Supplementary data

Effects of antenatal multiple micronutrient supplementation on lung function in mid-childhood: follow-up of a double-blind randomised controlled trial in Nepal

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The study was a follow-up of children born in a trial of antenatal multiple micronutrient supplementation in Nepal. Lung function was measured in 80% of children at 7-9 years of age. The online data supplement contains additional information and tables. This information provides some background detail on the analysis and further results.

Supplementary data 1: Exclusion criteria for spirometry analysis

The supplementary data show the criteria used to define exclusion because of illness. Data were obtained from questionnaires, using open questions based on recall by parents or guardians. Data were coded by a clinician (DD), with additional questioning if required. Illnesses were divided into three categories:

(1) Acute illness or symptoms during spirometry

(2) Chronic illness (asthma, congenital heart disease, hydronephrosis, nephritic syndrome, recurrent pneumonia, rheumatic fever, single kidney and tuberculosis)

(3) History of pneumonia requiring hospital treatment at any point

Supplementary tables

The supplementary tables show additional data on lung function results when interpreted according to preliminary equations for South Asian children rather than those based on white children (Table S1), for the whole cohort stratified by sex (Table S2) and a summary of air pollution exposure according to allocation group (table S3).

Table S1: Lung function based on preliminary South Asian reference equations and anthropometry by allocation group in children with acceptable spirometry, for both the entire cohort and after excluded those with any prior significant disease

Entire cohort	**Controls n=393 Mean (SD)**	**Intervention n=400 Mean (SD)**	**Unadjusted difference (95% CI)**	**Multivariable regression [c] (95% CI)**
Age (years)	8.5 (0.4)	8.4 (0.4)		
Weight z-score [a]	-2.1 (1.0)	-2.0 (1.0)	0.05 (-0.09 to 0.19)	0.11 (-0.02 to 0.24)
Height z-score [a]	-1.5 (0.9)	-1.5 (0.9)	0.03 (-0.10 to 0.16)	0.08 (-0.04 to 0.19)
BMI z-score [a]	-1.7 (0.9)	-1.6 (1.0)	0.04 (-0.09 to 0.17)	0.08 (-0.05 to 0.21)
FEV_1 z-score[b]	-0.19 (1.0)	-0.27 (0.9)	-0.09 (-0.22 to 0.04)	-0.07 (-0.20 to 0.06)
FVC z-score[b]	-0.19 (1.0)	-0.25 (0.9)	-0.06 (-0.19 to 0.07)	-0.05 (-0.18 to 0.09)
FEV_1/FVC z-score[b]	0.09 (0.9)	0.04 (0.9)	-0.05 (-0.17 to 0.08)	-0.04 (-0.17 to 0.08)
$FEF_{25\%-75\%}$ z-score[b]	0.13 (1.1)	0.06 (1.1)	-0.06 (-0.22 to 0.09)	-0.05 (-0.21 to 0.10)
Children without evidence of prior significant disease	**Controls n=350**	**Intervention n=357**		
Age (years)	8.5 (0.5)	8.5 (0.5)		
Weight z-score [a]	-2.1 (0.9)	-2.0 (1.1)	0.04 (-0.11 to 0.19)	0.10 (-0.03 to 0.23)
Height z-score [a]	-1.5 (0.9)	-1.5 (0.9)	0.03 (-0.10 to 0.16)	0.08 (-0.04 to 0.20)
BMI z-score [a]	-1.7 (0.9)	-1.6 (1.0)	0.03 (-0.11 to 0.17)	0.06 (-0.07 to 0.20)
FEV_1 z-score[b]	-0.14 (0.9)	-0.24 (0.9)	-0.10 (-0.23 to 0.04)	-0.08 (-0.21 to 0.06)
FVC z-score[b]	-0.18 (0.9)	-0.23 (0.9)	-0.05 (-0.19 to 0.09)	-0.03 (-0.17 to 0.11)
FEV_1/FVC z-score[b]	0.15 (0.8)	0.05 (0.9)	-0.09 (-0.22 to 0.03)	-0.09 (-0.22 to 0.04)
$FEF_{25\%-75\%}$ z-score[b]	0.19 (1.1)	0.10 (1.1)	-0.09 (-0.25 to 0.07)	-0.08 (-0.25 to 0.08)

[a] anthropometry z-scores calculated according to WHO reference ranges.[1]
[b] spirometry z-scores calculated according to Quanjer GLI-2012 spirometry equations adapted for South Asian children.[2, 3]
[c] Multivariable regression controlled for air pollution, dietary diversity, food security, maternal education and height, household asset score, residence and, for lung function outcomes, the spirometer used using robust standard errors. Analysis was restricted to children with technically satisfactory results. Air pollution data was not available for 14 children.

As indicated by 95% confidence intervals for the mean differences, which encompass zero, there were no significant differences between the intervention and control groups for any of the comparisons undertaken, whether using the unadjusted values or those obtained from multiple regression analysis.

Supplementary table S2: Lung function by allocation group, by sex

		Control Mean (SD)	Intervention Mean (SD)	Unadjusted difference (95% CI)	Multivariable regression (95% CI)	Multivariable regression restricted to children without illness (95%CI)
FEV_1 [a]	Girls	-1.18 (0.81)	-1.36 (0.72)	-0.18 (-0.34 to -0.02)*	-0.15 (-0.31 to 0.02)	-0.15 (-0.32 to 0.02)
	Boys	-1.04 (0.86)	-1.04 (0.82)	0.00 (-0.16 to 0.16)	-0.02 (-0.19 to 0.14)	-0.05 (-0.22 to 0.12)
FVC [a]	Girls	-1.13 (0.84)	-1.26 (0.82)	-0.14 (-0.30 to 0.03)	-0.10 (-0.28 to 0.07)	-0.10 (-0.29 to 0.08)
	Boys	-0.92 (0.80)	-0.91 (0.76)	0.01 (-0.14 to 0.16)	-0.00 (-0.16 to 0.15)	-0.00 (-0.17 to 0.16)
FEV_1/FVC [a]	Girls	-0.15 (0.74)	-0.23 (0.80)	-0.08 (-0.23 to 0.08)	-0.06 (-0.23 to 0.10)	-0.08 (-0.25 to 0.09)
	Boys	-0.24 (0.76)	-0.24 (0.76)	-0.00 (-0.15 to 0.14)	-0.03 (-0.18 to 0.12)	-0.08 (-0.24 to 0.07)
$FEF_{25\%-75\%}$ [a]	Girls	-0.57 (0.96)	-0.69 (0.95)	-0.12 (-0.32 to 0.07)	-0.07 (-0.27 to 0.14)	-0.08 (-0.29 to 0.12)
	Boys	-0.39 (1.07)	-0.40 (1.07)	-0.01 (-0.22 to 0.19)	-0.06 (-0.27 to 0.15)	-0.10 (-0.31 to 0.11)

[a] spirometry z-scores calculated according to spirometry equations based on Caucasian subjects.[2]
[b] Multivariable regression adjusted for air pollution, dietary diversity, food security, maternal education and height, household asset score, residence and spirometer using robust standard errors. Analysis limited to those with acceptable spirometry data.

Table S2 shows unadjusted and adjusted lung function results stratified by sex. As indicated by 95% confidence intervals for the mean differences which encompass zero, with the exception of the univariable comparison of FEV_1, in girls which was significant at the 5% level, there were no significant differences between the intervention and control groups for any of the comparisons undertaken.

Supplementary table S3: Air pollution, total micro-environment exposure

Micro-environment	Control, n=416 Median (IQR) $\mu g/m^3$	Intervention, n=411 Median (IQR) $\mu g/m^3$
Bedroom/living room	1622 (1434,2017)	1622 (1390,2017)
Veranda	445 (0,891)	592 (0-891)
Kitchen during cooking	0	0
Kitchen when there is no cooking	0	0
Outdoors	908 (654,1110)	807 (588,1110)
School	677 (605,726)	666 (605,726)
Total concentration in 24 hours	3951 (3600,4443)	4004 (3605,4446)
24 hr TWA PM_4	165 (150,185)	167 (150,185)

IQR = Interquartile range

Table S3 shows the total exposure over a 24-hour period for children in the control and intervention groups and the 24-hour time-weighted average (TWA). The total concentration was calculated as the average concentration in a location (measured as described in the methods section, main paper) multiplied by the average time spent in that location by each child on a normal school day, if they attended school. The kitchen concentrations were high, but the average kitchen exposure was low because the majority of children did not spend time in this location. The 24-hour TWA is the total concentration in 24 hours divided by 24, to give an hourly average.

References

1. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bulletin of the World Health Organization* 2007: 85(9): 660-667.
2. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J, E. R. S. Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012: 40(6): 1324-1343.
3. Bonner R, Stocks J, Quanjer PH, Lee S, Raywood E, Legg S, Sears D, Kirkby J, Sonnappa S, Lum S. Interpreting spirometry data from South Asian children using the GLI-2012 equations: the SLIC study. *Eur Resp J* 2013: 990s-991s.