
Zinc	−0.08	−0.30 to +0.14	0.46	**−0.25**	**−0.48 to −0.01**	**0.04**

* Adjusted for all covariates in Table 1, for exact gestational age at delivery and for total energy intake

birth length and head circumference on the other. Nevertheless, our data indicate that pantothenic acid, sodium, vitamin E and zinc intake during pregnancy deserve attention in future investigations. It should also be noted that the large confidence intervals of the regression coefficients concerning the other micronutrients do not allow confident exclusion of minor effects of these micronutrients on one or more birth size parameters.

When evaluating the results of this investigation, it is important to recognize the shortcomings implicit in the generation of quantitative estimates from a semi-quantitative food frequency questionnaire that assumes standard portion sizes and utilizes standard food composition tables. The net result is misclassification of individual nutrient intakes. In a prospective study, however, this misclassification is generally non-differential and, as such, tends to attenuate existing associations rather than generate false ones or amplify weak ones [11].

Advantages of this study are its prospective nature, reliance on a strict protocol, and the use of a validated food frequency questionnaire and a reliable and relevant nutritional database. The measurement of several birth size parameters also allows assessment of internal consistency. Support for the study validity is also provided by the demonstration of expected association between maternal height and pre-pregnancy BMI on the one hand and birth size parameters on the other. There were too few smokers in the present study to allow documentation of the established inverse association between smoking and birth size, the absence of uneducated women in the study group hindered an evaluation of the association between educational level and birth size, and the variability of birth size by maternal age and parity was not large enough to emerge in this moderately sized investigation. Among the limitations of the study is the undertaking of many comparisons without underlying solid biomedical foundation, a process that complicates the interpretation of the generated p values. After application of the Bonferroni correction, none of the associations reported in this paper would have been nominally significant. The Bonferroni correction, however, is very conservative and may impart a non-significant label on a genuine association [12].

Several studies have explored the association between maternal intake of various vitamins, or maternal blood or cord blood vitamin levels in relation to birth size parameters. The majority of these studies were restricted to associations with birth weight. With respect to vitamins B1, B2, niacin, B6 and B12, most studies found no association [13–15], although an inverse association with birth weight has been reported for niacin [16]. With respect to folate, several studies indicate a positive association [17–20], but there are also reports indicating absence of an association [14,21]. For retinol, vitamin D and vitamin E, all studies in healthy women reported null associations [14, 19, 21]. Viewed in this background, our overall findings concerning vitamins may be viewed as null, particularly since the Hill criteria on establishing causation through epidemiological investigations are not met [22]. A possible exception concerns pantothenic acid. We found no evidence in the literature concerning this vitamin in relation to birth weight or other birth size parameters, but our findings point to a fairly consistent pattern of positive associations, significant with respect to birth length. Pantothenic acid is converted in the body to co-enzyme A (CoA) and is involved in the synthesis and acetylation of small molecules and the modification of numerous proteins with acetyl and fatty acyl groups. It may be relevant that many proteins involved in signal transduction are acetylated [23].

With respect to minerals, the results of studies exploring the relations of their intakes or blood levels with birth weight and other birth size parameters are also largely contradictory. Thus, associations have been reported for: iron, positive [24–26] and null [14, 15]; calcium, positive [24, 25] and null [14]; copper, null [15, 24, 25]; magnesium, suggestively positive [27, 28] and null [14, 24, 25]; sodium, positive [27] and mostly null [29–31]; and zinc, positive [32–36] and more often null [14, 15, 17, 20, 24, 37–40]. In view of this collective evidence, the apparent associations in our study between sodium intake (positive) and zinc intake (inverse) on the one hand and at least one of the studied birth size parameters on the other must be viewed with caution. Caution is also dictated by the fact that, as in all observational studies, direction of association cannot be directly evaluated and reverse causation cannot be excluded. Thus, zinc could in theory have been prescribed to prevent fetal growth retardation.

Conclusion

In a moderately sized prospective study undertaken with a strict protocol and contemporary methodology, we found evidence that intake of pantothenic acid, vitamin E and sodium are positively associated with at least one of the studied birth size parameters, whereas an inverse association was found with respect to zinc intake. There is no contradictory evidence in the literature concerning pantothenic acid, whereas for vitamin E and sodium the existing evidence is limited and contradictory, and for zinc largely null. For the remaining sixteen micronutrients, our results are compatible with the existing empirical evidence which, on the basis of scarce data, indicates that they are not associated with birth size parameters, at least within the range of intake encountered in this investigation. The results of this exploratory analysis need to be confirmed before pathophysiologic interpretations and generalizations are attempted.

Acknowledgment This study was supported in part by grant no. CA54220 from the U. S. National Institutes of Health.

References

1. King JC, Bronstein MN, Fitch WL, Weininger J (1987) Nutrient utilization during pregnancy. World Rev Nutr Diet 52:71–142
2. Picciano MF (1996) Pregnancy and lactation. In: Ziegler EE, Filer LJ (eds) Present knowledge in nutrition, 7th ed. ILSI Press, Washington, pp 384–395
3. Lipworth L, Hsieh CC, Wide L, Ekbom A, Yu SZ, Yu GP, Xu B, Hellerstein S, Carlstrom K, Trichopoulos D, Adami HO (1999) Maternal pregnancy hormone levels in an area with a high incidence (Boston, USA) and in an area with a low incidence (Shanghai, China) of breast cancer. Br J Cancer 79:7–12
4. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE (1985) Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 122:51–65
5. Department of Nutrition, Harvard School of Public Health. Semi-quantitative food frequency questionnaires http://www.hsph.harvard.edu/nutrition/department/ffq.htm
6. Romieu I, Stampfer MJ, Stryker WS, Hernandez M, Kaplan L, Sober A, Rosner B, Willett WC (1990) Food predictors of plasma beta-carotene and alpha-tocopherol: validation of a food frequency questionnaire. Am J Epidemiol 131:864–876
7. Adams CF (1975) Nutritive values of American foods. United States Department of Agriculture No. 456
8. Mclaughlin PJ, Weihrauch JL (1979) Vitamin E content of foods. J Am Diet Assoc 75:647–665
9. Consumer and Food Economics Institute (1982) Composition of foods: raw, processed, prepared. Washington, DC: US Department of Agriculture (USDA handbook series no 1–9)
10. Rothman KJ (1986) Modern Epidemiology. Boston, Little Brown
11. Willett W (1998) Correction for the effects of measurement error. In: Nutritional Epidemiology, 2nd ed. New York: Oxford University Press, pp 302–320
12. Armitage P, Berry G (1994) Statistical methods in medical research, 3rd Edition, Blackwell, Oxford, p 331
13. Vir SC, Love AH, Thompson W (1980) Thiamin status during pregnancy. Int J Vitam Nutr Res 50:131–140
14. Johnson AA, Knight EM, Edwards CH, Oyemade UJ, Cole OJ, Westney OE, Westney LS, Laryea H, Jones S (1994) Dietary intakes, anthropometric measurements and pregnancy outcomes. J Nutr 124(6 Suppl):936S–942S
15. Tamura T, Weekes EW, Birch R, Franklin JC, Cosper P, Davis RO, Finley SC, Finley WH (1994) Relationship between amniotic fluid and maternal blood nutrient levels. J Perinat Med 22:227–234

16. Tierson FD, Olsen CL, Hook EB (1986) Nausea and vomiting of pregnancy and association with pregnancy outcome. Am J Obstet Gynecol 155:1017–1022
17. Tamura T, Goldenberg RL, Freeberg LE, Cliver SP, Cutter GR, Hoffman HJ (1992) Maternal serum folate and zinc concentrations and their relationships to pregnancy outcome. Am J Clin Nutr 56: 365–370
18. Schroll TO, Hediger ML, Schall JI, Khoo CS, Fischer RL (1996) Dietary and serum folate: their influence on the outcome of pregnancy. Am J Clin Nutr 63: 520–525
19. Tamura T, Goldenberg RL, Johnston KE, Cliver SP, Hoffman HJ (1997) Serum concentrations of zinc, folate, vitamins A and E, and proteins, and their relationships to pregnancy outcome. Acta Obstet Gynecol Scand (Suppl) 165: 63–70
20. Neggers YH, Goldenberg RL, Tamura T, Cliver SP, Hoffman HJ (1997) The relationship between maternal dietary intake and infant birthweight. Acta Obstet Gynecol Scand (Suppl) 165:71–75
21. Mathews F, Yudkin P, Neil A (1999) Influence of maternal nutrition on outcome of pregnancy: prospective cohort study. BMJ 319:339–343
22. MacMahon B, Trichopoulos D (1996) Epidemiology: principles and methods. Boston: Little, Brown, pp 22–25
23. Plesofsky-Vig Nora (1996) Pantothenic acid. In: Ziegler EE, Filer LJ (eds) Present knowledge in nutrition, 7th ed. ILSI Press, Washington, DC, pp 236–244
24. Bogden JD, Thind IS, Kemp FW, Caterini H (1978) Plasma concentrations of calcium, chromium, copper, iron, magnesium, and zinc in maternal and cord blood and their relationship to low birth weight. Lab Clin Med 92: 455–462
25. Bogden JD, Thind IS, Louria DB, Caterini H (1978) Maternal and cord blood metal concentrations and low birth weight–a case-control study. Am J Clin Nutr 31:1181–1187
26. Achadi EL, Hansell MJ, Sloan NL, Anderson MA (1995) Women's nutritional status, iron consumption and weight gain during pregnancy in relation to neonatal weight and length in West Java, Indonesia. Int J Gynaecol Obstet 48(Suppl):S103–119
27. Doyle W, Crawford MA, Wynn AH, Wynn SW (1989) Maternal magnesium intake and pregnancy outcome. Magnes Res 2:205–210
28. Makrides M, Crowther CA (2001) Magnesium supplementation in pregnancy. Cochrane Database Syst Rev (4): CD000937
29. Steegers EA, Van Lakwijk HP, Jongsma HW, Fast JH, De Boo T, Eskes TK, Hein PR (1991) (Patho)physiological implications of chronic dietary sodium restriction during pregnancy; a longitudinal prospective randomized study. Br J Obstet Gynaecol 98:980–987
30. van der Maten GD (1995) Low sodium diet in pregnancy: effects on maternal nutritional status. Eur J Obstet Gynecol Reprod Biol 61:63–64
31. van Buul BJ, Steegers EA, Jongsma HW, Rijpkema AL, Eskes TK, Thomas CM, Baadenhuysen H, Hein PR (1995) Dietary sodium restriction in the prophylaxis of hypertensive disorders of pregnancy: effects on the intake of other nutrients. Am J Clin Nutr 62:49–57
32. Neggers YH, Cutter GR, Acton RT, Alvarez JO, Bonner JL, Goldenberg RL, Go RC, Roseman JM (1990) A positive association between maternal serum zinc concentration and birth weight. Am J Clin Nutr 51:678–684
33. Speich M, Bousquet B, Auget JL, Gelot S, Laborde O (1992) Association between magnesium, calcium, phosphorus, copper, and zinc in umbilical cord plasma and erythrocytes, and the gestational age and growth variables of full-term newborns. Clin Chem 38:141–143
34. Garg HK, Singhal KC, Arshad Z (1993) A study of the effect of oral zinc supplementation during pregnancy on pregnancy outcome. Indian J Physiol Pharmacol 37:276–284
35. Goldenberg RL, Tamura T, Neggers Y, Copper RL, Johnston KE, DuBard MB, Hauth JC (1995) The effect of zinc supplementation on pregnancy outcome. JAMA 274:463–468
36. Yang YX, Chen XC, Liu JY, Pan LM, Yan HC, Xu QM (2000) Effect of zinc intake on fetal and infant growth among Chinese pregnant and lactating women. Biomed Environ Sci 13:280–286
37. Mahomed K, James DK, Golding J, McCabe R (1989) Zinc supplementation during pregnancy: a double blind randomised controlled trial. BMJ 299: 826–830
38. Lao TT, Loong EP, Chin RK, Lam CW, Lam YM (1990) Zinc and birth weight in uncomplicated pregnancies. Acta Obstet Gynecol Scand 69:609–611
39. Caulfield LE, Zavaleta N, Figueroa A, Leon Z (1999) Maternal zinc supplementation does not affect size at birth or pregnancy duration in Peru. J Nutr Aug 129:1563–1568
40. Osendarp SJ, van Raaij JM, Arifeen SE, Wahed M, Baqui AH, Fuchs GJ (2000) A randomized, placebo-controlled trial of the effect of zinc supplementation during pregnancy on pregnancy outcome in Bangladeshi urban poor. Am J Clin Nutr 71:114–119