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Title:
Pneumonia and exposure to household air pollution in children under the age of 5 in rural Malawi: findings from the Cooking And Pneumonia Study (CAPS)

Short title:
Pneumonia and air pollution in Malawian children

Author list:
*[$]Mortimer Kevin (PhD)[1], [$]Lesosky Maia (PhD) [2], Semple Sean (PhD)[3], Malava Julita (MPH) [4], Katundu Cynthia (Diploma)[4], Crampin Amelia (MPH)[4,5], Wang Duolao (PhD)[1], Weston William (MB ChB)[1], Pope Dan (PhD) [6], Havens Deborah (DO)[1], Gordon Stephen B (MD)[1,7], Balmes John (MD)[8,9]

[1] Liverpool School of Tropical Medicine, UK
[2] University of Cape Town, South Africa
[3] Stirling University, UK
[4] Malawi Epidemiology and Intervention Research Unit, Malawi
[5] London School of Hygiene and Tropical Medicine, UK
[6] University of Liverpool, UK
[7] Malawi Liverpool Wellcome Trust Programme, Blantyre, Malawi
[8] University of California, Berkeley, USA
[9] University of California, San Francisco, CA, USA
[$] Joint first authors
*Corresponding author

Corresponding author:
Kevin Mortimer
Liverpool School of Tropical Medicine,
Pembroke Place
Liverpool
L3 5QA
UK
Kevin.mortimer@lstmed.ac.uk

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ABBREVIATION LIST

CO	Carbon monoxide
COHb	Carboxyhemoglobin
CAPS	Cooking And Pneumonia Study
IRR	Incident Rate Ratios
IQR	Interquartile range
WHO	World Health Organization
IMCI	Integrated Management of Childhood Illness
CI	Confidence Interval
LOD	Limit of detection
SD	Standard deviation
Ppm	Parts per million

ABSTRACT

Background
Exposure to household air pollution is associated with an increased risk of pneumonia in children in low- and middle-income countries, however exposure-response data are limited and there are uncertainties around the extent to which biomass-fueled cookstoves can reduce these exposures.

Research question
What is the association between exposure to household air pollution and pneumonia in children under the age of 5 years in rural Malawi and what are the effects of a biomass-fueled cookstove intervention on personal exposure to household air pollution?

Study design and methods
We measured personal exposure to carbon monoxide (CO) [48 hours of continuous measurement and transcutaneous carboxyhemoglobin (COHb)] 6-monthly in children participating in a cluster-randomised controlled trial of a cleaner-burning biomass-fueled cookstove intervention to prevent pneumonia in children under the age of 5 years in rural Malawi – the Cooking And Pneumonia Study (CAPS). Exposure-response and multi-variable analyses were done.

Results
We recruited 1805 (928 intervention; 877 control) children (mean age 25.6 months, 50.6% female). We found no evidence of an association between exposure to CO (IRR=1.0 95% CI:0.967-1.014; p=0.53) or COHb (IRR=1.00 95% CI:0.993-1.003; p=0.41)) in children who experienced pneumonia versus those who did not. Median exposure to CO in the intervention and control groups was was 0.34 ppm (IQR 0.15-0.81) and 0.37 ppm (IQR 0.15-0.97), respectively. The group difference in means was 0.46 (95% CI:-0.95-0.012; p=0.06).

Interpretation
Exposure to CO in our population was low with no association seen between exposure to CO and pneumonia incidence and no effect of the CAPS intervention on these exposures. These findings suggest that CO may not be an appropriate measure of household air pollution exposure in settings like rural Malawi and that there is a need to develop ways to directly measure particulate matter exposures in young children instead.

Clinical Trial Registration Number
ISRCTN59448623.

Malawi has one of the world's highest infant and under 5 mortality rates (42 and 63 per 1000 live births, respectively, in 2015-2016) despite having made progress towards meeting the Millennium Development Goal of reducing child mortality (1). Pneumonia is the leading cause of death and one of the most common causes of morbidity (2,3).

Exposure to smoke produced when biomass fuels (animal or plant material) are burned in open fires is understood to be a major avoidable risk factor for pneumonia in young children (4-6). In Africa, biomass fuels are widely used to provide energy for cooking, heating and lighting. Women and young children experience high levels of smoke exposure when meals are cooked over open fires due to partial combustion of fuel and poor ventilation (5,6). Household air pollution from open fires is a major threat to health, ranking 10th in the World Health Organization (WHO) comparative risk assessment for the global burden of disease (7). The 2017 Global Burden of Disease Study suggests there are 1.6 million deaths attributable to household air pollution annually, of which around half a million are deaths from pneumonia in young children (8). In Malawi, where at least 95% of households depend on biomass as their main source of fuel and household air pollution levels are high, biomass smoke exposure has been thought to be responsible for a substantial burden of this disease (5,6,9).

In this context, we did a cluster-randomized controlled trial of introducing cleaner-burning biomass-fueled cookstoves to prevent pneumonia in children under 5 years of age in rural Malawi (the Cooking and Pneumonia Study – CAPS) (10). CAPS included 10 750 children from 8626 households across 150 community-level clusters with 10 543 children from 8470 households contributing 15 991 child-years of follow-up data to the intention-to-treat analysis. Although the Integrated Management of Childhood Illness (IMCI)-defined pneumonia incidence rate overall was substantial – 15.7 per 100 child-years – we found no difference in the pneumonia incidence rate between the intervention and control groups – incidence rate ratio of 1.01 (95% CI: 0.91-1.13; p=0.80). To explore possible explanations for this finding we now report data from CAPS on: 1) the association between exposure to carbon monoxide (CO) and carboxyhemoglobin (COHb) and pneumonia; 2) a comparison of CO exposures and COHb levels in children with and without an episode of pneumonia during the trial; and 3) the effects of the intervention on personal exposure to CO and COHb levels among the one in four children who underwent these measurements. The primary CAPS trial outcome data and CO and COHb data collected at the point of recruitment to CAPS have been published previously (10,11).

METHODS

Study design
CAPS was a cluster-randomized controlled trial with two arms of equal size comparing the effects of a cleaner-burning biomass-fueled cookstove intervention to the continued use of traditional open fire cooking on pneumonia incidence (primary outcome previously reported) and CO exposures (secondary outcomes) in children under 5 years of age living in rural Malawi over a 2-year period.

Setting
We defined 150 community-level clusters within villages across two districts of Malawi; Chikwawa in the southern Shire river valley and Karonga on the northern Malawi lakeshore. The Malawi College of Medicine Research Ethics Committee (ethics committee reference number P.11/12/1308) and the Liverpool School of Tropical Medicine Research Ethics Committee (ethics committee reference number 12.40) approved the CAPS trial protocol. Study registration ISRCTN 59448623.

Participants
Following community engagement exercises with village leaders and communities and the identification of a representative for each cluster, households with at least one child up to 4.5 years old were invited to participate. Written informed consent (or witnessed thumbprint for those unable to read and write) was obtained at cluster and household-level (parent or guardian of child) prior to participation. The trial was open to all consenting households with a child in the eligible age range. Households that became eligible for inclusion during the course of the trial (through birth, adoption or in-migration) were recruited up to 6 months before the end of the trial.

Randomisation and masking
Clusters were allocated to intervention and control arms using a computer-generated randomization schedule with stratification by site, distance from health center and cluster size. An additional level of randomization was done to select participants for this study using a randomization function built in to the electronic case report form (CRF) that selected one in four children included in CAPS to be invited to participate in the sub-study. Individuals were assigned to the randomization arm based on their cluster membership at baseline.

Procedures
Intervention households received two cleaner-burning biomass-fueled cookstoves (Philips HD4012LS), a solar panel and user training. A fan incorporated into these cookstoves improves combustion efficiency; smoke emissions have been found to be reduced by around 90% compared to the open fire in laboratory testing. Cookstoves were repaired and replaced as needed. Control households continued using traditional cooking methods (typically open fires). At the start of the trial control households were informed they would receive the intervention at the end of the study period for equity and to maximise retention. Each household was visited every 3 months by fieldworkers, although by the time the 21-month visit was due we were 3 months behind schedule and so moved directly onto the final 24-month visit.

Primary outcome
The primary outcome was the incidence of WHO IMCI-defined pneumonia diagnosed by physicians, medical officers or other appropriately trained staff at local healthcare facilities that were routinely accessed by trial participants, unaware of intervention allocation. Secondary outcomes included severe IMCI-defined pneumonia and severe pneumonia with oxygen saturation below 90%.

Carbon monoxide exposure outcomes

We measured personal exposure to CO directly in all participating children with EasyLog-USB-CO Lascar monitors that measured CO with an electrochemical cell and indirectly in children aged 6 months and older using Masimo Radical-57 Rainbow SET Pulse CO-Oximeters that measured COHb levels transcutaneously using a pediatric sensor that was placed on a digit (11). The CO-Oximeters were checked daily using the manufacterer's testing device (Masimo Rainbow Tester) to quality assure the measurements. As the finger sensors for the COHb levels were only suitable for children above the age of 6 months (according to to the manufacturer's instructions), children below this age had personal exposure to CO but not COHb levels measured. CO and COHB levels were both measured at baseline and at 6-monthly follow-up visits.

CO monitors were set to take measurements every 30 seconds and then placed in a fabric holder that was worn around the neck of the child so that the monitor was close to the child's breathing zone. CO monitors were worn continuously for 48 hours except during sleeping hours when they were placed beside the child. At the end of the monitoring period a fieldworker visited the child's home to retrieve the monitor and upload the data from it onto a study laptop. At this same visit, a short questionnaire about factors potentially related to CO exposure was completed and COHb levels were measured by taking three recordings (four when there was a greater than 6% variation between recordings).

Data from CO monitors were downloaded onto a study laptop in the field at the time they were collected while questionnaire and COHb data were entered into electronic CRFs that had been programmed onto smart phones (Samsung Galaxy S3) using Open Data Kit software. All data were transferred to a secure server at each study site when the fieldworkers returned to base whereupon data checking and cleaning were done before being forwarded on to a central secure server in Liverpool, UK ready for analysis.

Sample size

Sample size considerations for CAPS have been reported previously. In brief, we aimed to include 150 community-level clusters representing approximately 10 600 eligible children to provide, over the 2-year study period, approximately 21 200 child-years of follow-up and 90% power to detect a 20% difference in the pneumonia incidence rate between the intervention and control groups assuming a baseline rate of 5 per 100 child years. One in four children included in CAPS were randomized for inclusion in this sub-study.

Statistical methods

Individual characteristics at baseline were summarized by frequency (proportion) or median (IQR), as appropriate. Incidence (95% CI) of pneumonia was estimated by taking total number of pneumonia events over total sum of person-time (randomization until last contact) with Poisson exact confidence intervals. R software was used to process the CO monitor measurements. CO monitor files with less than 20 h of measurement [2 files] were excluded. Measurements exceeding the upper limit of detection (LOD) of the instrument were set to the upper limit (1000 parts per million (ppm)), and the total minutes above LOD per 24 h-period calculated. Any files with > 14 min of observation above the upper limit were excluded [0 files]. Each period of monitoring over 20 h was split into one or two periods, the first from 0 – 24 h, the second from 24 h – 48 h, labelled period "A" and "B". If period B was less than 20 h in duration, only the first period was retained. Four files with incorrect data based on graphs and outlying values (malfunctioning monitors) were removed. Values below the LOD were set to 0.5*LOD. CO measurements for each individual 24-h period were summarised using arithmetic mean, maximum, geometric mean, and geometric standard deviation (SD) resulting in a single value for each 24-h monitoring period. We also calculated the minutes above and below the instrument LOD. These values were then summarized as median (IQR). Mean CO was transformed to $\log_{10}$ for modelling purposes, although it is described in text and tables as (ppm). Summary statistics were calculated and group differences (95% confidence intervals) estimated. Group comparisons were by two-sided Wilcoxon rank sum test.

Generalized estimating equations using a Poisson model with log link function were used to estimate associations between number of episodes of pneumonia (alternatively severe pneumonia or severe pneumonia with oxygen saturation below 90%) and exposure measures, fitting separate models to assess CO exposure and COHb measures, assuming an exchangeable correlation structure, adjusting for age, sex, presence of smokers in the household, visit, randomization arm and including an offset for duration of follow-up. Clustering was on time periods (due to possibility of two 24-h monitoring periods in the same visit) within individuals within village, and CO was entered into these models as $\log_{10}$ CO. Age-stratified models were run for CO exposure, considering visits up to, or after, 6 months of age seperately. Results are presented as estimated incident rate ratios (IRR) and 95% confidence intervals. Multilevel linear mixed models were fit using CO measures as a time varying outcome to estimate adjusted association with the randomization arm. Separate models were run using CoHb and $\log_{10}$ CO as the outcome variable. Age, sex, visit, and the presence of smokers in the household were included as adjustment factors and random intercepts were fit for individuals, nesting time period (due to possibility of two 24-h monitoring periods), and for cluster at randomization.

Role of the funding source
The funders had no role in the study design, data collection, analysis, interpretation or writing of the report. The corresponding author had full access to all the study data and had final responsibility for the decision to submit for publication.

RESULTS

Participants

Between December 9, 2013 and February 28, 2016, 2294 children were invited to take part in this study of whom 1994 assented with parental/guardian consent and 1805 from 1744 households contributed data at baseline. We lost 25 (13 intervention; 12 control) children from 3 households between the baseline and first follow-up visit. Data were therefore available from 1805 (928 intervention; 877 control) children at baseline and from 1780 (915 intervention; 865 control) children with at least one follow-up visit, who were included in the dataset for analysis. The mean (SD) age of participating children was 25.6 (15.5) months and 50.6% were female. Participants' characteristics at baseline were similar in the intervention and control groups (Table 1). The last participant follow-up visit was on September 14, 2016 (Figure 1 Consort Diagram).

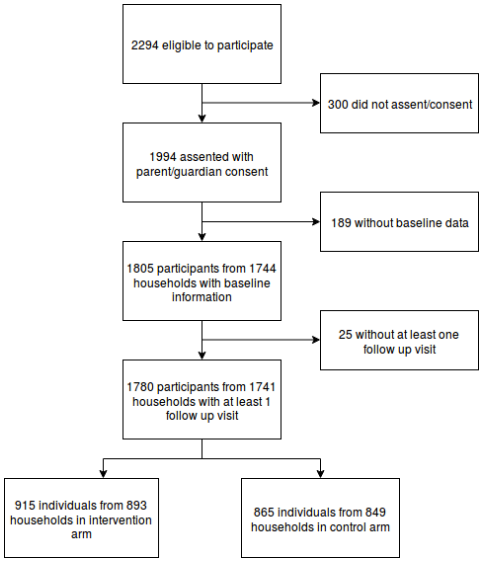
Table 1: Baseline characteristics of the intention to treat population

		Intervention	Control
Individual-level data		**n=928**	**n=877**
Age in months (mean [SD])		25·7 [15.8]	25·5 [15·2]
Female (n (%))		454 (48·9)	460 (52·4)
Vaccination status (course completed) (n (%))*			
	Diphtheria, Tetanus, Pertussis, Hepatitis B and Haemophilus influenzae B	522 (84·1)	534 (87·3)
	Pneumococcal conjugate	378 (60.9)	391 (63·9)
	Polio	496 (79·9)	517 (84·5)
	Rotavirus	298 (48·0)	291 (47·5)
	Measles	391 (63·0)	411 (67·2)
Had pneumonia at least once in the preceding 12 months (n (%))		146 (15·7)	161 (18·4)
Had a cooking-related burn in the preceding 3 months (n (%))		50 (5·4)	65 (7·4)
Household-level data		**n=892**	**n=851**
Fuel used regularly for cooking (n (%)): **			
	Electricity	0 (0)	0 (0)
	Gas	0 (0)	0 (0)
	Paraffin/kerosene	0 (0)	2 (0)
	Charcoal	107 (12·0)	156 (18·3)
	Wood	489 (54·8)	441 (51·8)
	Crop residues	304 (34·1)	278 (32·7)
	Dung	8 (0.1)	2 (0)
	Other	1 (0)	0 (0)
Tobacco smoker in the household (n (%))		146 (16·4)	126 (14·8)
Daily or almost daily exposure to smoke from (n (%)): **			
	Burning rubbish	362 (40·6)	308 (36·2)
	Cooking as business	129 (14·5)	113 (13·3)
	Paraffin/kerosene lamps	24 (2·7)	18 (2·1)

	Beer production	14 (1·6)	4 (0)
	Mosquito coils	9 (1.0)	17(2.0)
	Brick production	33 (3.7)	43 (5.1)
	Other sources	17 (1.9)	6 (0.7)
Source of drinking water (n (%)): **			
	Tap to house	74 (8·3)	77 (9·1)
	Shared communal tap	99 (11·1)	69 (8·1)
	Covered well	52 (5·8)	53 (6·2)
	Open well	47 (5·3)	56 (6·7)
	Bore hole	376 (42·2)	358 (42·1)
	Lake or river	62 (7·0)	30 (3·5)
	Other	0 (0)	1 (0)
Toilet facilities (n (%)):			
	Water toilet	6 (0.7)	2 (0.2)
	Ventilated improved pit	1 (0)	4 (0.5)
	Simple pit latrine	703 (78·8)	698 (82·0)
	None	182 (20·4)	147 (17·3)
Experienced a time in the last year when there was not enough food for the household to have its normal meals (n (%))		491 (55·0)	465 (54·6)
Experienced a time in the last year when the household did not have money to buy bathing soap (n (%))		603 (67·6)	574 (67·5)

* Vaccination status available for 1233 (621 intervention; 612 control) children; ** A household could give multiple responses.

Figure 1: Consort diagram



CO and COHb measurements

CO and COHb measurements were done at baseline on 1697 (900 intervention; 837 control) and 1574 (807 intervention; 767 control) children, respectively. The median (IQR) of 24-h averaged CO exposures at baseline was 0.45 (0.18, 0.92) ppm and the mean (SD) of COHb levels was 5.85% (3.36); similar in intervention and control groups (Table 2). Over the 2 years of follow-up, there were 5521 (2911 intervention; 2620 control) and 4065 (2113 intervention; 1952 control) measurements of 24h CO exposure and COHb levels, respectively. A total of 377 24-h CO periods had all measurements below the LOD (204 intervention, 173 control).

Table 2: Summary statistics of CO (ppm) and COHb (%) over visit schedule.

	Baseline	Follow up visit 1	Follow up visit 2	Follow up visit 3	Follow up visit 4
Mean CO ppm, median (IQR)	0.45 (0.18, 0.92)	0.27 (0.13, 0.84)	0.25 (0.10, 0.88)	0.25 (0.09, 0.88)	0.25 (0.09, 0.83)
Max CO ppm, median (IQR)	32.8 (19.0, 54.0)	26.5 (12.0, 52.0)	24.0 (8.5, 58.0)	20.5 (7.0, 49.0)	22.5 (8.5, 40.5)
Control arm Mean CO ppm, Median (IQR)	0.49 (0.21, 1.02)	0.33 (0.15, 0.89)	0.25 (0.09, 1.08)	0.25 (0.09, 0.76)	0.65 (0.22, 0.88)
Intervention arm Mean CO ppm, Median (IQR)	0.48 (0.18, 0.86)	0.25 (0.12, 0.79)	0.25 (0.12, 0.79)	0.26 (0.10, 0.92)	0.25 (0.08, 0.50)
Difference (intervention - control) in mean CO ppm (95% CI)	0.37 (-0.17, 0.93)	1.09 (-0.16, 2.34)	-0.36 (-1.07, 0.33)	-0.09 (-1.35, 1.17)	-0.05 (-0.93, 0.86)
Average minutes of observation (per '24-h' periods)	1407	1419	1420	1427	1437
Mean COHb% Mean (SD)	5.85 (3.36)	5.33 (3.73)	5.26 (3.65)	5.40 (3.44)	5.23 (3.54)
Control arm Mean COHb% Mean (SD)	5.94 (3.73)	5.34 (3.73)	5.48 (3.64)	5.68 (3.44)	5.69 (3.63)
Intervention arm Mean COHb% Mean (SD)	5.75 (3.74)	5.31 (3.74)	5.05 (3.65)	5.13 (3.43)	4.88 (3.44)
Difference (intervention - control) in COHb (95% CI)	-0.18 (-0.52, 0.15)	-0.03 (-0.41, 0.34)	-0.42 (-0.83, -0.02)	-0.55 (-1.01, -0.09)	-0.81 (-1.56, -0.06)

Exposure-response analysis ***[Figures 2A and 2B]***

There were 517 pneumonia episodes giving an incidence rate of 0.176 (95% CI: 0.161 – 0.191) per person-year. Adjusted GEE models demonstrated no evidence of association between CO (IRR=1.0 95% CI: 0.967, 1.014; p = 0.53) or COHb (IRR=1.00 95% CI: 0.993, 1.003; p = 0.41)) and rate of pneumonia. Analysis of secondary endpoints was similar with no association identified for severe pneumonia (n=192 episodes) and CO (IRR = 0.95 95% CI: 0.90, 1.01; p = 0.083) or COHb (IRR=1.01 95% CI 0.998, 1.02; p = 0.11), nor severe pneumonia with oxygen saturation < 90 (n=27 episodes) and CO (IRR = 1.03 95% CI: 0.92, 1.15; p = 0.67). Severe pneumonia with oxygen saturation <90 was associated with COHb (IRR=0.95 95% CI: 0.91, 0.99; p = 0.011) where higher COHb levels were mildly protective. However, once corrected for false-discovery-rate, no results remain statistically significant at p<0.05. Each model was adjusted for age, presence of smokers in the household, sex, randomization arm, visit number,

follow up time, and clustered on an individual period. Age stratified sub-analyses were run, considering episodes occurring up to and including 6 months of age separately from those occurring after 6 months of age. Results were unchanged with all IRR estimates for CO association (where appropriate) between 0.95 and 1.06 and none were statistically significant.

Figure 2A: Estimated IRR (95% CI) for the association between pneumonia and log10 (ppm) exposure fit as a categorical variable in quintiles. The lowest quintile (lowest 20% of exposure values) is the reference level for other estimates. Models are adjusted for age, presence of smokers in the household, sex, randomization arm, visit number, follow up time, and clustered on an individual period.

Figure 2B: Estimated IRR (95% CI) for the association between pneumonia and COHb exposure fit as a categorical variable in quintiles. The lowest quintile (lowest 20% of exposure values) is the reference level for other estimates. Models are adjusted for age, presence of smokers in the household, sex, randomization arm, visit number, follow up time, and clustered on an individual period.

***CO and COHb* levels in children with and without a pneumonia outcome**

Median (IQR) CO exposures in children with and without an episode of pneumonia during the trial were 0.31 (0.13, 0.92) ppm and 0.36 (0.15, 0.88) ppm, respectively, giving a difference (pneumonia - not) of 0.02 (95% CI: -0.58 to 0.62; p=0.18). Children experiencing an episode of severe pneumonia had median (IQR) CO of 0.44 (0.16, 1.23) ppm, and those with severe pneumonia with low oxygen saturation a median (IQR) CO of 0.25 (0.20, 0.57) ppm. Mean (SD) COHb levels in children with and without an episode of pneumonia during the trial were 5.34% (3.54) and 5.46% (3.64), respectively, giving a difference of -0.09 (95% CI: -0.33 to 0.16; p=0.49). Children with an episode of severe pneumonia had mean (SD) COHb of 5.24% (3.99) and those with an episode including low oxygen saturation had mean (SD) COHb of 4.03% (2.27).

Intention to treat (ITT) analysis

Median exposure to CO in the intervention and control groups was 0.34 ppm (IQR 0.15 to 0.81) and 0.37 ppm (IQR 0.15 to 0.97), respectively, giving a difference of -0.46 ppm (95% CI: -0.95 to 0.012; p=0.06) [Figure 3~~2~~A]. In linear mixed models, after adjustment for time, age, sex and the presence of smokers in the household, the difference was -0.029 ppm (95%CI: -0.12 to 0.06). Taking the intervention group alone, median CO (IQR) was 0.50 (0.02, 0.80) ppm and 0.2 (0.1, 0.8) ppm before and after receiving the intervention, respectively (p<0.08).

Mean COHb levels in the intervention and control groups were 5.31% (95% CI: 5.17 to 5.43) and 5.60% (95% CI 5.47 to 5.74), respectively, giving a difference of -0.30% (95% CI: -0.48 to -0.11; p=0.0017) [Figure 3~~2~~B]. After adjustment in linear mixed models for time, age, sex and the presence of smokers in the household, the difference was -0.24% (95% CI: -0.57 to 0.07). Taking the intervention group alone, mean COHb levels were 5.75% (SD 3.27) and 5.13% (SD 3.53) before and after receiving the intervention, respectively (p<0.0001).

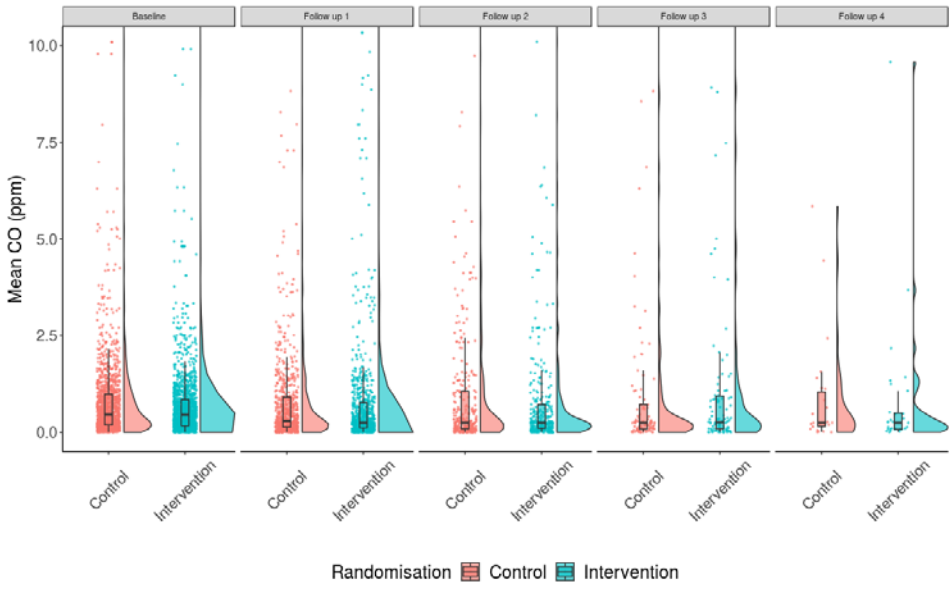


Figure 3~~2~~A: Mean CO ppm measured at baseline (visit 1) and following four follow-up visits (visits 2-5) for each individual. The plotted shape represents a density estimate. Y-axis truncated at a value of 10 (max observed mean CO = 303 ppm).

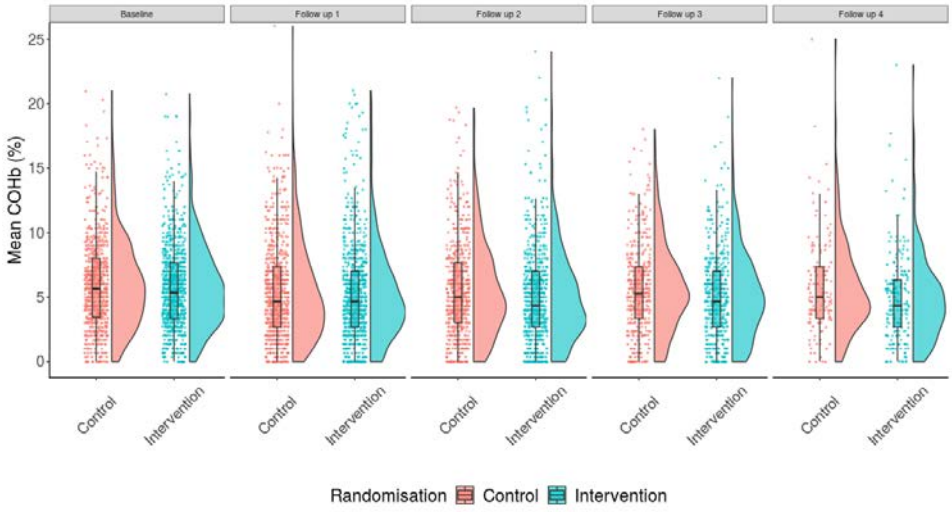


Figure 3~~2~~B: Mean COHb per individual measured at at baseline and following four follow-up visits for each individual. The plotted shape represents a density estimate. Y-axis truncated at a value of 25 (max observed COHb = 26).

DISCUSSION

This longitudinal study of personal exposure to household air pollution (assessed through measurement of CO and COHb) and its association with pneumonia in children under the age of 5 in Malawi included 1780 children who contributed 3549 and 4065 measurements of CO exposure and COHb levels, respectively, over 2 years of follow-up. While personal exposure to CO was low, COHb levels were consistently elevated over the 2 years of follow-up. We found no association between exposure to CO averaged over a 24-h period or levels of COHb and the incidence of pneumonia. In addition there were no differences in the average levels of CO exposure or COHb% in children with or without an episode of pneumonia during the trial. There was no difference observed in average CO exposure and only a minor difference in COHb levels between intervention and control group participants, consistent with the lack of intervention effect observed in the main intention-to-treat analysis.

In our main clinical trial report, we put forward two main explanations for the lack of effect of the intervention on pneumonia incidence: 1) that potential effects of the intervention may have been overwhelmed by other sources of air pollution; and 2) that the intervention did not reduce exposures sufficiently. An alternative explanation is that the causal relationship between exposure to household air pollution and pneumonia in children is not as strong as previously thought and that confounding – for example by the many dimensions of poverty – is also a factor. If true, then an intervention that aimed to reduce exposure to household air pollution from cooking in isolation would have less potential to impact on this outcome.

The low (below WHO 24-h CO exposure level of 7 ppm) (12) personal CO exposure levels seen over the course of the trial in both trial arms is consistent with other studies of household air pollution done in Africa and elsewhere (e.g. in RESPIRE it was 3.4 ppm (13)). This could be related to lower levels of this pollutant in combusted biomass fuel relative to other pollutants and/or where measurements are conducted when cooking is outside the home (14-16). It also suggests that the measurement of personal CO exposure for short periods of time may not always be a sensitive indicator for studies of the effects of household air pollution exposure reduction interventions, especially when cooking is done outdoors, and there is no straightforward way to confirm that these personal monitoring devicdes are worn as instructed. The possibility of poor concordance with wearingwearning the devices is another potential explanation for the apparently low CO exposures. In contrast, COHb levels were high and inconsistent with the personal CO exposure data. This finding might suggest that exposure to CO as a component of household air pollution is high after all, and that COHb may offer a more sensitive, and more biologically relevant indicator of CO exposure. The finding of a clearer, albeit weak, signal of effect of the intervention on COHb than CO is consistent with this conclusion. We acknowledge, however, that our interpretation of COHb data is limited in the very youngest children in whom pneumonia incidence is highest as limitations of the technology we were using meant we were unable to measure COHb in children under the age of 6 months.

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It is also possible that there was behavior change while the children were wearing the monitors leading to lower exposures. At the same time, it is $PM_{2.5}$ rather than CO exposure, that has been considered to be mechanistically implicated in increasing the risk of pneumonia by way of impairing host defenses. However, work we have done in Malawi (at the same time as the work described in this paper) and others have done elsewhere in the world, suggest that these two exposures are not always well correlated ((R^2=0.11) in our CAPS-linked study of non-communicable respiratory disease and air pollution exposure in Malawian adults (17)) and therefore CO exposure cannot be assumed to be an accurate proxy for $PM_{2.5}$ exposure, especially where cooking is done outside (17,18). In general, $PM_{2.5}$ is more complex and costly to measure than CO and requires equipment that is not well suited for personal monitoring in young children or on the kind of scale we achieved in this study. We are therefore left with uncertainty about the extent to which children in rural Malawi are exposed to household air pollution as would have been measured by $PM_{2.5}$ had this been feasible; the clinical relevance

of reductions in these exposures of the magnitude we observed; and the value of measuring CO as an indicator of household air pollution exposure in studies such as this. In more densely populated urban settings where biomass use is common and there are multiple other sources of air pollution, this may not be the case.

Although there is biological plausibility for a causal link between exposure to household air pollution and pneumonia in young children and strong indirect evidence, there is a relative paucity of direct evidence for this (4-6,19,20). Many of the individual exposure-response studies to date have been limited by indirect assessments of either exposure or outcome while pooled/meta-analyses used to create exposure-response curves have drawn substantially on extrapolation from studies of ambient and tobacco-related air pollution exposures (5,19,20). An exception is the RESPIRE trial of a chimney cookstove in Guatemala where an exposure-response relationship between measured CO (as a modeled proxy for $PM_{2.5}$) and pneumonia during the first 18 months of life was observed (21). Unlike many of the published studies of household air pollution and childhood pneumonia, cooking was done indoors by RESPIRE households and the infant was typically carried on mother's back during cooking periods. A recent systematic review of household air pollution exposures and pneumonia in children found that while associations were seen when questionnaires were used for exposure assessment, these associations were not usually seen (RESPIRE was an exception) when air pollutants including CO and particulate matter were measured directly (19). This conclusion is also consistent with the findings of our other recently published work from Malawi which has found no evidence that exposure to household air pollution was associated with pneumonia in adults, respiratory symptoms or lung function in children and adults or rate of decline on lung function in adults (17,22-25).

The strengths of this study include that it is the largest longitudinal study of personal exposure to CO and COHb levels in children in rural Africa, and that as part of CAPS, it benefited from the randomized controlled trial design, conduct, completeness of quality-assured data collection and analysis. Lost to follow-up and use of an aggregate endpoint (total pneumonia episodes) may impact the accuracy of estimated associations, but the main limitation is the lack of tools to measure personal exposure to $PM_{2.5}$ in young children in a straightforward and cost-effective way that can be done frequently for prolonged durations of time on large numbers of participants. While CO monitors are available that can meet these requirements, CO exposure is less biologically relevant to pneumonia development and may be a poor surrogate marker of $PM_{2.5}$ exposure, especially in settings where cooking is done outdoors.

INTERPRETATION

We found that young children in rural Malawi experience exposure to household and other types of air pollution on a day-to-day basis when questionnaire data are considered but that data from more direct measurements – personal CO exposure and COHb levels – are contradictory. We found no association between exposure to CO and pneumonia incidence and no effect of the CAPS intervention on these exposures, suggesting that CO may not be an appropriate measure of household air pollution exposure in settings like rural Malawi and that there is a need to develop ways to directly measure particulate matter exposures in young children instead. There is also a need to re-examine the role of cleaner-burning cookstoves and fuels as standalone health interventions. Addressing individual sources of air pollution alone is unlikely to be sufficient for improving health; instead a comprehensive approach to emission control from all sources is required to improve air quality both inside and outside the home.

AUTHOR CONTRIBUTIONS
Design: KM, DW, DP, SBG, JB
Acquisition of data: KM, CK, AC, WW, DP, DH, SBG, JB
Analysis of data: ML
Interpretation of data: All authors
Writing the manuscript, approval of the version to be published and agreement to be accountable for all aspects of the work: All authors

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TAKE HOME POINT

Study question

What is the association between exposure to household air pollution and pneumonia in children under the age of 5 years in rural Malawi and what are the effects of a biomass-fueled cookstove intervention on personal exposure to household air pollution?

Results

Exposure to carbon monoxide in our population was low with no association seen between exposure to carbon monoxide and pneumonia incidence and no effect of a biomass-fueled cookstove intervention on these exposures.

Interpretation

Carbon monoxide may not be an appropriate measure of household air pollution exposure in settings like rural Malawi. The role of cleaner-burning cookstoves and fuels as standalone health interventions needs to be re-examined.