Supplementary Online Content

Litonjua AA, Care VJ, Laranjo NM, et al. Effect of prenatal supplementation with vitamin D on asthma or recurrent wheezing in offspring by age 3 years. *JAMA*. doi:10.1001/jama.2015.18589

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods
Additional Detailed Methods

Additional Aspects of Study Design

Interval Prenatal Visits, Delivery, and Postnatal Visits. The study design has been previously published[1] and the Study Protocol is online as Supplement 1. Additional details are provided in this Online Supplement 2. Study staff met with the participants monthly, in conjunction with their regularly scheduled obstetrical visits. At these visits, a short maternal health questionnaire was administered, MEMS® cap information was downloaded, and study medication and prenatal vitamins were refilled. At these monthly prenatal visits, the research staff conducted monthly reviews of electronic medical records to check for pregnancy complications; these were logged and a Severe Adverse Event form or an Adverse Event form was filled out as indicated. At 32-38 weeks gestation, in addition to the monthly routine, a blood draw, skin pigmentation determination, and a number of the questionnaires that were administered at the enrollment visit were repeated. At delivery, cord blood was collected and the research staff collected information regarding the type of delivery, birth weight, and other anthropometric measures from the delivery records. After delivery, the research staff made telephone calls every 3 months and inquired about the health and symptoms of the infant, medication use, the type and frequency of feeding of the child, and supplement use. The mother and child came in for 3 yearly follow-up visits, during which blood was drawn (at the first and third years), skin pigmentation tests were performed, additional questionnaires were administered, and anthropometric measurements of the child were obtained. A summary of the data collected is presented in eTable 1, and the number of scheduled and completed calls and visits are presented in eTable 2.

Study Medications. The study medications, including prenatal vitamins, the vitamin D capsules, and the placebo capsules were manufactured by Tishcon Corp. (www.tishcon.com). For 50 individuals from the St. Louis site, an alternate formulation of a chewable prenatal vitamin (containing the same amount of vitamin D – 400 IU), produced by Vitafusion, was provided in an effort to enhance study compliance, as some women found the study prenatal vitamin difficult to swallow. After delivery, all mothers were given a bottle of vitamin D drops (Carlson Laboratories, Inc., Arlington, IL) containing 400 IU vitamin D per drop and were encouraged to give 1 drop each day to the infants, in accordance with the recommendations from the American Academy of Pediatrics for minimum vitamin D intake.[2] There were no differences in the proportion of infants whose mothers reported administering the daily vitamin D drops in the 4,400 IU/day vs the 400 IU/day arm (Table 2, 46% vs 43%, respectively; p=0.49).

Adherence. Adherence to the study drugs was assessed via data that the Medication Event Monitoring System (MEMS®) collected. Each monitor recorded the time and date of each opening and closing of the medication container through integrated microcircuitry. This recorded data was downloaded at the monthly prenatal visits via a reader to a MS-Windows based computer. Adherence was calculated as the mean percentage of the number of prescribed doses (1 per day) divided by the number of successfully monitored days.

Monitoring of Urinary Calcium to Creatinine Ratio. Study staff met with the participants monthly, in conjunction with their regularly scheduled obstetrical visits. At these visits, in addition to administration of questionnaires, downloading of MEMS® cap information, and refilling study medication and prenatal vitamins, urine was collected and urinary calcium and creatinine values were measured to monitor urine calcium-to-creatinine ratios. At the start of the study, a urine calcium to creatinine ratio ($U_{Ca:Cr}$) value of ≥ 1.0 (when Ca and Cr are measured in mmol/L) was used as the value that triggered stopping the study medication and initiating an investigation into possible hypercalcemia. This value is equivalent to the ratio of 0.37, when Ca and Cr are measured in mg/dl, and has been used as a value for early detection of potential hypercalcemia in prior studies of vitamin D supplementation.[3,4] After only 2 months of the study, however, three subjects exceeded this value but had 25(OH)D values that were < 100 nmol/L (40 ng/ml) and serum Ca levels that were well within normal limits. Because these previous studies were performed in non-pregnant women, it was possible that this ratio was not applicable for the pregnant state. There have been several studies of calcium excretion in pregnancy, mostly with 24-hour urine determinations, and this prompted further investigation. It is established that pregnancy is a state of physiologic absorptive hypercalciuria. Gertner et al[5] showed that 24-hour calcium excretion is increased three-fold in all three trimesters of pregnancy compared with the post-partum state, often to the point of hypercalciuria. Increased calcium excretion occurred despite the fact that serum calcium remained within the normal range throughout pregnancy. Similarly, Seely et al[6]

showed that urinary calcium excretion was 250% to 300% higher during pregnancy than the post-partum state, with serum calcium remaining in the normal range throughout pregnancy and the post-partum period. We then took data from a previous study of vitamin D supplementation in pregnancy[7] and examined the $U_{Ca:Cr}$ ratios. Urine Ca and Cr in that study were reported in mg/dl, similar to reporting in the 3 clinical centers in VDAART. Based on descriptive statistics and histogram of $U_{Ca:Cr}$ ratio measures of 672 untreated pregnant females provided by the research team of Dr. Bruce Hollis, a 95% bootstrap confidence interval was computed for the 99th percentile of the distribution of this ratio. The lower bound of this confidence interval was 0.55. We, therefore, proposed to change the cutoff for $U_{Ca:Cr}$ ratios for our trial from ≤ 0.37 to ≤ 0.55 at the DSMB meeting on February 5, 2010, and this was approved.

Ethnicity and Race. Participants (mothers) were asked to first categorize themselves as either Hispanic or non-Hispanic, then to categorize their race into one or more of the following: white, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian/Alaskan Native, or Other. She was then asked to do the same for her partner or biologic father of the child. The child's ethnicity and race was determined by responses to the questions regarding maternal or paternal ethnicity and race. If any parent was identified as Hispanic, then the child's ethnicity was assigned Hispanic. Then race was assigned starting with if any parent was identified as Black or African American, then the child was labeled as African American; among the remaining children, if any parent was identified as Asian, then the child was labeled Asian; next, among the remaining children, if any parent was identified as Native Hawaiian or Other Pacific Islander, then the child was labeled as Pacific Islander; next, if any parent was identified as Native American/Alaskan Native, then the child was labeled Native American; finally, the child was labeled white if both parents were identified as white. In the analyses, ethnic and racial groups were collapsed into 4 groups: African American, white Hispanic, non-white Hispanic, and Other.

Primary Outcome. The elements of the composite primary outcome were ascertained from questionnaires administered every 3 months during the 3-year follow-up of the children. The total and completed calls at which these questionnaires were administered are shown in eTable 2. A parental report of a physician's diagnosis of asthma was ascertained by a positive response from the question: "Since [birth/the last time we talked], has a health care provider said that [Child] has asthma?" Wheeze was ascertained by a positive response from the question: "Since [birth/the last time we talked], has [CHILD] had wheezing or whistling in his/her chest?" Medication use was ascertained from the following questions:

"4. Since [birth/the last time we talked], has [CHILD] been given any medication for wheezing, wheezy or asthmatic bronchitis, or asthma?

No ..... 0 **[SKIP TO 5]**
Yes 1
Don't know 2

4a. Since [birth/the last time we talked], which of the following types of medication has [CHILD] been given?
(Refer to Medication Reference at the end of this form for common examples of each medication category)

	Yes	No
4a1. Bronchodilator inhalers/nebulizers, pills, or syrups	1	0
4a2. Steroid inhalers/nebulizers	1	0
4a3. Leukotriene modifiers	1	0
4a4. Steroid pills or liquids	1	0 "

Two hundred and eighteen (27%) of the eligible 806 children developed asthma/recurrent wheezing according to the composite definition by their 3rd year visit with many children simultaneously fulfilling multiple criteria. Of these 218 children, 125 children (57.3 %) had a doctor's diagnosis of asthma, 172 children (78.9%) reported wheezing in years 1 or 2, and year 3, 86 children (39.4 %) had early wheezing episodes and were on controller medications in year 3, 8 children (3.7%) had no wheezing in year 1 but at least 2 episodes of wheezing in the third year, 47 children (21.6%) had at least 2 reports of controller medication usage in year 3, and 68 children (31.2%) reported a year 3 wheezing episode and controller medication usage at different visits (eTable 3). Two hundred eleven (96.7%) of the 218 children had either a doctor's diagnosis of asthma or recurrent wheeze defined as wheezing in years 1 or 2, and year 3. Of the 218 children with the primary outcome, 183 (83.9%) reported use of inhaled bronchodilators, inhaled or oral corticosteroids, or leukotriene modifiers at least once during the first 3 years of life, whereas only 91 (17.7%) of the 530 children in the no asthma/recurrent wheeze category reported use of these medications. There were 18 children who were reported to have had hospitalizations for wheezing or asthma in the first 3 years of life: 15 (83.3%) from the asthma/recurrent wheeze group and 3 (16.7%) from the no asthma/recurrent wheeze group. There

were 58 children for whom the outcome could not be resolved (29 in the 4,400 IU/day dose and 29 in the 400 IU/day dose) because they were missing intermittent or final visit data that would have categorized the outcome, however, all available data was used in the interval censored analysis.

Secondary Outcomes.
Eczema. This was ascertained from positive responses to the following questions:

"9. Since [birth/the last time we talked], has a health care provider said that [CHILD] has eczema?
Yes 1
No ..... 0 **[SKIP TO 10]**
10. Since [birth/the last time we talked], has [CHILD] had an itchy rash which was coming and going but did not completely get better?
Yes 1
No ..... 0 **[SKIP TO 11]**
10a. Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, on the back of the upper thighs, or around the neck, ears, eyes, or on the cheeks?
Yes 1
No ..... 0"
If the response to both of these questions was "Yes," then the child was said to have eczema and the first instance of this event was used for the time-to-event analysis.

Lower Respiratory Infections (LRI). LRIs were ascertained from questionnaires administered every 3 months, based on the question
"12. Has [CHILD] had any of the following illnesses since [birth/the last time we talked]?

	Yes	No
12c. Croup	1	0
12d. Pneumonia	1	0
12e. Bronchitis	1	0
12f. Bronchiolitis	1	0"

If the response to any of 12c-12f was "Yes," the child was said to have an LRI for that time period (usually 3 months). LRI was treated as an event that could repeat in each child.

Immunoglobulin E (IgE). Measurement of IgE from plasma collected at the 3rd year visit was performed by ThermoFisher PIRL lab (Phadia Immunology Reference Laboratory, Portage, MI). The allergens tested were: *Alternaria Alternata*, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, German cockroach, cat dander, dog dander, egg white, grass pollen mix, tree pollen mix, walnut tree, milk, peanut, soybean, and wheat. Sensitization was determined to be positive if at least 1 of the specific IgE levels was ≥ 0.35 kU/l or total IgE level was ≥ 60 kU/l.

Measurement of 25(OH)D. Circulating 25(OH)D was determined using the DiaSorin Liaison®. The method for quantitative determination of 25-hydroxyvitamin D is an FDA approved direct, competitive chemiluminescence immunoassay (CLIA)[8]. This assay is co-specific for 25-hydroxyvitamin D_3 and 25-hydroxyvitamin D_2. The assay utilizes a specific antibody to 25-hydroxyvitamin D for coating magnetic particles (solid phase) and a vitamin D analogue, 22-carboxy-23,24,25,26,27-pentanorvitamin D_3, linked to an isoluminol derivative. During the incubation, 25-hydroxyvitamin D is dissociated from its binding protein, and competes with the isoluminol labeled analogue for binding sites on the antibody. After the incubation, the unbound material is removed with a wash cycle. Subsequently, the starter reagents are added and a flash chemiluminescent reaction is initiated. The light signal is measured by a photomultiplier as relative light units (RLU) and is inversely proportional to the concentration of 25-hydroxyvitamin D present in calibrators, controls, or samples. The inter-and intra-assay CVs for this assay are 11.2 % and 8.1% respectively. For quality control, samples of US National Institute of Standards and Technology (NIST) level 1 SRM (Standard Reference Material) 972 Vitamin D in Human Serum were included in each run. All maternal samples and child 25(OH)D measurements were run using this method. Because the DiaSorin method has not been validated in cord blood (B. Hollis, personal communication), we sent the cord blood samples for measurement using liquid chromatography-tandem mass spectrometry (LC-MS/MS)[9] to the Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN. Briefly, 25(OH)D_2 and 25(OH)D_3, and their

respective 3-epimers, were measured from cord blood plasma samples using LC-MS/MS (ThermoFisher Scientific, Franklin, Massachusetts 02038 and Applied Biosystems-MDS Sciex, Foster City, CA 94404). Inter-assay C.V.'s for $25(OH)D_2$ and $25(OH)D_3$ were all $\leq 6.8\%$ at various concentrations. Inter-assay C.V.'s for the 3-epimers were all $\leq$ 12.8% at various concentrations. Only 32 cord blood samples had detectable 3-epimers for $25(OH)D_3$; no sample had detectable 3-epimer for $25(OH)D_2$. Total 25(OH)D values, the sum of $25(OH)D_2$ and $25(OH)D_3$, was used for analyses. 3-epimer levels were not included in total 25(OH)D levels in the current analysis.

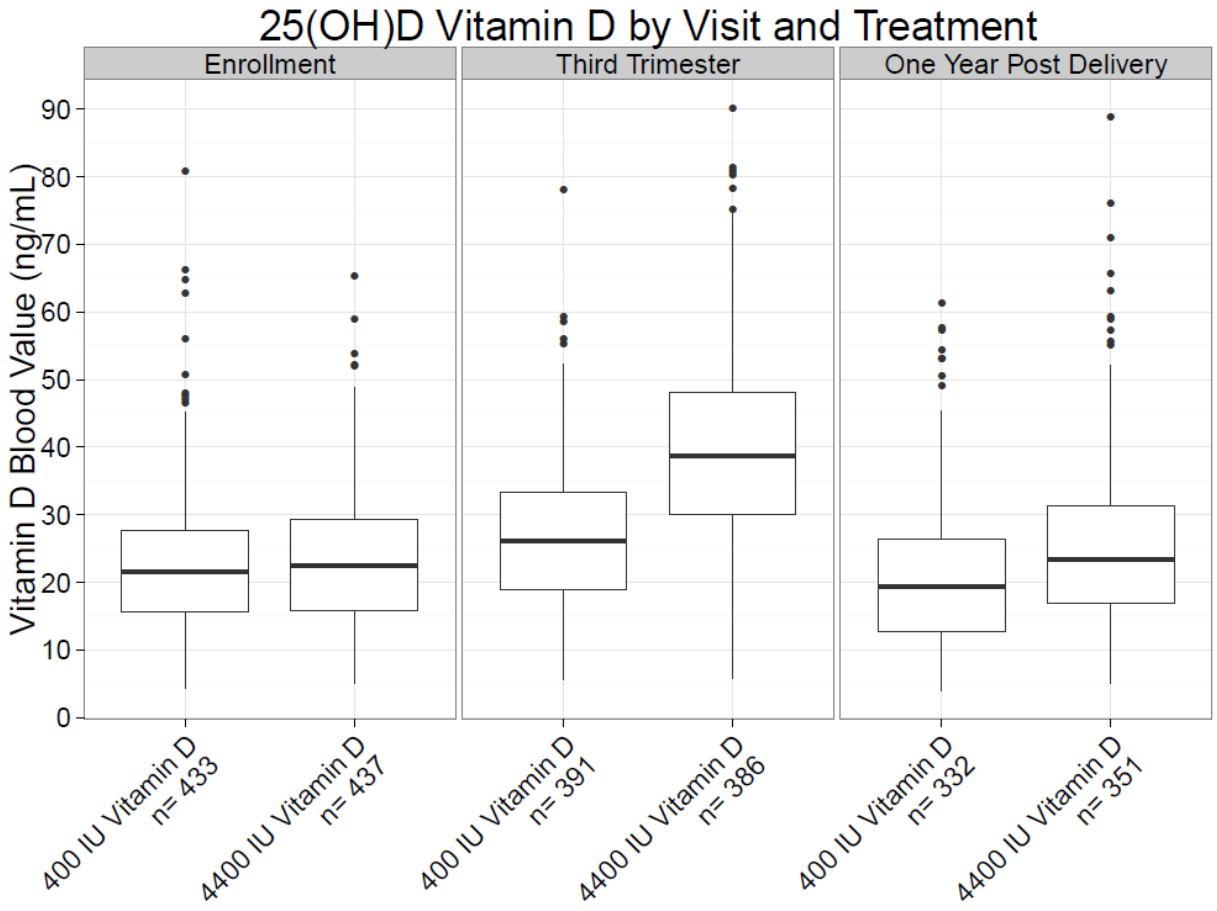
Additional Results

Sensitivity analyses. Sensitivity analyses for the ITT analyses are presented in eTable 4. The first 2 models are logistic regression models that make use of the data from 748 children who contributed complete information that enabled determination of the outcome of asthma or recurrent wheeze. Model 1 is an intent-to-treat model without adjustment for covariates. Model 2 is a multivariable model that adjusts for Clinical Center and maternal education. The next 2 models are Weibull regression analyses of the interval-censored response data (making use of all data from 806 children). Similar to the logistic regression models, the first model is the pure ITT analysis and the second is the adjusted model. Both these methods yield similar risk estimates (OR = 0.72-0.74 and HR = 0.74-0.77). Adjustments for site and maternal education had essentially no impact on the estimate of treatment effect and tended to increase the estimated precision of the treatment effect estimate, so that adjusted p-values fell below 0.05 (eTable 4). We take these findings as confirmation that our nonparametric intent-to-treat inference is highly robust and reliable.

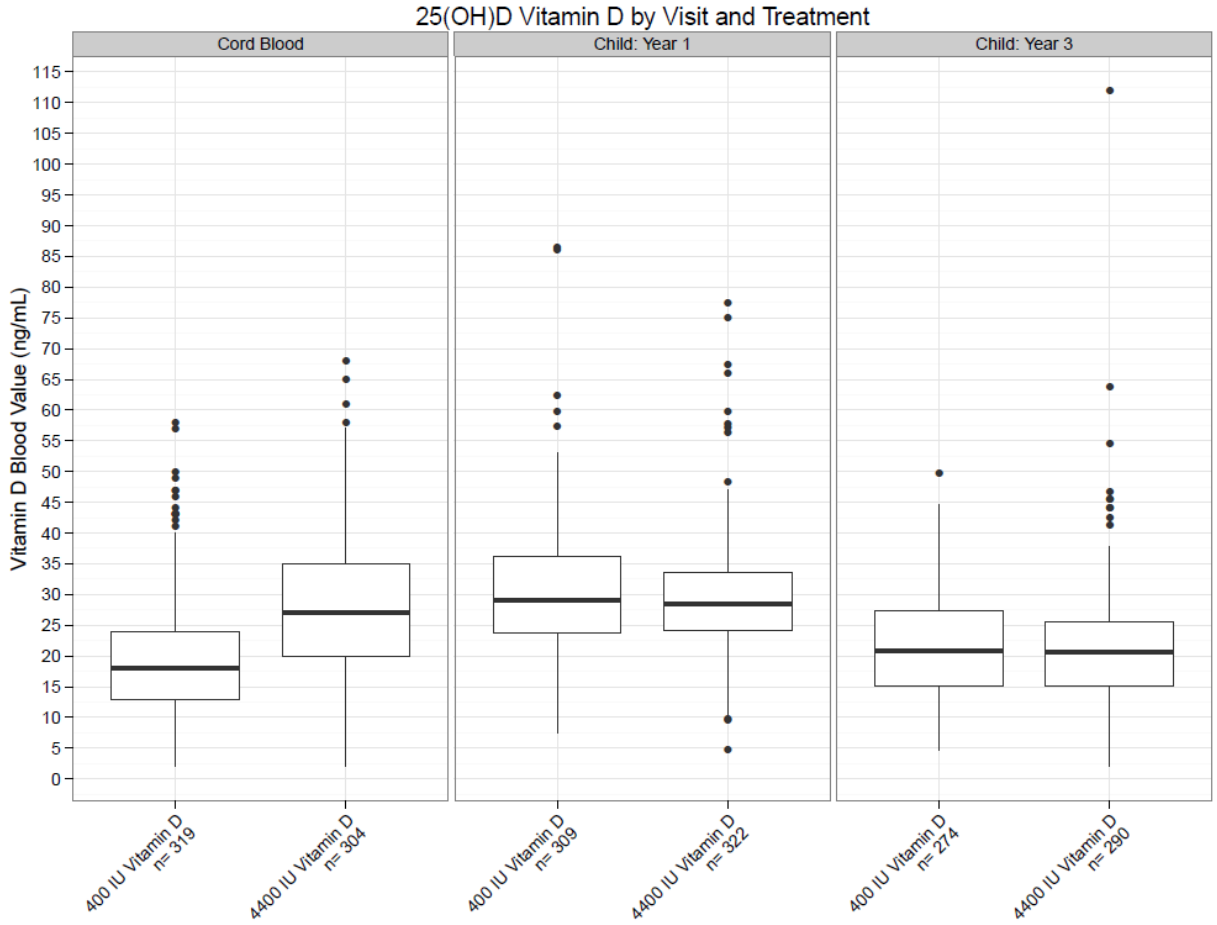
Safety. There were no significant differences in the rates of severe adverse events between the 2 treatment groups, and, according to independent review by the DSMB, no severe adverse events were attributed to study treatment (eTable 5). Most importantly, no events of hypercalcemia in the mothers occurred with vitamin D treatment. Treatment was discontinued for three individuals owing to elevated urine calcium/creatinine ratio (UCCR) at a threshold of 0.37. None of these 3 individuals had elevated blood calcium levels or 25(OH)D levels. DSMB review led to a revision of the threshold of 0.55 for elevated UCCR in February 2010, as detailed above. The individuals for whom study drug was held were included in the intent-to-treat analysis.

eFigure 1 – Results of analyses of circulating 25-hydroxyvitamin D levels.* 1a. Baseline, third trimester, and 1-year post-partum maternal levels; 1b. Cord blood, age 1-year, and age 3-year levels.

eFigure 1A.



eFigure 1B.



* Cord blood samples were measured using LC-MS/MS, while 1-year and 3-year samples were measured by the Diasorin Liaison® method. Shown in these figures are standard Tukey boxplots. Boxes are limited by the upper and lower quartiles of the distribution, with the horizontal bar for the median; whiskers are drawn to "outer fences," defined as maximum and minimum data values lying within 1.5 times the interquartile range (beyond the lower or upper quartiles); all data points outside the outer fences are labeled with dots and are Tukey outliers.

eTable 1. Summary of questionnaires and measurements for the trial.*

	Enrollment (10-18 weeks gestation)	Monthly	Third Trimester (32-38 weeks gestation)	Delivery	Quarterly	6 Months after delivery	Year 1	Year 2	Year 3
Study Admission Criteria Questionnaire	x								
Maternal Questionnaire	x								
Food Questionnaire (Maternal)	x		x			x	x		
Food Questionnaire (Child)							x	x	x
Baseline Sun Exposure Questionnaire	x								
Follow-Up Sun Exposure Questionnaire			x				x (mother and child)	x (mother and child)	x (child)
Monthly Maternal Questionnaire		x	x						
Obstetric Medical Record Review (electronic and or paper)	x	x	x						
Determination of skin pigmentation	x		x				x (mother and child)		x (child)
Blood draw	x[1] (mother)		x[1] (mother)	x[2] (cord blood)			x[1,3] (mother and child)		x[4] (child)
Urine for Ca/Cr ratio[5]		x	x						
Patient Health Questionnaire	x		x				x	x	x
Hardships Questionnaire	x						x	x	x
Labor and Delivery Form				x					
Quarterly Infant Follow-up Questionnaire					x		x	x	x
In-person visit	x	x	x				x	x	x
Anthropometric Measurements							x (child)	x (child)	x (child)
MEMS information download		x	x	x (after delivery)					

*** Modified from Litonjua et al[1], Table 2.**
[1] Mother: 25(OH)D, blood for DNA extraction and gene expression studies.
[2] Child: 25(OH)D, total IgE, and blood for DNA extraction and gene expression studies.
[3] Child: total IgE and 25(OH)D
[4] Child: total IgE and specific IgE, 25(OH)D, DNA extraction and gene expression studies.
[5] Urinary calcium, creatinine.

eTable 2. Total and completed calls and yearly visits* for the VDAART children up to age 3 years.

	Month											
	3	6	9	12 visit	15	18	21	24 visit	27	30	33	36 visit
Total potential (scheduled) calls or visits (n)	810	809	808	806	803	800	800	800	800	798	798	797
Completed calls (n)	765	761	746	736	708	745	741	753	725	733	740	738
Percent competed (%)	94	94	92	91	88	93	93	94	91	92	93	93

*Follow-up of the children consisted of questionnaires administered over the telephone every 3 months and yearly in-person visits at around the child's birthdate.

eTable 3. Number of children who met each of the components of the composite primary outcome definition, all children and stratified by treatment group. There is broad overlap between the components. For example, 125 children received a diagnosis of asthma, and of those 125, 86 also had recurrent wheeze, 66 had wheeze in either year 1 or year 2 + controller medication in year 3, 3 had two distinct episodes of wheeze in year 3, 44 had two distinct reports of controller medications, and 56 had a wheeze episode and a separate report of controller medication in year 3. Components are not exclusive, thus, for the asthma example, 211 (96.8 %) had either asthma diagnosis or recurrent wheeze, and 7 (3.2 %) met the definitions for at least one of the other components (but did not meet the asthma diagnosis or recurrent wheeze definitions).

All children	Event Classification n(%)	Asthma	Recurrent Wheeze	Y1 or Y2 Wheeze + Y3 Medication	Two Y3 Wheeze Episodes	Two Y3 Medication Episodes	Y3 Medication and Wheeze at Different Times
Asthma	125 (57.3)	125	86	66	3	44	56
Recurrent Wheeze	172 (78.9)	86	172	79	0	43	65
Y1 or Y2 Wheeze + Y3 Medication	86 (39.4)	66	79	86	0	46	65
Two Y3 Wheeze Episodes	8 (3.7)	3	0	0	8	0	2
Two Y3 Medication Episodes	47 (21.6)	44	43	46	0	47	44
Y3 Medication and Wheeze at Different Times	68 (31.2)	56	65	65	2	44	68
4,400 IU Group	**Event Classification n(%)**	**Asthma**	**Recurrent Wheeze**	**Y1 or Y2 Wheeze + Y3 Medication**	**Two Y3 Wheeze Episodes**	**Two Y3 Medication Episodes**	**Y3 Medication and Wheeze at Different Times**
Asthma	60 (61.2)	60	42	30	2	22	27
Recurrent Wheeze	76 (77.6)	42	76	37	0	20	31
Y1 or Y2 Wheeze + Y3 Medication	40 (40.8)	30	37	40	0	22	31

Two Y3 Wheeze Episodes	5 (5.1)	2	0	0	5	0	2
Two Y3 Medication Episodes	23 (23.5)	22	20	22	0	23	21
Y3 Medication and Wheeze at Different Times	34 (34.7)	27	31	31	2	21	34
400 IU Group	**Event Classification n(%)**	**Asthma**	**Recurrent Wheeze**	**Y1 or Y2 Wheeze + Y3 Medication**	**Two Y3 Wheeze Episodes**	**Two Y3 Medication Episodes**	**Y3 Medication and Wheeze at Different Times**
Asthma	65 (54.2)	65	44	36	1	22	29
Recurrent Wheeze	96 (80)	44	96	42	0	23	34
Y1orY2 Wheeze + Y3 Medication	46 (38.3)	36	42	46	0	24	34
Two Y3 Wheeze Episodes	3 (2.5)	1	0	0	3	0	0
Two Y3 Medication Episodes	24 (20)	22	23	24	0	24	23
Y3 Medication and Wheeze at Different Times	34 (28.3)	29	34	34	0	23	34

eTable 4. Sensitivity analysis for inference on the VDAART co-primary outcome asthma or recurrent wheeze by age 3.*

Model	Crude data for logistic models: #outcomes/N in cell		Logistic 1 N=748		Logistic 2 N=748		Weibull 1 N=806		Weibull 2 N=806	
			OR (CI)	p	OR (CI)	p	HR (CI)	p	HR (CI)	p
Treatment										
400 IU (reference)	120/372		1.0		1.0		1.0	-	1.0	-
4400 IU	98/376		0.74 (0.54,1.02)	0.063	0.72 (0.52,1.00)	0.049	0.77 (0.59,1.00)	0.051	0.74 (0.56,0.97)	0.029
Clinical Center	**4400 IU**	**400 IU (reference)**								
San Diego (reference)	22/122	28/123	-	-	1.0	-	-	-	1.00 (0.56,0.97)	-
Boston	32/104	44/110	-	-	1.85 (1.19, 2.88)	0.006	-	-	1.71 (1.18, 2.49)	0.006
St. Louis	44/150	48/139	-	-	1.62 (1.07, 2.46)	0.024	-	-	1.72 (1.21, 2.46)	0.003
Education										
<High School (reference)	17/60	18/36	-	-	1.0	-	-	-	1.0	-
High school, technical school	28/103	44/118	-	-	0.88 (0.53, 1.47)	0.618	-	-	0.86 (0.57, 1.30)	0.488
Some college	25/86	29/86	-	-	0.88 (0.52, 1.51)	0.652	-	-	0.85 (0.55, 1.32)	0.476
College grad, graduate school	28/127	29/132	-	-	0.61 (0.35, 1.04)	0.071	-	-	0.64 (0.41, 1.00)	0.053

* Logistic regression models based on N=748 for individuals who met the asthma or recurrent wheeze definition or provided full 3 year observations; Weibull models for interval-censored event times based on all available observations for N=806 individuals. Logistic 1 is a pure intent-to-treat analysis for the binary response; Logistic 2 is an enhancement of

Logistic 1 including adjustment for covariates requested by referees. Weibull 1 is a pure intent-to-treat analysis for the interval-censored time to primary outcome; Weibull 2 is an enhancement of Weibull 1 including adjustment for covariates requested by referees. Cell entries are odds ratio (OR) for logistic regression, and hazard ratio (HR) for Weibull modeling. Two-sided 95% confidence intervals are provided in parentheses.

eTable 5. Counts of maternal and infant severe adverse events

Mother	**4400 IU N=440**	**400 IU N=436**	**Rate difference (events per pregnancy, 4400IU - 400IU) (95% CI)**
Symptomatic hypercalcemia	0	0	0.0 (-0.005-0.005)
Eclampsia	0	0	0.0 (-0.005-0.005)
Preeclampsia	36	38	-0.005 (-0.044-0.034)
HELLP syndrome	2	1	0.002 (-0.008-0.012)
Hospitalization of the mother*	44	44	0.00 (-0.042-0.040)
Postpartum hospitalization	11	7	0.009 (-0.012-0.030)
Maternal death (2 years post delivery)	0	1	-0.002 (-0.009-0.004)

Newborn/infant			
Pre-term delivery <32 weeks gestation	5	11	-0.014 (-0.033-0.062)
Major fetal or congenital anomaly*§	15	14	0.002 (-0.24-0.028)
Still birth or intrauterine fetal death	13	11	0.004 (-0.020-0.028)
Neonatal demise	3	3	0.0 (-0.011-0.011)
Neonatal ICU admission	36	28	0.017 (-0.019-0.054)

* Cell entries for first two columns are event counts; column 3 provides difference in event rate per pregnancy (rate for 4400IU minus rate for 400 IU) along with 95% CI. Counts are for reports for individual participants: for maternal hospitalizations, there were 111 events in 88 mothers, 44 mothers in each arm; for fetal or congenital anomalies, there were 31 events in 29 subjects, 15 in the 4,400 IU arm and 14 in the 400 IU arm. Testing for these conditions was done on the number of individuals rather than the number of events.

§ Congenital anomalies included abnormal echocardiogram (n=2), abnormal fetal growth (n=1), displaced anus (n=1), G6PD deficiency (n=1), hepatic calcification (n=1), hydronephrosis (n=2), hypospadias (n=1), neck cyst (n=1), polydactyly (n=2), pulmonary cyst (n=1), pyelectasis (n=13), renal agenesis (n=2), tracheoesophageal fistula (n=1), Trisomy 21 (n=2), and ventriculomegaly (n=1). No anomaly was predominant in either treatment group.

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