



The influence of mother's dietary intake during pregnancy on brain development and cognitive ability

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A few earlier studies

The role of iron in neurodevelopment: fetal iron deficiency and the developing hippocampus

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Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study

Joseph R Hibbeln, John M Davis, Colin Steer, Pauline Emmett, Imogen Rogers, Cathy Williams, Jean Golding

Maternal *MTHFR* 677C>T genotype and dietary intake of folate and vitamin B₁₂: their impact on child neurodevelopment

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Folate and the methylenetetrahydrofolate reductase 677C → T mutation correlate with cognitive performance

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Oily fish intake during pregnancy – association with lower hyperactivity but not with higher full-scale IQ in offspring

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Fish Intake During Pregnancy and Early Cognitive Development of Offspring

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The Effect of Early Human Diet on Caudate Volumes and IQ

ELIZABETH B. ISAACS, DAVID G. GADIAN, STUART SABATINI, WUI K. CHONG, BRIAN T. QUINN, BRUCE R. FISCHL, AND ALAN LUCAS

Iodine deficiency in pregnancy, infancy and childhood and its consequences for brain development

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Higher Maternal Plasma Folate but Not Vitamin B-12 Concentrations during Pregnancy Are Associated with Better Cognitive Function Scores in 9- to 10- Year-Old Children in South India¹⁻³

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Objective

- To determine whether exposure to specific dietary factors *in utero* and infancy influences cognition

Hypotheses

- Suboptimum levels of nutrients *in utero* lead to impaired neurodevelopment and cognitive ability
- Variation in genes related to nutrient metabolism is associated with neurodevelopment in infancy
- Association of maternal genotype with measurements of cognitive ability, independent of child's genotype, will indicate a role of the prenatal environment



- Association between diet and cognition can be affected by confounding by lifestyle factors, reverse causality and measurement error
- Polymorphisms in genes that metabolise nutrients can be used as proxies for differences in dietary intake and therefore to infer causal relationships between nutrients and cognition without the above problems



🦋 ALSPAC (Avon Longitudinal Study of Parents and Children)

- Population-based prospective study conducted in Bristol, England to evaluate factors that affect health and development of children
- ~ 14,000 pregnant women enrolled between April 1991 and December 1992
- Information on mother and child collected at regular intervals and ongoing
- DNA samples available for mothers and children (~10000 each, ~7000 duos)



Main Outcome

- IQ at age 8 years: WISC-III (Wechsler, Golombok and Rust, 1992), age-adjusted
- 5 verbal subtests: information, similarities, arithmetic, vocabulary, comprehension
- 5 performance subtests: picture completion, coding, picture arrangement, block design, object assembly
- Short term storage capacity: forwards and backwards digit span task



Secondary Outcomes

- Strengths and Difficulties Questionnaire
 - @ 8 years
 - emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems = total difficulties score
 - prosocial behaviour
- Ball skills @ 7 years
- Stereoacuity @ 7 years
- SATs results



Genetic Analysis

- SNPs selected in candidate genes or genes emerging from GWAS

Genotyped

- 60 SNPs in 52 genes
- 9007 mothers
- 11009 children

Analysis

- 58 SNPs in 50 genes
- ~4000 mother/child duos with genotype & IQ
- ethnicity = white



gene	associated SNP	nutrient/disease
BCMO1	rs6564851	beta carotene
TAS2R38	rs1726866	bitter taste receptor
TAS2R38	rs713598	bitter taste receptor
CASR	rs1801725	calcium
TRPV5/C7orf34	rs11979330	calcium
TRPV6	rs4987667	calcium
SLC8A1	rs2110922	calcium
CELSR2	rs646776	cholesterol
LDLR	rs2228671	cholesterol
SLC5A7	rs1013940	choline
SLC5A7	rs333229	choline
MTHFR	rs1801133	folic acid
GCK	rs1799884	glucose
DIO1	rs2235544	iodine
HFE	rs1799945	iron
HFE	rs1800562	iron
TF	rs3811647	iron
TMPRSS6	rs4820268	iron
LCT	rs4988235	lactose
APOB	rs693	lipids
APOE	rs2075650	lipids
LIPC	rs1532085	lipids
TRPM6	rs2274924	magnesium
TRPM6	rs3750425	magnesium
TRPM7	rs8042919	magnesium
MAT1A	rs1143693	methionine
MAT2A	rs17026419	methionine
MTR	rs1805087	methionine
MTRR	rs1801394	methionine
FTO	rs9939609	obesity

gene	associated SNP	nutrient/disease
PTGS2	rs20417	omega-3 fatty acids
GPX4	rs713041	selenium
ADAMTS9	rs4607103	T2D
CDC123/CAMK1D	rs12779790	T2D
CDKAL1	rs10946398	T2D
HHEX-IDE	rs1111875	T2D
HNF1B	rs757210	T2D
IGFBP2	rs4402960	T2D
KCNJ11	rs5219	T2D
NOTCH2	rs10923931	T2D
TCF7L2	rs7903146	T2D
THADA	rs7578597	T2D
TSPAN8-LGR5	rs7961581	T2D
WFS1	rs10010131	T2D
PPARG	rs1801282	T2D/obesity
GCKR	rs780094	triglycerides
CDKN2A/B	rs10811661	triglycerides/T2D
JAZF1	rs864745	triglycerides/T2D
SLC2A9	rs16890979	uric acid
FUT2	rs492602	vitamin B12
TCN2	rs1801198	vitamin B12
ALPL/NBPF3	rs4654748	vitamin B6
SLC23A1	rs33972313	vitamin C
VDBP	rs7041	vitamin D
VDR	rs2228570	vitamin D
VDR	rs1544410	vitamin D
VDR	rs731236	vitamin D
VDR	rs7975232	vitamin D
APOA5	rs12272004	vitamin E
SLC30A8	rs13266634	zinc

Potential Confounders

Mother:

- Age
- Education
- Social class
- Marital status
- Parity
- Inter-pregnancy interval
- Any infection during pregnancy
- Housing tenure
- Ever smoked
- Alcohol consumption
- Iron, zinc, calcium, folic acid, vitamins, other supplements during pregnancy



Potential Confounders

Child:

- Sex
- Age
- Gestation
- Birth weight
- Breastfeeding duration



Population Characteristics

	total IQ	verbal IQ	performance IQ
mean	104.1	107.0	99.5
sd	16.5	16.7	17.1
min	45	46	46
max	151	155	151
N	4111	4124	4127

	mean	sd	N	p-value*
maternal age (years)	28.5	4.7	6590	<0.0001
child's age (months)	103.5	3.1	4183	<0.0001
gestation (weeks)	39.5	1.8	7373	0.525
birthweight (grams)	3422.4	536.8	7294	<0.0001

*p-value for association with total IQ



total IQ	mean	sd	N	p-value
maternal factors I				
education				<0.0001
less than O level	95.9	15.4	855	
O level	102.1	15.0	1411	
more than O level	110.4	15.8	1730	
social class				<0.0001
manual	98.5	15.3	551	
non-manual	106.2	16.2	2941	
marital status				<0.0001
never married	101.4	16.8	493	
married	104.8	16.3	3347	
separated/divorced/widowed	101.1	15.8	176	
parity				<0.0001
no children	105.7	16.4	1869	
1 child	104.4	16.0	1411	
2 children	100.7	16.9	534	
3 or more children	98.3	15.9	169	
interpregnancy interval				0.016
< 3 months	105.2	16.8	165	
3-5 months	103.0	16.6	120	
6-11 months	104.8	16.3	313	
12-17 months	103.7	16.7	388	
18-35 months	103.4	16.3	778	
36-59 months	102.4	16.6	275	
60+ months	99.7	14.8	192	
any infection during preg				0.038
no	104.6	16.5	3101	
yes	103.3	16.2	827	
housing tenure				<0.0001
mortgaged	105.3	16.2	3407	
rented/other	102.2	16.3	294	
council rented	93.6	15.3	309	

total IQ	mean	sd	N	p-value
maternal factors II				
ever smoked				<0.0001
no	105.2	16.5	2273	
yes	103.0	16.3	1735	
alcohol consumption				
<i>before this pregnancy</i>				<0.0001
never	98.3	17.0	215	
< 1 glass per week	103.1	16.0	1482	
1+ glasses per week	105.3	16.5	1836	
1+ glasses per day	106.4	16.6	483	
<i>during this pregnancy</i>				0.009
never	103.8	16.3	1731	
< 1 glass per week	104.4	16.7	1646	
1+ glasses per week	105.8	15.8	562	
1+ glasses per day	99.9	18.8	72	
iron supplements				0.595
no	104.2	16.4	3256	
yes	104.5	16.8	755	
zinc supplements				0.001
no	104.1	16.4	3948	
yes	111.0	18.2	64	
calcium supplements				0.039
no	104.2	16.5	3875	
yes	107.1	16.1	134	
folate supplements				0.004
no	104.0	16.4	3651	
yes	106.7	16.8	359	
vitamin supplements				<0.0001
no	103.7	16.4	3320	
yes	106.8	16.4	680	
other supplements				0.029
no	104.3	16.3	3753	
yes	107.7	17.0	115	



Confounders continued

total IQ	mean	sd	N	p-value
child-related factors				
sex				0.831
male	104.0	17.1	2053	
female	104.1	15.9	2058	
duration of breastfeeding				<0.0001
never	98.1	15.2	782	
< 3 months	102.5	15.8	885	
3-5 months	104.5	16.0	674	
6 months+	108.8	16.5	1487	

confounder	dbSNP	p-value
mother's age	rs2075650	0.012
education	rs1799945	0.023
interpreg. Interval	rs7041	0.020
any infection	rs492602	0.053
	rs1726866	0.003
	rs713598	0.006
housing tenure	rs10811661	0.015
gestation	rs10811661	0.005
	rs1544410	0.013
	rs731236	0.008
breastfeeding	rs864745	0.058
iron supps	rs731236	0.028
zinc supps	rs1799945	0.057
folate supps	rs13266634	0.024
	rs1544410	0.017
	rs731236	0.014
vitamin supps	rs10811661	0.040
other supps	rs1726866	0.045
child's age	rs1544410	0.015
	rs1799945	0.044
	rs731236	0.022



Preliminary Results: mother's genotype

dbSNP	gene	nutrient	total IQ			verbal IQ			performance IQ		
			crude	adjusted 1	adjusted 2	crude	adjusted 1	adjusted 2	crude	adjusted 1	adjusted 2
rs1726866	TAS2R38	bitter taste receptor	0.181	0.488	0.426	0.023	0.101	0.212	0.675	0.439	0.939
rs713598	TAS2R38	bitter taste receptor	0.306	0.590	0.584	0.033	0.131	0.232	0.615	0.505	0.783
rs1799945	HFE	iron	0.095	0.066	0.058	0.040	0.029	0.052	0.436	0.340	0.219
rs2075650	APOE	lipids	0.017	0.098	0.091	0.109	0.381	0.332	0.013	0.043	0.040
rs713041	GPX4	selenium	0.132	0.112	0.687	0.492	0.451	0.682	0.048	0.041	0.240
rs12779790	CDC123/CAMK1D	T2D	0.215	0.228	0.139	0.059	0.066	0.043	0.603	0.688	0.816
rs1801282	PPARG	T2D/obesity	0.120	0.138	0.235	0.078	0.089	0.166	0.386	0.424	0.492
rs10811661	CDKN2A/B	TG/T2D	0.014	0.245	0.230	0.054	0.567	0.377	0.049	0.234	0.101
rs864745	JAZF1	TG/T2D	0.004	0.001	0.004	0.014	0.016	0.310	0.002	0.001	0.016
rs492602	FUT2	vitamin B12	0.008	0.006	0.040	0.022	0.022	0.256	0.013	0.008	0.008
rs4654748	ALPL/NBPF3	vitamin B6	0.111	0.099	0.134	0.073	0.059	0.047	0.149	0.159	0.168
rs33972313	SLC23A1	vitamin C	0.130	0.113	0.076	0.042	0.036	0.034	0.935	0.922	0.452
rs7041	VDBP	vitamin D	0.230	0.429	0.094	0.566	0.857	0.223	0.078	0.193	0.076
rs10735810	VDR	vitamin D	0.217	0.162	0.598	0.074	0.051	0.330	0.659	0.575	0.892
rs1544410	VDR	vitamin D	0.042	0.039	0.040	0.357	0.361	0.236	0.010	0.008	0.018
rs731236	VDR	vitamin D	0.078	0.076	0.056	0.414	0.428	0.309	0.026	0.021	0.023
rs13266634	SLC30A8	zinc	0.035	0.012	0.095	0.009	0.004	0.046	0.356	0.199	0.258

- Adjusted 1: by child's age and confounders/SNP
- Adjusted 2: by child's age, confounders/SNP, and child's genotype
- N ~ 4000

Preliminary Results: children's genotype

dbSNP	gene	nutrient	total IQ		verbal IQ		performance IQ	
			crude	adjusted by age	crude	adjusted by age	crude	adjusted by age
rs1726866	TAS2R38	bitter taste receptor	0.562	0.493	0.393	0.449	0.060	0.050
rs713598	TAS2R38	bitter taste receptor	0.592	0.523	0.325	0.375	0.048	0.040
rs1801725	CASR	calcium	0.023	0.016	0.022	0.015	0.103	0.084
rs2110922	SLC8A1	calcium	0.370	0.360	0.685	0.695	0.051	0.049
rs1013940	SLC5A7	choline	0.069	0.109	0.009	0.018	0.268	0.240
rs20417	PTGS2	fatty acids	0.044	0.034	0.159	0.132	0.009	0.007
rs2235544	DIO1	iodine	0.604	0.623	0.353	0.338	0.033	0.034
rs1532085	LIPC	lipids	0.022	0.002	0.001	0.001	0.055	0.049
rs8042919	TRPM7	magnesium	0.179	0.181	0.021	0.021	0.685	0.682
rs10811661	CDKN2A/B	TG/T2D	0.024	0.033	0.114	0.145	0.024	0.030
rs7961581	TSPAN8-LGR5	T2D	0.170	0.249	0.063	0.102	0.899	0.973
rs1801282	PPARG	T2D/obesity	0.010	0.023	0.021	0.026	0.063	0.073
rs7041	VDBP	vitamin D	0.316	0.259	0.631	0.552	0.022	0.020
rs10735810	VDR	vitamin D	0.086	0.115	0.028	0.040	0.313	0.375
rs1544410	VDR	vitamin D	0.050	0.058	0.063	0.073	0.258	0.261
rs731236	VDR	vitamin D	0.043	0.052	0.072	0.087	0.282	0.274
rs12272004	APOA5	vitamin E	0.015	0.011	0.041	0.034	0.059	0.051

N ~ 6000

Preliminary Conclusions

- Polymorphisms in FUT2 (vit B12), JAZF1 (TG/T2D) and VDR (vit D) appear to have an influence on child's IQ through maternal genotype
- Association of IQ with child's genotype was detected for genes APOA5 (vit E), CASR (calcium), CDKN2A/B (TG/T2D), PTGS2 (fatty acids), LIPC (lipids), PPARG (T2D) and VDR (vit D)
- There is some variation in the association between verbal and performance IQ and genotypes (not exactly the same genes)
- Other outcomes to be examined
- Replication needed



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