Diet during pregnancy and the risk of cerebral palsy

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The role of maternal diet in the development of the fetal brain has not been adequately explored. Marine *n*-3 fatty acids have, however, been proposed to be important for brain development. The present case–control study aimed to investigate the relationship between dietary intake during pregnancy and the occurrence of cerebral palsy (CP) in the offspring. Children with CP (*n* 109), born between 1984 and 1988 to mothers residing in the Greater Athens area, were identified at any time in 1991 or 1992 through institutions delivering care and rehabilitation. Successful nutritional interviews were conducted with ninety-one of these children. Controls were chosen among the neighbours of the CP cases or were healthy siblings of children with neurological diseases other than CP, seen by the same neurologists as the children with CP. A total of 278 control children were chosen, and 246 of them were included in the nutritional study. Guardians of all children were interviewed in person on the basis of a questionnaire covering obstetric, perinatal socioeconomic and environmental variables. A validated semiquantitative food-frequency questionnaire of 111 food items was used to estimate maternal dietary intake during pregnancy. Statistical analysis was done by modelling the data through logistic regression. Food groups controlling for energy intake were alternatively and simultaneously introduced in a core model containing non-nutritional confounding variables. Consumption of cereals (mostly bread) and fish intake were inversely associated with CP ($P < 0{\cdot}05$ and $P < 0{\cdot}09$ respectively) whereas consumption of meat was associated with increased risk ($P < 0{\cdot}02$). A protective effect of fish consumption and a detrimental effect of meat intake have been suggested on the basis of earlier work and appear to be biologically plausible. If corroborated by other studies, these results could contribute to our understanding of the nutritional influences on fetal brain development.

Cerebral palsy: Maternal diet: *n*-3 Fatty acids

It has been suggested that marine *n*-3 fatty acids may have beneficial effects on pregnancy duration and, perhaps, human brain development (Crawford & Sinclair, 1972; Olsen *et al.* 1990, 1993; Olsen, 1993). However, the evidence has not been entirely consistent (Olsen *et al.* 1991, 1992). Cerebral palsy (CP) is a manifestational entity that includes patients with chronic non-progressive disorders of movement or posture of early onset (Stanley & Alberman, 1984). The aetiology of CP is poorly understood, but several prenatal and postnatal factors have been incriminated; prematurity and growth retardation appear to be common conditions in most series, acting, perhaps, by compromising vascular integrity (Pharoah *et al.* 1990; Leaf *et al.* 1992; Uvebrant & Hagberg, 1992; Blair & Stanley, 1993; Cummins *et al.* 1993; Allan *et al.* 1994). We have undertaken a case–control study of nutritional intake during pregnancy in relation to CP in the offspring. No previous study has assessed the role of maternal diet during pregnancy in the development of CP. Long-chain, highly unsaturated fatty acids (marine *n*-3 fatty acids) may be particularly important for brain development (Crawford, 1993; Olsen, 1993) but most nutritional databases, including those concerning

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Abbreviations: CP, cerebral palsy; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.
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Greek foods, do not contain adequate information on these fatty acids (Trichopoulou, 1992). Therefore, our analysis has focused on major food categories.

Methods

There is no population-based CP registry in Greece. We have attempted to identify all children with an established diagnosis of CP born in the Greater Athens area (total population 3·5 million) between 1 January 1984 and 31 December 1988 and residing in this area at any time during the period 1 January 1991 and 31 December 1992. Children with CP were identified through the collaboration of governmental and non-governmental institutions dedicated to the care and rehabilitation of children with CP. On the basis of repeat identification of CP cases from different sources and hospital statistics, we estimate that we have covered more than two-thirds of the target number. The protocol of the study was approved by the Biomedical Research Committee of the Central Health Council of Greece (Petridou *et al.* 1996). A total of 109 children with CP were identified; for 103 of them collaboration with their guardian was established and the diagnosis of CP was confirmed by one of the participating childhood neurologists. Two control series were assembled from the same study base. For the first series the closest neighbour of the CP case of similar sex and age (±12 months) was invited to participate. In some instances, when it was difficult to decide which one was the closest neighbour, two controls were chosen for each case. There were twelve refusals and eventually 155 neighbourhood control children were included. For the second control series, the first neurological patient seen by the attending physician after a visit by the CP patient, with a healthy sibling of similar sex and age (±12 months) to the CP case was identified; these siblings formed the second control series. There were four refusals, and for eight cases no matching controls were identified; eventually ninety-nine health-care-matched control children were considered for the analysis. The guardians of all cases and controls (mothers, in 90 % of all instances, equally distributed among cases and controls) were interviewed by the same paediatrician (MK). The interview covered several obstetric, perinatal, socioeconomic and environmental variables as well as a validated semiquantitative food-frequency questionnaire (Gnardellis *et al.* 1995) of maternal dietary habits during pregnancy. The questionnaire has not been validated for dietary intakes during pregnancy, but it is assumed that women report more reliably, if anything, information concerning this important period in their lives. All food-frequency questionnaires were interviewer-administered. In the absence of evidence from human subjects suggesting a particular window of susceptibility, diet in pregnancy overall was evaluated. It was not possible to ascertain maternal dietary intakes reliably during the index pregnancy for twelve CP cases and eight controls.

The two control series were, as expected, very similar (Petridou *et al.* 1996) since they both represent the same secondary study base (Miettinen, 1985). They were, therefore, combined for the analysis. Conditional and unconditional analysis generated similar results and techniques of the latter type were chosen for this presentation (Breslow & Day, 1980).

A core model including all non-nutritional variables for which there was either empirical evidence or biological plausibility for association with CP was constructed (Petridou *et al.* 1996). The following variables were always included in the core model: age of the child (in four 2-year groups, categorically); sex (categorically); maternal age at delivery (in 5-year groups, continuously); maternal age at menarche (in 2-year groups, continuously); maternal chronic disease, in a total of eighteen cases and twenty-five controls, including simple goitre, duodenal ulcer, chronic respiratory problems, and mild peripheral neurologic conditions like lumbago or metatraumatic epilepsy in one instance (yes *v.* no); previous spontaneous abortions (yes *v.* no); persistent vomiting during index pregnancy (subjective: yes *v.* no); multiple pregnancy (yes *v.* no); number of obstetric visits as indicator of obstetric care (continuously); timing of membrane rupture in relation to index delivery (more *v.* less than 24 h); use of general anaesthesia in the index delivery (yes *v.* no); mode of delivery (normal and suction, forceps, emergency Caesarean, planned Caesarean, categorically); abnormal placenta (based on medical record: yes *v.* no); head circumference (large (i.e. ≥ 370 mm) *v.* not large); evident congenital malformation (yes *v.* no); place of index delivery (private *v.* public hospital); use of supplementary Fe during index pregnancy (yes *v.* no); intentional physical exercise during index pregnancy (more *v.* less than 2 h/week) and painless delivery classes (yes *v.* no). In this dataset smoking and consumption of coffee or alcoholic beverages during pregnancy were unrelated to CP and had no confounding influence (Petridou *et al.* 1996); accordingly they were not included in the core model. Gestational age, birth weight conditional on gestation and maternal weight gain during pregnancy were strong predictors of CP, but were not included in the model, since they are probably intermediate stages in a possible link between diet and CP (mediators) rather than genuine confounders (Breslow & Day, 1980).

The dietary information was evaluated in terms of major food categories (Davidson & Passmore, 1979; Trichopoulou *et al.* 1995). Mothers were asked to indicate the average frequency of consumption, during their entire index pregnancy, of 111 food items according to precoded levels of intake per month, per week or per d. The frequency of consumption of different food items was eventually quantified, approximately, in terms of the number of times per month the food was consumed (Graham *et al.* 1978; Katsouyanni *et al.* 1991; Trichopoulou *et al.* 1995). Thus a value of 30 was assigned to food items consumed almost every day, a value of 4 to those consumed once a week; a value of 2 to those consumed at least once monthly but not every week; and a value of 0 to food items rarely or never consumed. Seasonal adjustment of food intake was undertaken when needed. Individual food items were combined into food groups following the classification suggested by Davidson & Passmore (1979). Because of the particular interest in fish intake the group concerning meats and allied products was divided into 'fish and fish products' and 'meat and meat products'. Energy intake for each individual was

Table 1. Classification into food groups of food items considered in the food-frequency questionnaire

Food group	Food item
Cereals and starchy roots	White bread, brown bread, traditional bread, rice, pasta, various breakfast cereals, trahana, cheese pie (1/2)*, meat pie (1/2), vegetable pie (1/2), pizza (1/2), pastitsio (1/2), potatoes
Sugars and syrups	Sugar, cookies, chocolate bars, wafers, baklava, kataifi and other Greek sweets with syrup, spoonful sweets (Greek delicacies), jellies, glazed fruits, cream pastries, pancakes with syrup, bonbons, honey, compote (1/2)
Pulses, nuts and seeds	Dry beans, chick peas, lentils, fava beans, dry broad beans, nuts
Vegetables	Raw tomatoes, cooked tomatoes, cucumbers, peppers, raw cabbage, cooked cabbage, lettuce, raw carrots, cooked carrots, courgettes, onions, green beans, aubergines, spinach, leeks, okra, dandelions, artichokes, fresh broad beans, peas, cauliflower, broccoli, beets, mushrooms, vegetable pie (1/2), moussaka (1/2)
Fruits	Watermelon, melon, mandarins, oranges, apples, peaches, pears, grapes, apricots, cherries, strawberries, bananas, figs, pineapple, grapefruit, fresh fruit juice, dried fruits, compote (1/2)
Meats and meat products	Pork, veal, beef, lamb, goat, chicken, turkey, ham, salami and sausages, liver and other offal, eggs, meat pie (1/2), moussaka (1/2), pastitsio (1/2)
Fish and fish products	Fish, shellfish
Milk and milk products	Feta cheese, kaseri cheese, other cheese, whole milk, skimmed milk, full-fat yoghurt, reduced-fat yoghurt, milk pudding, rice milk pudding, ice-cream, cheese pie (1/2), pizza (1/2)
Oils and fats	Butter on bread, butter for cooking, margarine on bread, margarine for cooking, seed oils, olive oils, olives

* 1/2 indicates the cooked meals that were allocated to two food groups (one half in each).

Table 2. Frequency distribution of ninety-one children with cerebral palsy and 246 controls by sociodemographic variables (Athens, about 1992)

		Cases		Controls	
Variable	Category	*n*	%	*n*	%
Sex	male	48	52·7	132	53·7
	female	43	47·3	114	46·3
Year of birth	1984–6	49	53·8	115	46·7
	1987–8	42	46·2	131	53·3
Maternal education	≤11 years	71	78·0	180	73·2
	>11 years	20	22·0	66	26·8
Maternal occupation	housewife	64	70·3	135	54·9
	sedentary	10	11·0	46	18·7
	standing	13	14·3	52	21·1
	manual worker	4	4·4	13	5·3
Paternal occupation	manual	42	46·1	74	30·0
	non-manual	49	53·9	172	70·0
Marital status	married	87	95·6	234	95·1
	not married	4	4·4	12	4·9

estimated by multiplying the energy content of a selected typical portion of each specified food item by frequency at which the food was eaten each month and adding together these estimates for all food items (Gnardellis *et al.* 1995). Portion size is described in natural units (e.g. number of eggs) or in comparison to a standard portion (average serving). Energy content data were derived from tables of composition of Greek foods and dishes (Trichopoulou, 1992).

In order to investigate the association of the estimated food group intakes with CP, a preliminary analysis was undertaken based on the comparison of the frequency distributions of cases and controls by food group consumption. Because most food intakes are positively correlated with total energy intake, energy adjustment was used to control for potential confounding by energy intake (Willett & Stampfer, 1986). The data were eventually modelled through multiple logistic regression controlling for the core variables previously indicated and total energy intake. Food groups were alternatively and simultaneously introduced into the models. The latter approach allows better control of confounding and generates more valid results, since it also accommodates intercorrelations among the various food groups. The association of each food group with CP is expressed through the odds ratio (and the respective confidence limits), which indicates how much higher or lower the risk of CP becomes when the consumption of the corresponding food category changes by one unit. The unit is arbitrarily defined, but usually refers to a plausible increase (or decrease) of consumption frequency.

Results

Of the ninety-one cases, forty-eight were males and the mean age was 5·07 (SD 1·39) years; of the 246 controls, 132 were males and the mean age was 4·84 (SD 1·42) years. Table 2 shows the distribution of cases and controls by sociodemographic variables. There were no statistically significant differences in the distributions by these variables.

Table 3. Frequency distribution of ninety-one children with cerebral palsy and 246 control children by frequency of consumption (by the mother) of food items in different categories

Food category		Cases *n*	Cases %	Controls *n*	Controls %
Cereals and starchy roots	≤1 per d	11	12·1	38	15·4
	2	59	64·8	89	36·2
	>2	21	23·1	119	48·4
Sugars and syrups	≤1 per d	11	12·1	21	8·5
	2	31	34·0	104	42·3
	>2	49	53·9	121	49·2
Pulses, nuts and seeds	≤1 per week	15	16·5	32	13·0
	2	15	16·5	63	25·6
	>2	61	67·0	151	61·4
Vegetables	≤4 per d	18	19·8	63	25·6
	5	22	24·2	86	35·0
	>5	51	56·0	97	39·4
Fruits	≤2 per d	12	13·2	21	8·5
	3–4	16	17·6	64	26·0
	>4	63	69·2	161	65·5
Meats and meat products	≤4 per week	7	7·7	35	14·2
	5–6	23	25·3	88	35·8
	7–8	24	26·4	72	29·3
	>8	37	40·6	51	20·7
Fish and fish products	<1 per week	33	36·3	80	32·5
	1	42	46·1	124	50·4
	>1	16	17·6	42	17·1
Milk and milk products	≤1 per d	8	8·8	13	5·3
	2	25	27·5	68	27·6
	>2	58	63·7	165	67·1
Oils and fats	≤8 per week	10	11·0	32	13·0
	9	25	27·4	67	27·2
	10	23	25·3	64	26·0
	>10	33	36·3	83	33·8
Energy intake (MJ/d)	≤6·7	47	51·6	143	58·2
	6·7–7·5	19	20·9	40	16·2
	≥7·5	25	27·5	63	25·6

Table 4. Multiple logistic regression-derived odds ratios (OR) and 95 % CI for cerebral palsy, associated with an increase in the frequency of consumption of particular food groups in ten alternative models*

Model	Food group	Unit	OR	95 % CI	*P* value
1	Cereals and starchy roots	3 times per week	0·83	0·72–0·96	0·01
2	Sugars and syrups	once daily	1·08	0·73–1·62	0·69
3	Pulses, nuts and seeds	once weekly	1·16	0·81–1·66	0·41
4	Vegetables	once daily	1·36	1·07–1·73	0·01
5	Fruits	once daily	1·15	1·03–1·29	0·01
6	Meats and meat products	twice weekly	1·45	1·11–1·89	0·01
7	Fish and fish products	once weekly	0·77	0·48–1·24	0·28
8	Milk and milk products	once daily	1·12	0·75–1·69	0·58
9	Oils and fats	once weekly	1·09	0·85–1·39	0·49
10 Simultaneous model					
	Cereals and starchy roots	3 times per week	0·85	0·72–1·00	0·05
	Sugars and syrups	once daily	1·21	0·77–1·90	0·41
	Pulses, nuts and seeds	once weekly	1·06	0·73–1·55	0·75
	Vegetables	once daily	1·19	0·88–1·61	0·25
	Fruits	once daily	1·11	0·98–1·27	0·10
	Meats and meat products	twice weekly	1·42	1·07–1·88	0·02
	Fish and fish products	once weekly	0·63	0·37–1·08	0·09
	Milk and milk products	once daily	1·12	0·66–1·88	0·68
	Oils and fats	once weekly	1·08	0·84–1·40	0·55

* Models 1–9 cover core variables (see p. 408), energy intake (not interpretable in case–control studies) and alternatively the indicated food groups; model 10 covers core variables, energy intake, and simultaneously, all food groups.

Table 3 shows distributions of cases and controls by frequency of consumption of foods of different categories without any adjustments. This table is descriptive, since the strong intercorrelation between food groups generates powerful mutual confounding; moreover, confounding influences of core model variables are not accounted for.

Table 4 presents odds ratios for CP associated with increases in the frequency of consumption (by specified units) of food items in particular categories controlling for the core variables and energy intake; each food item was introduced separately in models 1–9, whereas in model 10 they were mutually adjusted. From the most valid results indicated in model 10 there is evidence that increased meat consumption during pregnancy was associated with elevated risk of CP in the offspring ($P=0{\cdot}02$) whereas increased consumption of cereals ($P=0{\cdot}05$) and fish ($P=0{\cdot}09$) were associated with reduced risk. For the other food groups there is no evidence that frequency of consumption during pregnancy was associated with the risk of CP in the offspring. Introduction into model 10 in Table 4 of gestational age, birth weight conditional on gestation, and maternal weight gain during pregnancy had little effect: the odds ratio for cereals was reduced to 0·81 ($P=0{\cdot}02$), that for fish was reduced to 0·51 ($P=0{\cdot}04$), and that for meat was increased to 1·44 ($P=0{\cdot}02$); moreover, the other nutritional variables in the model remained non-significant in their relationships to CP.

We substituted in model 10 (Table 4) the ratio meat and meat products : fish and fish products in the place of these two food groups. The association with the ratio was stronger and statistically more significant ($P=0{\cdot}01$) than those with either of the two contributing variables, thus suggesting an interactive effect.

We also evaluated the consistency of findings when CP cases were separately compared with each control series. The results were remarkably consistent, although the reduction in power made confidence intervals wider. Thus the odds ratio for meats was 1·38 with neighbourhood controls and 1·44 with health-care controls; the corresponding odds ratios for fish were 0·57 and 0·69; and for cereals 0·85 and 0·86. Again, none of the other food groups emerged as a significant predictor of CP in either comparison.

Discussion

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are, biologically, the most important long-chain *n*-3 fatty acids and are found almost exclusively in fish and other marine sources. A number of compounds essential for endothelial integrity and coagulation regulation are derived from EPA (thromboxane A_3, leukotriene B_5 and prostacyclin PGI_3). It has been suggested that a diet rich in fish oil during pregnancy, possibly on account of its content of EPA and DHA, could reduce the frequency of occurrence of obstetric complications such as pre-eclampsia (Williams *et al.* 1995), counter fetal growth retardation (Olsen *et al.* 1986) and increase birth weight. (Olsen *et al.* 1990). DHA also appears to be essential in neural development, while DHA deficiency has been implicated in periventricular haemorrhage and CP (Crawford, 1993). CP is intimately linked to short gestational age and low birth weight conditional on gestional age (Stanley & Alberman, 1984; Pharoah *et al.* 1990; Uvebrant & Hagberg, 1992; Petridou *et al.* 1996) and both of these entities have been associated with reduced intake of marine *n*-3 fatty acids. Therefore, an inverse relationship between *n*-3 fatty acids intake and CP appears biologically plausible and has also been postulated on pathophysiological grounds (Crawford, 1993). However, no previous study has evaluated the relationship between nutrition during pregnancy in general, or fish intake during that period in particular, and the occurrence of CP in the offspring.

The present case–control study was fairly large and there was adequate comparability between the case and the control series due to control generation from an explicitly defined secondary study base and the very low proportion of refusals. Information bias is a concern in all case–control studies but the Greek women were not aware of the working hypothesis of this study involving a role of *n*-3 marine fatty acids in the aetiology of CP. Poor information provided by some of the study participants may have generated non-differential exposure misclassification, but this form of bias does not, as a rule, generate positive results when these do not actually exist (MacMahon & Trichopoulos, 1996). There was no information about specific birth outcomes following the birth of a CP child (a possible source of information bias) but spontaneous abortions preceding the index pregnancy were accounted for in the analysis and total sibship size was not a risk factor for CP in this dataset. It appears, therefore, that there is converging and apparently valid evidence for an important role of *n*-3 fatty acids in fetal growth and development, including neural development. However, additional work is needed to establish whether consumption of fish or marine *n*-3 fatty acids protects against the development of CP and, if so, whether the effect is mediated through fetal growth or is specific to CP. Studies of CP cases with aberrant brain configurations should allow clarification of the degree of specificity in the apparent inverse association of CP with fish consumption and intake of marine *n*-3 fatty acids.

It has been generally accepted that a high intake of saturated fatty acids is a causative factor in atherosclerosis and cardiovascular mortality. Cystic periventricular leucomalacia, an ischaemic lesion involving the vascular system, is an antecedent of CP (Fujimoto *et al.* 1994). The richest natural source of saturated fatty acids in the diet is the fat of ruminant animals. Therefore, one would expect meat from ruminants to be positively correlated with vascular disease or disorder. Fish and sea foods, on the other hand, contain unsaturated fatty acids mainly of the long-chain *n*-3 variety, with fish flesh and oils being the richest sources of EPA and DHA.

A weakness of the present study is that it focused on food rather than nutrient exposures, and did not directly address the role of the putatively critical intake of DHA. Greek nutrient databases, however, do not contain such information at present (Trichopoulou, 1992), and it is not clear whether information from other databases is applicable to the fish mix consumed in Greece. The statistically significant and strong association of CP with the meat : fish ratio strengthens the proposed interpretation of the findings of this study, because there is strong metabolic competition among the fatty acids of different types. The meat : fish ratio is a variable with strong biological bearings, but its empirical relevance needs to be confirmed in other independent datasets.

The present study provides intriguing evidence that a maternal diet rich in fish and with modest meat intake during pregnancy may reduce the risk of CP in the offspring. It appears justified to undertake a large, perhaps multicentre, cohort study on diet during pregnancy and CP in the offspring. Such a study, however, would have to follow a birth cohort of more than 100 000 over a period of more than 4 years in order to generate statistically reliable results.

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