

ONLINE SUPPLEMENT

Maternal 17q21 Genotype Influences Prenatal Vitamin D Effects on Offspring Asthma/Recurrent Wheeze

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Table E1. Number of subjects randomized to each prenatal supplementation group in COPSAC₂₀₁₀ stratified by maternal 17q21 genotype.

	Mother rs12936231 genotype			P value
	GG	GC	CC	
N	152	263	148	
Placebo only	40 (26%)	65 (25%)	42 (28%)	0.579
Vitamin D ₃ only	41 (27%)	67 (26%)	36 (24%)	
Fish oil only	41 (27%)	62 (24%)	29 (20%)	
Vitamin D ₃ and fish oil	30 (20%)	69 (26%)	41 (28%)	

Table E2. The effect of prenatal vitamin D₃ supplementation on the development of early life asthma/recurrent wheeze stratified by maternal 17q21 genotype when excluding subjects receiving fish oil supplementation in COPSAC₂₀₁₀.

Mother rs12936231 genotype	Cases/Total	HR (95% CI)	P value
GG/GC*	39/213	0.44 (0.23-0.86)	0.016
CC	19/78	0.92 (0.38-2.27)	0.863

*Combined maternal GG-genotype and GC-genotype.

Analyses were performed using Cox proportional hazard regression. G is considered as the dominant low-risk allele and C as the recessive high-risk allele.

Table E3. The effect of prenatal vitamin D₃ supplementation on the development of early life asthma/recurrent wheeze stratified by maternal and child 17q21 genotype based on maternal 25-hydroxyvitamin D (25[OH]D) level at randomization (10-18 gestational weeks).

25(OH)D level <30 ng/ml						
Mother	VDAART			COPSAC ₂₀₁₀		
rs12936231	Cases/Total	HR	P value	Cases/Total	HR	P value
genotype						
GG/GC*	99/326	0.51	0.002	35/201	0.70	0.294
GG	27/103	0.39	0.030	13/66	0.28	0.094
GC	72/223	0.56	0.017	22/135	1.05	0.910
CC	43/145	1.26	0.448	14/68	1.37	0.576
25(OH)D level ≥30 ng/ml						
Mother	VDAART			COPSAC ₂₀₁₀		
rs12936231	Cases/Total	HR	P value	Cases/Total	HR	P value
genotype						
GG/GC*	28/105	0.62	0.209	35/210	0.46	0.030
GG	7/29	0.42	0.295	12/85	0.85	0.783
GC	21/76	0.68	0.372	23/125	0.32	0.018
CC	6/35	0.29	0.254	16/80	0.93	0.877

*Combined GG-genotype and GC-genotype.

Analyses were performed using Cox proportional hazard regression. G is considered as the dominant low-risk allele and C as the recessive high-risk allele.

Table E4. Multivariable model† for the interaction between maternal 17q21 genotype and prenatal fish oil supplementation on the risk of offspring asthma/recurrent wheeze at age 0-3 years in COPSAC₂₀₁₀ (n=563).

	Estimate	P value
Additive model		
Mother rs12936231 genotype	0.01	0.665
Fish oil intervention	0.04	0.524
Mother rs12936231 genotype*Fish oil intervention	0.01	0.860
Dominant model		
Mother rs12936231 genotype	<0.01	0.930
Fish oil intervention	0.03	0.452
Mother rs12936231 genotype*Fish oil intervention	0.05	0.473

†Based on the model: asthma/recurrent wheeze ~ mother genotype*fish oil intervention + child sex.

The additive model compares maternal genotypes GG vs. GC vs. CC and the dominant model compares maternal genotypes GG/GC vs. CC.

Table E5. Association between blood peak intensity of sphingolipid metabolites at ages 1 and 3 years and vitamin D₃ supplementation of children in the VDAART cohort stratified by the mother and child 17q21 genotype combinations.

	Coefficient	p
Sphinganine-1-phosphate		
Mother and child GG/GC	0.028	0.013
Mother GC and child CC	-0.013	0.593
Mother CC and child GC	-0.024	0.258
Mother and child CC	-0.033	0.799
Sphinganine		
Mother and child GG/GC	0.048	0.025
Mother GC and child CC	-0.026	0.558
Mother CC and child GC	-0.042	0.192
Mother and child CC	-0.008	0.831
Sphingosine-1-phosphate		
Mother and child GG/GC	0.015	0.032
Mother GC and child CC	-0.007	0.620
Mother CC and child GC	-0.011	0.388
Mother and child CC	-0.032	0.010
Sphingosine		
Mother and child GG/GC	0.049	0.012
Mother GC and child CC	-0.027	0.489
Mother CC and child GC	-0.044	0.134
Mother and child CC	-0.015	0.635
Phosphoethanolamine		
Mother and child GG/GC	0.003	0.791
Mother GC and child CC	0.025	0.326
Mother CC and child GC	-0.037	0.125
Mother and child CC	-0.016	0.512

Number of children with data on age 1 and/or 3 year sphingolipid levels:

Mother and child GG/GC n=291,

Mother GC and child CC n=66,

Mother CC and child GC n=78,

Mother and child CC n=79.