

Global Health Activities in Developing Countries to Combat Non-Communicable Chronic Cardiovascular and Pulmonary Diseases (CVPD) - Centers of Excellence Additional Funding Opportunity- Cookstoves and Child Survival

Lower respiratory tract illness in children younger than five years of age and adverse pregnancy outcomes related to household indoor air pollution in Bariloche (Argentina) and Temuco (Chile).

Technical Proposal

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Abstract of Proposal

Globally about 3 billion people rely on solid fuels for cooking, namely coal and traditional biomass (wood, dung, crop wastes and coal). The use of these fuels in poorly ventilated dwellings results in high levels of Indoor Air Pollution (IAP) causing approximately 2 million deaths every year, accounting for 2.7% of the global burden of disease. IAP has been linked to an increase risk of Lower Respiratory Tract Infections (LRTI), cancer, tuberculosis, eye disease and adverse perinatal outcomes.

There is reliable evidence that IAP increases the risk of pneumonia among children (OR= 1.78; CI95% 1.45-2.18), and emerging evidence that also links IAP with low birth weight (OR=1.38; CI95% 1.25, 1.52), and stillbirths (OR=1.51; CI95% 1.23, 1.85).

This Retrospective Cohort study will be implemented by the NHLBI sponsored Southern Cone Center of Excellence for Cardiovascular Health (CESCAS) at the Institute for Clinical Effectiveness and Health Policy (IECS), in collaboration with the Universidad de La Frontera in Temuco, Chile, to counter the impact of IAP due to use of biomass fuels in acute respiratory infections in children and adverse perinatal outcomes

We plan to include 900 households selected by systematic random sampling to obtain data, through questionnaires, on medical history related to respiratory infections and pregnancy outcomes, demographic information and smoking habits from the caregivers of children of less than 5 years.

The proposed study will evaluate whether exposure to IAP affects LRTI and pregnancy outcomes in two locations with high exposure to biomass fuel use in Argentina (Bariloche) and Chile (Temuco), two of the sites where the PRISA (**P**ulmonary **R**isk **I**n **S**outh **A**merica) study, a population-based cohort study sponsored by NHLBI, to detect risk of Chronic Obstructive Pulmonary Disease (COPD), is being conducted. This is, to our knowledge, the first study of its kind in our countries.

Environment/Resources

This Retrospective Cohort study will be implemented by the NHLBI sponsored Southern Cone Center of Excellence for Cardiovascular Health (CESCAS) at the Institute for Clinical Effectiveness and Health Policy (IECS), in collaboration with the Universidad de La Frontera in Temuco, Chile, to counter the impact of Indoor Air Pollution (IAP) due to use of biomass fuels on acute respiratory infections in children and adverse perinatal outcomes. Both centers have extensive experience in community-based NCD research. All of these settings have enough space for patient recruitment, intervention and data collection. The institutions have an internationally recognized experience in grant writing, research, capacity building, and advocacy in many areas, including chronic diseases.

IECS has 700 square meters of working space for 50 staff members, including administrative support staff. The office has a conference room with a capacity for 50 people and is equipped with computing software and hardware, high-speed internet connections statistical software photocopiers, network printers, telephones with conferencing capabilities, a scanner and a dedicated fax machine. IECS has strong links to the School of Public Health at the University of Buenos Aires, with an appropriate environment for academic activities. In there has working space for 20 staff members, including administrative support staff, equipped with 2 photocopiers, network printers, 5 telephones, and a dedicated fax machine and a classroom for 45 persons. The Clinica San Carlos in Bariloche in Argentina, have sufficient clinical space and personnel for patient recruitment, intervention, and data collection.

The University of La Frontera hosts CIGES (Center for Training, Research & Management for Evidence-based Health). CIGES works closely with the Chilean Ministry of Health and Temuco local health authorities on different projects involving community participation and will serve as the field center for this project in Chile and will provide study coordinators. The Center is available for the study and program coordinators. In addition there are clinical epidemiologists and biostatisticians with a wide range of research interests and expertise in clinical trials, economical evaluation, and CVD research. The researchers of Universidad de La Frontera have their offices at the Department of Internal Medicine equipped with computing software and hardware, high-speed internet connections and statistical software.

Introduction

Globally about 3 billion people depend on solid fuels for cooking (400 million use coal and 2.6 billion traditional biomass), 3% of these population lives in developing countries from Latin America & The Caribbean (LAC)¹. Most households in developing countries use wood as their primary cooking fuel, leaving charcoal and gas in second and third place¹. Only 5% of the users of biomass fuels for cooking, have access to clean cooking stoves.¹ Preliminary data of PRISA², an ongoing population-based cohort study conducted in Argentina, Chile and Uruguay by our Center of Excellence, showed an average exposure to IAP between 21% in Bariloche and 26% in Temuco.

Acute respiratory infections (ARI) represent a common cause of illness in children younger than five years of age and represent the major cause of pediatric consultations in Latin American countries, implying a high demand of medical care.³ One meta-analysis, published by IECS found a pooled incidence of community-acquired pneumonia of 918.81/100,000 child-years under five years of age (95%CI 488.52 -1349.1) in LAC.⁴ The World Health Organization estimated for the year 2008 an under-five mortality rate 18/1000 live births in LAC, with 12% of these deaths caused by pneumonia.⁵ Since 1995 the reduction of IAP related to the use of solid fuels for cooking has been identify as a potential intervention for preventing pneumonia in children¹¹. Several studies examined the link between pneumonia and the exposure to biomass fuels, one meta-analysis that include 24 studies showed an overall pooled odds ratio (OR) of 1.78 (CI95% 1.45-2.18).⁷

Annually, 15 million preterm births occur worldwide.⁸ The global prevalence of low birth weight (LBW) is 15.5% (20.6 million of births/year). LBW can be a consequence of prematurity, small size for gestational age, or both.⁹ Prematurity or LBW are well known as a cause of increased morbimortality and disabilities. Adverse pregnancy outcomes have been linked to exposure to secondhand smoke and ambient air pollution; a recent meta-analysis found an association between IAP and increased risk of LBW (OR=1.38; CI95% 1.25, 1.52) and stillbirths (OR=1.51; CI95% 1.23, 1.85).¹⁰

Specific aims

The main objective of this proposal is to evaluate the effect of IAP on the development of adverse pregnancy outcomes and the increase of LRTI in children younger than five years of age in two locations in Argentina (Bariloche) and Chile (Temuco).

Primary Aim: To estimate the effect of IAP on the incidence, hospital admissions and deaths caused by LRTI infections (Pneumonia and Bronchiolitis).

Hypothesis A: Exposure to IAP in the household is associated with an increase of LRTI incidence and mortality in children.

Secondary Aim: To evaluate whether adverse pregnancy outcomes are associated with exposure to IAP.

Hypothesis B: Exposure to IAP in the mother's household is associated with low birth weight and stillbirths.

The proposed study will evaluate whether exposure to IAP affects LRTI and pregnancy outcomes in two locations with high exposure to biomass fuel use in Argentina (Bariloche) and Chile (Temuco), capitalising on two of the sites where the PRISA (Pulmonary Risk In South America) study is being conducted by IECS. This is a population-based cohort study sponsored by NHLBI to detect risk of Chronic Obstructive Pulmonary Disease (COPD)². This is, to our knowledge, the first study of its kind in Argentina and Chile.

Research Approach

This retrospective cohort study will include 900 households identified by means of a randomized sampling from selected census radii with high exposure to IAP due to solid fuel use in Bariloche and Temuco. As mentioned above, these two locations have been selected on account of the percentage of population with high risk of IAP from cooking with biomass fuels in poorly ventilated dwellings.

PRISA is an NHLBI-sponsored prospective cohort study, conducted by IECS, aimed at examining the risk factors for COPD as well as its prevalence and incidence among 6,000 persons aged 45-74 years from four towns in Argentina (Bariloche and Marcos Paz), Chile (Temuco) and Uruguay (Canelones)². Preliminary data of this study shows that 20.61% of the population-based sample in Bariloche and 25.53% in Temuco have been heavily exposed to biomass use for cooking. Defining high level of exposure as more than 200 hour-years¹¹.

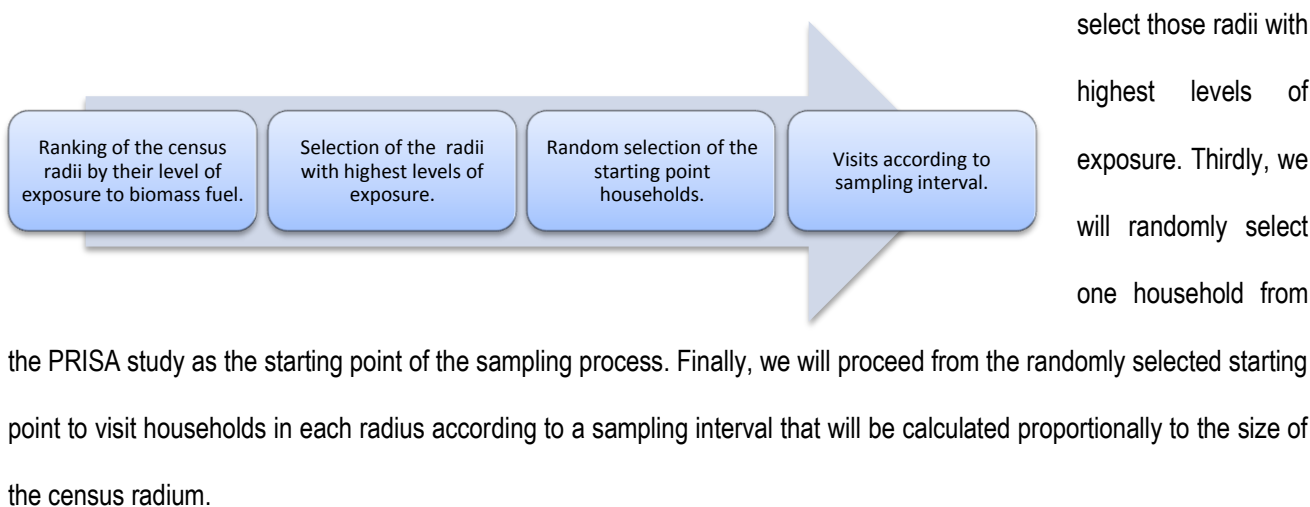
Inclusion and exclusion criteria

Inclusion criteria:

- Households with children under five years of age
- Households with a child born alive and/or a stillbirth in the last 3 years
- Permanent resident of Bariloche or Temuco
- Able and willing to provide written informed consent

Sampling Methods and Sample Size

We plan to conduct a systematic random sampling. Firstly, with the sample frame of the PRISA study for Bariloche and Temuco as a starting point, we will rank the census radii by their level of exposure to biomass fuels. Secondly, we will



The rationale for designing this sampling procedure, and not using the original sample straight away, is that we do not expect to find enough households which meet the inclusion criteria since the population of PRISA is older than 45 years of age. Based on an LRTI reported incidence between 50/1,000 and 60/1,000¹² and considering the increased risk of LRTI in exposed children (OR between 1.45 and 2.10)⁷, the estimated sample size is 450 households per group (exposed and not exposed).

Recruitment Plan

The selected household key informant will be invited to participate; the interviewer at the house will check whether they meet the inclusion criteria. When possible, the survey will be conducted at this time. Otherwise, the interviewer and participant will agree on another appointment. During the visit, the interviewer will collect information using questionnaires related to LTRI, adverse pregnancy outcomes and exposure to biomass fuels for cooking.

Definition of variables

Primary endpoints: LRTI

- Pneumonia assessed by recall of the caregiver of key symptoms and signs (fast breathing, fever, chest indrawing) and the use of antibiotics for treatment within the last year.
- Bronchiolitis assessed by recall of the caregiver of key symptoms and signs (fast breathing, chest indrawing, wheezing, fever) plus the treatment with bronchodilator drugs within the last year. We will assess the stay on guard or health center to receive short treatment (shortened hospitalization) for less than 24 hours.
- Pneumonia or bronchiolitis assessed by recall of the caregiver of key symptoms and signs (fast fast breathing, chest indrawing, wheezing, fever) and the use of antibiotics and or bronchodilators within the last year.
- LRTI hospitalizations within the children life span by recall of the caregiver and verified through hospital records.
- LRTI deaths as reported by the caregiver, and confirmed by hospital records or verbal autopsy.

Secondary endpoints: Adverse Pregnancy Outcomes

- Low birth weight (<2,500g) in newborns over the last three years, by mother's report and if possible confirmed by copies of hospital records available at home.
- Prematurity over the last three years, by mother's report and if possible confirmed by copies of hospital records available at home.

- Stillbirths (≥ 24 weeks of gestation) occurred in the last three years, by mother's report and if possible confirmed by copies of hospital records available at home.
- Miscarriages, by mother's report and if possible confirmed by copies of hospital records available at home.
- LBW or Stillbirths occurred in the last three years, by recall and if possible confirmed by hospital records (epicrisis, summary of hospitalization) available at home.

Exposure: Exposure to IAP

- Use and time spent using unprocessed solid fuels (wood, animal dung, crop wastes, coal, charcoal) for cooking by self-report
- Kind of device used to cook by direct observation
- Time children spend near the cooking stove, by self-report
- Children carried while cooking, by self-report
- Cooking done in the same room as where the child sleeps, by self-report
- Number of rooms in the house, by self-report
- Device and fuel used to warm the house

Other variables

- Sociodemographic data (age, sex, ethnicity and race, years of formal education, income), by self-report
- Parity of mothers, by self-report
- Smoking habits of the parents/cohabitants living in the same household, by self-report
- Overall health status, by self-report using SF-36 general health question.
- History of tuberculosis.
- History of Gestational diabetes, by recall and if possible confirmed by prenatal care records.
- History of Pregnancy-Induced Hypertension, by recall and if possible confirmed by prenatal care records
- Number of prenatal care visits during pregnancies occurred in the last three years, by recall and if possible confirmed by prenatal care records
- Gestational age at birth, by recall and if possible confirmed by prenatal care records

Instruments for data collection

We plan to obtain data on medical history related to respiratory infections, pregnancy outcomes, demographic information and smoking habits, from the caregivers of children under 5 years of age using **questionnaires** adapted from existing validated ones when possible. When a caregiver reports a death or a hospitalization due to respiratory cause, the interviewer will confirm this information through **hospital records** or **verbal autopsy** as appropriate.

Data Processing

A database will be designed at IECS using the OpenClinica open source software¹⁶. Entry of data will be carried out at each site by trained and certified personnel. All data will be double-keyed and checked for validity and consistency.

Monitoring Procedures

Quality monitoring of data collection process will be conducted at local and central levels. The study coordinators will monitor study personnel daily, ensuring compliance with the protocol. Specifically, all questionnaires will be reviewed for completeness prior to the end of the interview to able to correct errors or omissions. Also, IECS investigators will visit field centers as needed to monitor all aspects of the project. Monitors will record information about the quality of procedures and any deviations from the study protocol. Retraining of study staff will be conducted as necessary.

Statistical Analysis

We will describe the frequency and distribution of population variables in each location. In addition to descriptive analyses, logistic regression models will be used to examine the association between risk factors and development of LRTI, LRTI mortality and adverse pregnancy outcomes. Relevant potential confounders of the relationships of interest will be added to the models, as well as first order interaction terms involving the variables of interest. The statistical significance of such terms will be evaluated using the log likelihood test at a 0.05 significance level. We will assess the overall goodness of fit of the final model through the Hosmer-Lemeshow test, and perform model diagnostics, including deviance residuals and delta beta statistics. Statistical analysis will be performed using Stata Statistical Software version 11.0.

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Protection of Human Subjects

The proposed study will be conducted following strict guidelines for the protection of the rights of human volunteers. All investigators and study staff have attended a training session in protection of human subjects and are certified by the NIH. At the screening visit, informed consent will be signed by all participants. The consent form will clearly state the purpose, eligibility criteria, and protocol of the study, the potential benefit and risk of participation, and the subject's right to refuse to participate or withdraw. The study protocol will be approved by IRBs in all participating locations.

Data and Safety Monitoring Plan

Raw Data in Need of Safeguarding

- 1) Consent forms that include participant name.
- 2) Electronic files generated to link identifying information with study ID numbers.

Data Transmittal

Survey and clinical data will be strictly de-identified and will be electronically transmitted from the field to each country's main office location only by project staff. Data manager at IECS will integrate all information received from each site.

Disposition of the Data after the Study

Raw data and computer files will be kept at the research offices of project staff.

Potential Adverse Events

The proposed study is a questionnaire. There are no anticipated undesirable or adverse effects expected for this intervention.

Institutional Review Board Coverage

Each participating institution in Argentina and Chile will conduct its own independent IRB review.

Targeted/Planned enrollment

Key steps:

Activities	Months*																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Completion of the final protocol	█																	
Final protocol presentation for IRB approval	█	█																
Design of the sampling procedure	█	█																
Design and adaptation of specific forms and SOPs	█	█	█															
Training of interviewers and study personnel			█															
Pilot Study				█														
Pilot study Analysis					█													
Enrollment						█	█	█	█	█	█							
Verification and adjudication of events							█	█	█	█	█	█						
Data analysis													█	█	█			
Report and manuscript writing																█	█	█

*Eighteen months of work beginning in July 2012 and ending in December 2013, the start date may be modified depending on the approval of this protocol.

Contractual Arrangements

IECS will be the recipient institution of this grant from NHLBI. IECS will execute subcontracts with Universidad de la Frontera, Temuco, Chile in the amount specified in the budget related to this proposal.

