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# Environmental exposure to lithium during pregnancy and fetal size: A longitudinal study in the Argentinean Andes ☆

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ABSTRACT

*Background:* Lithium, used for treating bipolar disease, crosses freely the placenta and is classified as teratogenic. It is unclear to what extent environmental lithium exposure may affect fetal growth and development.
*Objectives:* To elucidate potential effects of lithium exposure through drinking water during pregnancy on fetal size.
*Methods:* We developed a prospective population-based mother–child cohort (N = 194) in an area with highly varying drinking water lithium concentrations (5-1600 μg/L) in northern Argentinean Andes. Blood and urinary lithium concentrations (sampled repeatedly during pregnancy) were measured using inductively coupled plasma mass spectrometry. We measured fetal size by ultrasound in second and third trimesters, and weight, length and head circumference at birth. Multivariable models were used to examine associations between lithium exposure (continuous and in tertiles) and fetal size measures.
*Results:* Lithium in maternal blood (median 25; range 1.9–145 μg/L) and urine (1645; 105–4600 μg/L) was inversely associated (apparently linearly) with all fetal measures (body, head and femur) in the second trimester, and with birth length (β −0.53 cm per 25 μg/L increase in blood lithium, 95%CI −1.0; −0.052). An increase of 100 μg/L in blood was associated with 2 cm shorter newborns (about one standard deviation).
*Conclusions:* Lithium exposure through drinking water was associated with impaired fetal size and this seemed to be initiated in early gestation. Further studies are warranted to confirm causality and to understand the mechanisms. If confirmed, these findings have public health relevance and emphasize the need for more data on lithium concentrations in drinking water, including bottled water.


## 1. Introduction

Lithium has long been used in the treatment of bipolar disease (Grandjean and Aubry, 2009b). It is classified as teratogenic (category D) by the U.S. Food and Drug Administration. Besides fetal cardiac and other malformations, lithium seems to increase the risk of miscarriages and prematurity, as well as fetal goiter and hypothyroidism (Cohen et al., 1994; Diav-Citrin et al., 2014; Gentile, 2012; Grandjean and Aubry, 2009c; Oyebode et al., 2012).

A source of more general exposure to lithium is drinking water, although data on concentrations are scarce. Lithium concentrations between <1 and 170 μg/L have been reported for drinking water in Texas, Japan and England (Bluml et al., 2013; Kabacs et al., 2011; Sugawara et al., 2013), while concentrations exceeding 1000 μg/L have been reported for certain areas in Austria (Kapusta et al., 2011) and northern Chile (Zaldivar, 1980). High concentrations have also been reported for certain bottled water, e.g. with almost 10 mg/L in a product from Slovakia (Reimann and Birke, 2010). Elevated lithium concentrations in drinking water (~1000 μg/L) and human urine (~4500 μg/L) were detected in the Andean part of northern Argentina (Concha et al., 2010).

We recently reported that lithium from drinking water easily passes the placenta to the fetus (Harari et al., 2012). As it is unclear to what extent lithium, even from medication, may affect fetal growth and development (Diav-Citrin et al., 2014; Jacobson et al., 1992; Kallen and Tandberg, 1983; Mroczka et al., 1983), we initiated a population-

*Abbreviations:* LMP, last menstrual period; ICP-MS, inductively coupled plasma mass spectrometry; LOD, limit of detection; iAs, inorganic arsenic; MMA, methylarsonic acid; DMA, dimethylarsinic acid; HPLC, high-performance liquid chromatography; HG, hydride generation; SD, standard deviation; BPD, biparietal diameter; OFD, occipitofrontal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length; BMI, body mass index.

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based mother–child cohort study aiming at elucidating such potential effects from maternal exposure to drinking water lithium during pregnancy.

## 2. Material and methods

### 2.1. Study population

All pregnant women living in the Andean part of the Salta province (Departamento Los Andes and part of Departamento La Poma and Rosario de Lerma), northern Argentina (altitude 3180–4070 m above sea level), with estimated delivery date between October 2012 and December 2013, were invited to participate in this longitudinal mother–child cohort, designed to evaluate potential health effects of early-life exposure to lithium and other water pollutants. The study area (totally 8135 inhabitants) included the main village San Antonio de los Cobres (5893 inhabitants; mean water lithium 640 μg/L) and the surrounding villages Santa Rosa de los Pastos Grandes (110 μg/L), Tolar Grande (8 μg/L), Salar de Pocitos (100 μg/L), Olacapato (23 μg/L), Cobres (135 μg/L), Las Cuevas (98 μg/L), El Toro (65 μg/L), El Palomar (13 μg/L) and Esquina de Guardia (140 μg/L). The presence of elevated concentrations of arsenic in the drinking water, particularly in San Antonio de los Cobres, has been known since long (Vahter et al., 1995), while the presence of lithium, boron and cesium was recently detected (Concha et al., 2010).

All pregnant women were invited to the study with the assistance of the primary health care personnel at the hospital in San Antonio de los Cobres and surrounding villages. The 23 trained community health care workers visit the 20 different administrative areas (San Antonio de los Cobres comprising 11 areas, and 9 surrounding villages) on a regular basis, about every 3 months to update demographic information, including health status and pregnancies. Between October 2012 and December 2013, 221 women were pregnant, out of whom 194 became enrolled (participation rate: 88%). Reasons for not participating included deliveries before recruitment (n = 11), twin pregnancy (n = 1), fetal loss before recruitment (n = 5), refusal or not located (n = 6), and migration (n = 4). In addition, two women had spontaneous abortions and 12 lacked prenatal exposure data, giving a final sample of 180 pregnant women (see Supplementary material, Fig. S1). We formally invited the women to the main hospital in San Antonio de los Cobres or the local primary health care clinics in surrounding villages for the investigation of exposures and pregnancy-related conditions. In case a woman was not able to attend at the scheduled date, she was asked to come any day before or after. In this manner, all women were given maximum opportunity to participate in the examinations. The study was designed to see the pregnant women at least once during pregnancy; preferably 2–3 times in order to obtain repeated measures of exposure and fetal size.

The study was approved by the regional ethical committee at Karolinska Institutet, Stockholm, Sweden, and by the Ministry of Health, Salta, Argentina. Prior to recruitment we obtained written informed consent from all women after oral and written explanation of study details. For women below 18 years of age, informed consent was also obtained from the closest caregiver. We regularly reported to and discussed measured water contaminant concentrations with the hospital and the Health Ministry in Salta.

### 2.2. Data and sample collection

All women were interviewed about age, last menstrual period (LMP), pre-pregnancy weight, parity, time and place of residence, tap water sources and type of water (tap/bottled water), dietary habits, family income, living conditions, smoking, passive smoking, alcohol consumption, coca chewing and personal and familial history of diseases. We measured the women's weight (HCG-210QM, GA.MA® professional, Italy; accurate to 100 g) and height in a standardized way at each visit. Hemoglobin levels were measured in whole blood by HemoCue® 201 + (HemoCue AB, Ängelholm, Sweden). Gestational age was calculated based on the date of LMP which was checked against the estimation based on ultrasound. If LMP was not available or clearly wrong, we used the data based on ultrasound.

All women were asked to donate blood and spot-urine samples at baseline and at each follow-up visit. Whole blood samples were collected in Trace Elements Sodium Heparin tubes (Vacuette®; Greiner bio-one, Kremsmünster, Austria) with butterfly needles (BD Safety-Lok™, Vacutainer®, Becton, Dickinson and Company, Franklin Lakes, USA; tested negative for trace element contamination). One tube was centrifuged for 10 min at 3000 rpm, 15 min after blood withdrawal, for plasma extraction. Spot-urine samples were collected at the hospital or at the local health clinics using disposable trace element free plastic cups and transferred to 20 mL polyethylene bottles. Instructions on wet wipe cleaning and appropriate mid-stream urine sample collection were given in order to avoid contamination. We repeatedly collected water samples (20 mL polyethylene bottles). Blood, urine and water samples were kept at −20 °C until transported to Karolinska Institutet, Sweden, where they were stored at −80 °C until analysis.

### 2.3. Exposure assessment

To assess lithium exposure, we measured the concentrations in blood, urine, and drinking water. We also measured arsenic, boron and cesium in the same media to control for potential confounding, as they are also present in the drinking water in the study area. All elements were determined using inductively coupled plasma mass spectrometry (ICP-MS, Agilent 7700× ORS ICP-MS, Agilent Technologies, Tokyo, Japan), with the collision/reaction cell in no gas mode (lithium, boron and cesium) or helium mode (arsenic). Before analysis, urine and water samples were diluted 1:10 with 1% nitric acid (65% w/w, ppb-trace analysis grade, Scharlau, Scharlab S.L., Sentmenat, Spain) (Concha et al., 2010). Aliquots (0.2 mL) of blood samples were diluted 1:25 with an alkali solution consisting of 1-butanol 2% (w/v), EDTA 0.05% (w/v), triton X-100 0.05% (w/v), $NH_4OH$ 1% (w/v) and internal standards (20 μg/L) (Lu et al., 2015). The mixture was sonicated for 5 min and centrifuged at 2000 rpm for 5 min (MSE centrifuge, Super Minor, MSE (UK) Ltd., London, England) before ICP-MS analysis. This method was found to provide more reliable results for blood lithium than acid digestion (Lu et al., 2014). For urine, acid and alkaline dilution gave essentially the same results ($r_s = 0.98$; n = 285). Results for commercially available reference materials and limits of detection are presented in Supplemental material, Table S1.

Concentrations of inorganic arsenic (iAs) and its methylated metabolites methylarsonic acid (MMA) and dimethylarsinic acid (DMA) in urine were determined using high-performance liquid chromatography (HPLC) coupled with hydride generation (HG) and ICP-MS as previously described (Harari et al., 2013). The sum of the metabolite concentrations in urine (iAs + MMA + DMA) was used as exposure marker for inorganic arsenic. For quality control, see Harari et al. (2013). The correlation between concentrations of sum of arsenic metabolites and total arsenic, measured in multi-element analyses, was 0.97 ($p < 0.001$), supporting reliable analytical data, and also that the women were exclusively exposed to inorganic arsenic (Vahter, 2002).

To compensate for variations in the dilution of urine, the measured element concentrations were adjusted to the mean urinary osmolality (694 mOsm/kg; range 141–1174), measured by a digital cryoscopic osmometer (OSMOMAT® 030, Gonotec Gesellschaft für Meß- und Regeltechnik mbH, Berlin, Germany). Osmolality was chosen since creatinine adjustment is markedly affected by muscle mass, age and meat intake (Suwazono et al., 2005) and specific gravity by urinary protein and glucose (Parikh et al., 2002). Microalbuminuria (urinary albumin 30–299 mg/L) was detected in 14% of all women and macroalbuminuria (>300 mg/L) in 6%, using HemoCue Albumin 201 (HemoCue AB,

Ängelholm, Sweden), in agreement with other studies (Singh et al., 2013).

### 2.4. Fetal growth parameters

Of the 180 included women, 136 participated in at least one ultrasound measurement (October 2012, January 2013 and April 2013) during the 2nd (n = 81) or 3rd (n = 98) trimester (43 of them had measurements in both 2nd and 3rd trimesters) and ten women were measured only in the 1st trimester (34 women had no measurement). The examinations were performed by an experienced senior obstetrician, using a portable ultrasound machine FFSonic, UF-4100, (Fukuda Denshi, Tokyo, Japan) with 3.5 MHz transducer (FUT-CS602-5AJ). The measurements included biparietal diameter (BPD), occipitofrontal diameter (OFD), head circumference (HC), abdominal circumference (AC), and femur length (FL). BPD, OFD, and HC were all calculated from a plane of the head where the thalamus, the cavum septum pellucidum and the choroid plexus were included. BPD was measured from the outer to inner skull bone, OFD from the outer to inner skull bone and HC around the outer table of the skull. AC was calculated from a cross section of the abdomen, circular in shape, and in right angle to the spine with the stomach, the umbilical vein and a cross section of the spine were included. AC was measured around the outer table of this abdominal picture. FL was measured as the whole diaphysis of the femur. Each site was measured three times, each time using a new picture, after which the average was calculated. Fetal weight was calculated by the instrument software according to the following formula: $\text{Log}_{10}\text{Fetal Weight (g)} = (\text{AC} * 0.046) - (\text{BPD} * \text{AC} * 0.002646) + (\text{BPD} * 0.166) + 1.2508$. Indicated abnormalities (heart malformation (n = 1), renal cysts (n = 1), polyhydramnios (n = 1) oligoamnios (n = 1)) were referred by the medical doctors to the main obstetric clinic in Salta.

### 2.5. Measurements at birth

Birth anthropometric measures were obtained within a few hours after birth for 174 of the women (see Supplemental material, Fig. S1). Of these, seven women (4.0%) had delivered at home and six women (3.5%), in the ambulance on the way to Salta hospital. Birth weight was measured using a baby balance (Seca 725 Mechanical Beam Baby Scale, Brooklyn, NY, USA), birth length using a portable wood infantometer to the nearest 5 mm with the child in supine position, and head circumference with a soft, non-stretchable plastic tape line. Gestational age at birth was calculated by subtracting the date for LMP from the date of birth. In the few cases of missing LMP, we used the ultrasound estimation.

### 2.6. Statistical methods

Statistical analyses were performed with STATA 12.1 (StataCorp LP, TX, USA). A p-value of $<0.05$ was considered statistically significant. Initial bivariate associations between exposure markers, fetal growth parameters and outcomes, and potential covariates were assessed with Spearman's rank correlation ($r_s$). We also visually evaluated scatter plots of all the outcomes against exposure measures and covariates and examined the associations with Lowess moving-average fitted curves. For the test of differences across tertiles of blood lithium, Kruskal–Wallis rank test (for continuous variables) and chi-square test (for categorical variables) were used.

To elucidate associations of maternal lithium exposure with fetal growth, we performed multivariable-adjusted linear regression analyses, including measurements in the 2nd and 3rd trimesters (only crown-rump length was measured in the first trimester), using blood and urine lithium as continuous variables as well as in tertiles. Because the fetal and exposure measurements were collected prospectively, we modeled the mean changes in these parameters over time using linear mixed effect models with random intercept and slope using maximum likelihood estimation. As blood and urine lithium seemed to change across pregnancy, based on linear mixed-effects models including all measurements obtained throughout pregnancy (N = 282), we also performed cross-sectional linear regression analyses with fetal size measurements in the second and third trimesters separately. For the birth outcomes we used linear regression models based on the apparent linear associations when visually examining the Lowess moving-average fitted curves for birth measurements against lithium concentrations during pregnancy (mean value for women with two or more measurements).

Initially, each fetal/birth measurement was regressed against blood or urinary lithium (measured at the same time as the outcome for fetal measurements, or average of blood and urine measurements during pregnancy for birth measurements) adjusting only for gestational age at measurement (in weeks) and gestational age as quadratic term, as the associations between fetal measurements and gestational age appeared to be quadratic. For comparison, we tested adjusting the models for centered gestational age and obtained the same results. Further adjustment was based on a priori selection of known risk factors for low fetal or birth size and on results from exploratory stepwise regression using an approach of bidirectional elimination of covariates, i.e. a combination of forward selection and backward elimination. All final models were adjusted for parity, family monthly income (from both mother and father in tertiles: ≤500, 500–3000, >3000 Argentine pesos), maternal height (cm), fetal sex, maternal urinary arsenic (continuous), blood cesium (continuous) and serum boron (< or ≥80 μg/L). Family monthly income was used as an index of socioeconomic status as this influenced the models more than maternal or paternal education level and living conditions. Other covariates such as coca chewing, hemoglobin concentrations, history of diseases, blood pressure and pre-pregnancy weight did not influence the estimates and were, therefore, not included in the final adjusted models. Because of collinearity between maternal age and parity ($r_s = 0.79$, $p < 0.001$), we only included parity in the models as that explained more than maternal age.

To test whether the right-skewed exposure data influenced the obtained estimates, we repeated the analyses using blood or urinary lithium categorized in tertiles, adjusting the models for the same variables as in the previous analyses. In sensitivity analyses, we excluded one individual with the highest blood lithium level (145 μg/L) and two women with preeclampsia from all models.

## 3. Results

Cohort characteristics and birth outcomes are presented in Table 1 by tertiles of blood lithium, and measurements of fetal BPD, OFD, HC, AC, and FL and calculated weight of the 136 fetuses (total number of measurements = 179) in fetal growth charts (see Supplemental material, Fig. S2). Thirteen percent of the women were younger than 18 years and 19% older than 30. Half of the women were shorter than 153 cm, in agreement with other Andean populations (Macdonald et al., 2004), which tended to give high body mass index (BMI). In total 12% of the women had a BMI of 25–30 kg/m$^2$ and 7% above 30. Thirty-five percent of the women were nullipara (age range 13–29 years) and the maximum number of previous births was 12. Eighteen percent of the women delivered preterm. The women were mostly of indigenous origin; with 85% reportedly belonging to the Kolla community (85%) and some to the Atacama and Tastil communities. Two thirds of the families owned their houses, which often (92%) were built of adobe, with floor of mud (40%) or cement (55%) and roof of tin and/or stones (51%) or straw and wood (43%). Only 13% lived in rented room or small apartment.

Median lithium concentration in maternal blood and urine among all 180 women (irrespective of number of samples per woman) was 25 (range 1.9–145) μg/L and 1491 (105–4598) μg/L, respectively. The exposure to all the metals lithium, arsenic, boron, and cesium increased significantly across tertiles of blood lithium (Table 1), however, they were, in general, weakly or moderately correlated (Supplemental

**Table 1**
Household and maternal characteristics and birth outcomes by tertiles of maternal lithium concentrations in blood[a] (μg/L).

| Mean (range): | Tertile 1 (n = 60) | | Tertile 2 (n = 60) | | Tertile 3 (n = 59) | | |
|---|---|---|---|---|---|---|---|
| | 11 (1.9–18.4) | | 25 (18.7–31.3) | | 47 (31.3–145) | | p-Value[b] |
| Household charactertistics | | | | | | | |
| Household (number of people) | 6.4 (3.5) | 2.0–17 | 7.4 (4.5) | 1.0–24 | 7.4 (4.4) | 2.0–32 | 0.22 |
| Water lithium (μg/L) | 126 | 8.2–819 | 670 | 27–819 | 750 | 6.5–958 | <0.001 |
| Water arsenic (μg/L) | 52 | 1.7–157 | 97 | 3.4–157 | 100 | 4.4–157 | <0.001 |
| Water boron (μg/L) | 3142 | 377–6655 | 5565 | 846–6525 | 6072 | 402–10,930 | <0.001 |
| Water cesium (μg/L) | 154 | 0.0061–356 | 299 | 0.15–366 | 325 | 0.058–392 | <0.001 |
| Maternal charactertistics | | | | | | | |
| Maternal age (years) | 25 (6.9) | 15–41 | 24 (6.3) | 14–37 | 25 (7.2) | 13–40 | 0.76 |
| Height (cm) | 154 (5.6) | 144–169 | 153 (5.5) | 144–168 | 151 (4.8) | 134–161 | 0.11 |
| Pre-pregnancy weight (kg)[c] | 56 (10) | 40–86 | 54 (8.3) | 42–74 | 52 (8.3) | 38–77 | 0.12 |
| Pre-pregnancy BMI ($Kg/m^2$) | 23 (3.4) | 18–35 | 23 (3.6) | 18–32 | 23 (3.9) | 17–35 | 0.65 |
| Maternal education level (years) | 8.9 (3.3) | 0.0–16 | 8.9 (3.7) | 0.0–17 | 9.2 (3.5) | 0.0–15 | 0.16 |
| Residence time (years) | 17 (9.8) | 0.25–40 | 19 (9.5) | 0.17–37 | 20 (10) | 0.13–40 | 0.24 |
| Parity (n) | 1.9 (2.7) | 0.0–11 | 2.0 (2.4) | 0.0–12 | 1.9 (2.4) | 0.0–8.0 | 0.84 |
| Nullipara (%) | 38% | | 37% | | 37% | | 0.99 |
| History of Preeclampsy (%) | 5% | | 10% | | 5% | | 0.44 |
| Coca users (%) | 43% | | 40% | | 49% | | 0.64 |
| Urinary lithium (μg/L)[a,d] | 745 | 105–1660 | 1478 | 920–4183 | 2516 | 1078–4598 | <0.001 |
| Urinary arsenic (μg/L)[a,d] | 59 | 13–943 | 149 | 25–556 | 218 | 57–2450 | <0.001 |
| Whole blood cesium (μg/L)[a] | 66 | 2.5–470 | 117 | 6.2–685 | 147 | 11–362 | <0.001 |
| Serum boron (μg/L)[a] | 78 | 0.13–212 | 127 | 59–245 | 198 | 112–605 | <0.001 |
| Birth outcomes | | | | | | | |
| Gestational age at birth (weeks) | 39 (2.7) | 29–42 | 39 (2.1) | 32–42 | 38 (2.5) | 30–42 | 0.48 |
| Preterm (gestational week <37, %) | 22% | | 15% | | 17% | | 0.63 |
| Low birth weight (<2500 g, %) | 5% | | 12% | | 7% | | 0.44 |
| Weight (g) | 3035 (489) | 1250–4500 | 3043 (454) | 1760–4130 | 3002 (461) | 1260–4165 | 0.76 |
| Length (cm) | 48 (2.5) | 40–51 | 48 (2.1) | 42–53 | 47 (2.5) | 39–51 | 0.24 |
| Head circunference (cm) | 34 (1.9) | 26–37 | 34 (1.7) | 30–40 | 34 (1.6) | 29–36 | 0.44 |

Values presented as mean (SD), median or percent (%), and range (minimum–maximum).
Abbreviations: BMI: body mass index.
[a] Based on the mean concentration during pregnancy.
[b] Based on Kruskal–Wallis rank test for continuous variables and Chi square test for categorical variables.
[c] Based on post-pregnancy weight (3–6 months post-partum) in 13.5% of individuals.
[d] Urinary concentrations are adjusted for the mean urinary osmolality from all women (694 mOsm/Kg).

material, Table S2). The Spearman's correlation coefficient ($r_s$) for blood and urinary lithium was 0.84 ($p < 0.001$), that for blood and water lithium 0.40 ($p < 0.001$) and that for urine and water lithium 0.44 ($p < 0.001$). Blood lithium increased during pregnancy, particularly in the last trimester, while urine lithium increased more constantly across gestation (32% over 30 weeks; see Supplemental material, Fig. S3A and B). None of the women reported being diagnosed with mental diseases or under lithium treatment.

### 3.1. Associations between lithium exposure and fetal size

The initial linear mixed-effect regression analyses showed no associations between blood lithium and the different fetal measurements, neither using the basic adjustment (gestational age (in weeks and as quadratic term)), nor with the further adjustment (parity, family monthly income, maternal height, fetal sex, maternal urinary arsenic, blood cesium and serum boron) (see Supplemental material, Table S3). Associations between urinary lithium and all fetal measurements were generally inverse, although not statistically significant. Arsenic in urine was not statistically significant in any of the models.

In the fully adjusted cross-sectional linear regression models (Table 2), both blood and urine lithium concentrations were inversely associated with all fetal measurements in the second trimester (N = 81; p values generally <0.1), but not in the third trimester. In general, the full adjustment of the 2nd trimester models markedly strengthened the associations, compared to the model adjusted for gestational age only (data not shown). The estimates based on blood lithium (per 25 μg/L) corresponded to about one eighth of a standard deviation (SD) for BPD, OFD, HC, AC and femur length.

### 3.2. Associations between lithium exposure and birth measurements

In the linear regression models assessing birth outcomes in relation to maternal lithium exposure (n = 174), adjusted for gestational age in weeks and as quadratic term (Model 1), blood and urine lithium (women's average blood and urine lithium concentrations during pregnancy) were inversely associated (non-significantly) with birth weight and length (Table 3). Further adjusting (Model 2) strengthened the inverse associations, which became statistically significant for blood lithium and birth length. Every 25 μg/L increase in blood lithium concentration was associated with a decrease of 0.53 cm (95%CI −1.0; −0.052) in birth length. Similarly, newborns in the highest tertile of lithium exposure (mean blood lithium 47 μg/L) were 0.81 cm shorter compared with those in the lowest tertile (<18 μg/L, Table 3). In sensitivity analyses, we excluded the individual with the highest blood lithium levels (145 μg/L; leaving the next highest concentration at 109 μg/L) and the two women with preeclampsia, which didn't change the estimate for birth length (β −0.55, 95%CI −1.1; −0.0065, p = 0.047).

## 4. Discussion

This population-based cohort study indicates, for the first time, that exposure to elevated drinking water lithium during pregnancy may adversely affect fetal development. Both blood and urine lithium showed consistent inverse associations with all fetal measurements (head, femur, and abdomen) in the second trimester, indicating effects of lithium in early gestation. Indeed, a younger and less developed fetus may be particularly sensitive to the stress of lithium, as shown for other insults (Barouki et al., 2012). At birth, infant length showed the strongest

**Table 2**
Linear regression models of fetal size measurements during the second (n = 81) and third trimesters (n = 98) of pregnancy in relation to maternal blood and urinary lithium concentrations.

| Fetal measurements | Whole blood lithium[a] | | | | Urinary lithium[a] | | | |
|---|---|---|---|---|---|---|---|---|
| | 2nd trimester | | 3rd trimester | | 2nd trimester | | 3rd trimester | |
| | β (95%CI)[b] | p | β (95%CI)[b] | p | β (95%CI)[b] | p | β (95%CI)[b] | p |
| Biparietal diameter (cm) | Mean ± SD: 5.0 ± 1.2 | | Mean ± SD: 8.1 ± 0.59 | | Mean ± SD: 5.0 ± 1.2 | | Mean ± SD: 8.1 ± 0.59 | |
| All | −0.14 (−0.29; 0.014) | 0.073 | 0.067 (−0.024; 0.16) | 0.15 | −0.091 (−0.19; 0.00051) | 0.063 | 0.00063 (−0.060; .072) | 0.85 |
| Tertile 1 | Ref: 5.0 cm | | Ref: 8.1 cm | | Ref: 5.0 cm | | Ref: 8.1 cm | |
| Tertile 2 | 0.033 (−0.14; 0.21) | 0.71 | −0.043 (−0.27; 0.18) | 0.72 | −0.11 (−0.29; 0.068) | 0.22 | −0.095 (−0.27; 0.082) | 0.29 |
| Tertile 3 | −0.068 (−0.31; 0.17) | 0.57 | −0.054 (−0.28; 0.18) | 0.64 | −0.18 (−0.40; 0.041) | 0.11 | −0.059 (−0.26; 0.14) | 0.56 |
| Occipitofrontal diameter (cm) | Mean ± SD: 6.1 ± 1.4 | | Mean ± SD: 10 ± 0.76 | | Mean ± SD: 6.1 ± 1.4 | | Mean ± SD: 10 ± 0.76 | |
| All | −0.19 (−0.40; 0.018) | 0.073 | 0.012 (−0.15; 0.17) | 0.88 | −0.080 (−0.21; 0.052) | 0.23 | −0.056 (−0.17; 0.059) | 0.33 |
| Tertile 1 | Ref: 6.1 cm | | Ref: 10.0 cm | | Ref: 6.1 cm | | Ref: 10.0 cm | |
| Tertile 2 | 0.026 (−0.21; 0.26) | 0.83 | 0.095 (−0.31; 0.50) | 0.64 | −0.11 (−0.35; 0.13) | 0.36 | −0.091 (−0.40; 0.22) | 0.56 |
| Tertile 3 | −0.18 (−0.50; 0.15) | 0.28 | −0.043 (−0.44; 0.36) | 0.83 | −0.23 (−0.52; 0.064) | 0.12 | −0.14 (−0.49; 0.21) | 0.42 |
| Head circumference (cm) | Mean ± SD: 19 ± 4.3 | | Mean ± SD: 30 ± 2.2 | | Mean ± SD: 19 ± 4.3 | | Mean ± SD: 30 ± 2.2 | |
| All | −0.52 (−1.2; 0.13) | 0.12 | 0.16 (−0.21; 0.53) | 0.40 | −0.32 (−0.72; 0.079) | 0.11 | −0.093 (−0.36; 0.17) | 0.49 |
| Tertile 1 | Ref: 19 cm | | Ref: 30 cm | | Ref: 19 cm | | Ref: 30 cm | |
| Tertile 2 | 0.29 (−0.42; 1.0) | 0.41 | 0.13 (−0.81; 1.1) | 0.79 | −0.43 (−1.2; 0.30) | 0.25 | −0.59 (−1.3; 0.15) | 0.12 |
| Tertile 3 | −0.40 (−1.4; 0.59) | 0.42 | −0.12 (−1.0; 0.80) | 0.79 | −0.83 (−1.7; 0.079) | 0.073 | −0.35 (−1.2; 0.47) | 0.40 |
| Abdominal circumference (cm) | Mean ± SD: 17 ± 3.9 | | Mean ± SD: 29 ± 2.8 | | Mean ± SD: 17 ± 3.9 | | Mean ± SD: 29 ± 2.8 | |
| All | −0.48 (−1.1; 0.089) | 0.097 | 0.35 (−0.18; 0.90) | 0.19 | −0.24 (−0.60; 0.12) | 0.19 | 0.055 (−0.33; 0.44) | 0.78 |
| Tertile 1 | Ref: 17 cm | | Ref: 29 cm | | Ref: 17 cm | | Ref: 29 cm | |
| Tertile 2 | 0.065 (−0.61; 0.74) | 0.85 | 0.57 (−0.78; 1.9) | 0.40 | −0.52 (−1.2; 0.16) | 0.13 | −0.93 (−2.0; 0.10) | 0.077 |
| Tertile 3 | −0.32 (−1.2; 0.55) | 0.47 | 0.33 (−1.0; 1.7) | 0.63 | −0.65 (−1.5; 0.17) | 0.12 | −0.55 (−1.7; 0.61) | 0.35 |
| Femur length (cm) | Mean ± SD: 3.5 ± 0.96 | | Mean ± SD: 6.3 ± 0.61 | | Mean ± SD: 3.5 ± 0.96 | | Mean ± SD: 6.3 ± 0.61 | |
| All | −0.11 (−0.25; 0.024) | 0.10 | 0.056 (−0.053; 0.17) | 0.31 | −0.074 (−0.16; 0.013) | 0.093 | −0.022 (−0.057; 0.10) | 0.58 |
| Tertile 1 | Ref: 3.5 cm | | Ref: 6.3 cm | | Ref: 3.5 cm | | Ref: 6.3 cm | |
| Tertile 2 | −0.061 (−0.22; 0.096) | 0.44 | −0.018 (−0.30; 0.26) | 0.90 | −0.12 (−0.28; 0.039) | 0.14 | −0.052 (−0.27; 0.16) | 0.63 |
| Tertile 3 | −0.13 (−0.35; 0.079) | 0.22 | −0.035 (−0.31; 0.24) | 0.80 | −0.23 (−0.43; −0.042) | 0.018 | −0.0071 (−0.25; 0.23) | 0.95 |
| Fetal weight (g) | Mean ± SD: 497 ± 281 | | Mean + SD: 2107 ± 555 | | Mean ± SD: 497 ± 281 | | Mean + SD: 2107 ± 555 | |
| All | −41 (−83; 1.5) | 0.058 | 74 (−18; 167) | 0.11 | −24 (−54; 5.0) | 0.10 | −9.2 (−58; 77) | 0.79 |
| Tertile 1 | Ref: 497 g | | Ref: 2107 g | | Ref: 497 g | | Ref: 2107 g | |
| Tertile 2 | 5.6 (−45; 56) | 0.83 | 48 (−191; 287) | 0.69 | −32 (−89; 25) | 0.26 | −169 (−348; 9.8) | 0.064 |
| Tertile 3 | −14 (−79; 51) | 0.67 | −1.7 (−238; 234) | 0.99 | −42 (−110; 27) | 0.23 | −101 (−301; 100) | 0.32 |

[a] Coefficients are expressed as change per 25 μg/L for whole blood lithium and as change per 1000 μg/L for urinary lithium.
[b] Adjusted for: Gestational age (weeks) and gestational age (weeks) quadratic term, parity (number of pregnancies), family monthly income (≤500, >500 & <3000, >3000 (tertiles) Argentinean pesos), maternal height (cm), infant sex (boys, girls), urinary arsenic (sum of arsenic metabolites in urine, μg/L), whole blood cesium (μg/L) and serum boron (<80, ≥80 μg/L).

inverse association with lithium. An increase in blood lithium concentrations of 100 μg/L (total range 1.9–145 μg/L), corresponding to about 140 μg/L in plasma, was associated with 2 cm shorter newborns (almost one SD), similar to the findings for fetal femur length in the 2nd trimester. To note, serum concentrations during lithium therapy are usually much higher, i.e. 3.5–10 mg/L (Grandjean and Aubry, 2009b). Our statistical models were robust and the associations became generally stronger after adjustments for potential confounders such as parity, family income, maternal height or fetal sex, as well as other concurrent exposures to arsenic, cesium or boron.

Unexpectedly, the associations with fetal size observed in the 2nd trimester disappeared in the longitudinal analyses, which should have

**Table 3**
Linear regression models of maternal exposure to lithium (whole blood and urinary lithium) in relation to size at birth (n = 174).

| Birth measurements | Whole blood lithium | | | | Urinary lithium | | | |
|---|---|---|---|---|---|---|---|---|
| | Model 1[b] | | Model 2[c] | | Model 1[b] | | Model 2[c] | |
| | β (95%CI) | p | β (95%CI) | p | β (95%CI) | p | β (95%CI) | p |
| Weight (g) | | | | | | | | |
| All[a] | −32 (−110; 48) | 0.43 | −35 (−126; 55) | 0.44 | −3.6 (−65; 58) | 0.91 | −16 (−89; 58) | 0.68 |
| Tertile 1 | Ref: 3025 g | | Ref: 3025 g | | Ref: 3008 g | | Ref: 3008 g | |
| Tertile 2 | −56 (−198; 87) | 0.44 | −72 (−233; 89) | 0.38 | −22 (−165; 122) | 0.77 | −35 (−199; 130) | 0.68 |
| Tertile 3 | −59 (−203; 85) | 0.42 | −54 (−225; 117) | 0.53 | −22 (−167; 122) | 0.76 | −56 (−228; 116) | 0.52 |
| Length (cm) | | | | | | | | |
| All[a] | −0.28 (−0.70; 0.13) | 0.18 | −0.53 (−1.0; −0.052) | 0.030 | −0.00066 (−0.32; 0.33) | 0.99 | −0.12 (−0.52; 0.28) | 0.55 |
| Tertile 1 | Ref: 47.6 cm | | Ref: 47.6 cm | | Ref: 47.4 cm | | Ref: 47.4 cm | |
| Tertile 2 | 0.080 (−0.68; 0.84) | 0.84 | −0.40 (−1.3; 0.47) | 0.37 | 0.42 (−0.34; 1.2) | 0.28 | 0.16 (−0.89; 0.89) | 1.00 |
| Tertile 3 | −0.39 (−1.1; 0.38) | 0.32 | −0.81 (−1.7; 0.12) | 0.086 | 0.26 (−0.52; 1.0) | 0.51 | −0.58 (−0.94; 0.93) | 0.99 |
| Head circumference (cm) | | | | | | | | |
| All[a] | 0.075 (−0.25; 0.4) | 0.65 | 0.046 (−0.35; 0.44) | 0.82 | −0.059 (−0.32; 0.20) | 0.66 | −0.14 (−0.48; 0.19) | 0.40 |
| Tertile 1 | Ref: 33.5 cm | | Ref: 33.5 cm | | Ref: 33.8 cm | | Ref: 33.8 cm | |
| Tertile 2 | 0.36 (−0.25; 0.96) | 0.24 | 0.33 (−0.38; 1.0) | 0.36 | 0.17 (−0.44; 0.77) | 0.58 | −0.010 (−0.74; 0.72) | 0.98 |
| Tertile 3 | 0.16 (−0.44; 0.77) | 0.60 | 0.17 (−0.57; 0.92) | 0.65 | −0.21 (−0.82; 0.40) | 0.50 | −0.45 (−1.2; 0.32) | 0.25 |

[a] Coefficients are expressed as change per 25 μg/L for whole blood lithium and as change per 1000 μg/L for urinary lithium.
[b] Adjusted for: Gestational age (weeks) and gestational age (weeks) quadratic term.
[c] Adjusted also for: parity (number of pregnancies), family monthly income (≤500, >500 & <3000, >3000 (tertiles) Argentinean pesos), maternal height (cm), infant sex (boys, girls), urinary arsenic (sum of arsenic metabolites in urine, μg/L) and whole blood cesium (μg/L), serum boron (<80, ≥80 μg/L).

provided more power with about twice as many women. Possibly, the well-documented uncertainties in fetal ultrasound measurements in late pregnancy at which time also the inter-individual variations in fetal growth increases (Geirsson, 1991), noted also in the present study (see Supplemental material, Fig. S2), overshadowed the associations. Also, the exposure measures might have been less representative in late gestation. Lithium concentrations in urine increased with increasing gestational age due to the physiologically change in glomerular filtration rate and thereby higher lithium clearance (30–50%) in late pregnancy (Grandjean and Aubry, 2009a). Hence, osmolality also decreased with advancing gestation (i.e. about 5.5 mOsm/Kg per gestational week; mean osmolality in 1st trimester: 748 mOsm/Kg) and the adjustment to the average osmolality in all urine samples may have contributed to higher adjusted urine lithium concentrations in late gestation. Less obvious to explain is the increase in blood lithium concentrations in late gestation. We speculate that it is related to the previously demonstrated increase in the sodium–lithium counter-transport activity in erythrocytes near term (Worley et al., 1982), possibly also an increase in lithium transport in the small intestine (Diamond et al., 1983).

Our results find some support in the literature, although the epidemiological data on associations between maternal lithium medication and pregnancy outcome are inconsistent. Two studies showed that lithium therapy during pregnancy was associated with a lower birth weight (Diav-Citrin et al., 2014; Kallen and Tandberg, 1983), while one found an association with newborns large for gestational age (Jacobson et al., 1992). None of these studies used fetal measurements by ultrasound or lithium concentrations as exposure biomarker, and they focused on birth weight only, not length or head circumference. An experimental study on mice found no difference in pup birth weight of dams given lithium in drinking water (347 mg/L) during pregnancy, compared to unexposed controls (Mroczka et al., 1983). However, the lithium-exposed group showed statistically significant impaired postnatal growth and development. Another experimental study found a decrease in organ weight in mouse pups of dams exposed to about 7 mg/L drinking water lithium ad libitum (Messiha, 1993). Both experimental studies reported that the developmental toxicity of lithium occurred particularly in the female pups. We were not able to evaluate sex-differences in the effects of lithium due to lack of power in the analyses.

The main findings of this study have also some support in the indicated mechanisms of lithium toxicity. Lithium, from both therapy and drinking water, crosses freely the placenta (Harari et al., 2012; Newport et al., 2005) and is known to impair the thyroid hormones (Broberg et al., 2011; Grandjean and Aubry, 2009c). Like most of the hormones, the thyroid hormones play a critical role in fetal growth and development (Forhead and Fowden, 2014). Other potential mechanisms of lithium toxicity include direct or indirect impairment of parathyroid hormone and vitamin D (McKnight et al., 2012; Rosenblatt et al., 1989), as well as increased cortisol levels (Bschor et al., 2002; Sugawara et al., 1988). Further studies are warranted to understand the mechanisms involved in the lithium-related impairment of fetal development.

The potential long-term consequences of the observed associations with fetal size remain to be elucidated. Low birth size has been shown to be associated with impaired cognitive function (Broekman et al., 2009; Kormos et al., 2014). Particularly, stunting during the first stages of life has been associated with e.g., insulin resistance and impaired cognitive functions later in life, as well as with low birth weight in the subsequent generation (Bennett et al., 2002; Dewey and Begum, 2011; Grantham-McGregor et al., 2007).

The strengths of our study include the population-based design with high participation rate and large variation in lithium exposure. Also, the studied women were nonsmokers with no alcohol consumption, which reduced potential confounding. We put much effort in following all women, even in the most distant villages, and we established collaboration with the main hospital in Salta to collect samples and measurements for the babies born there. We were able to adjust for potential confounders, such as exposure to boron, cesium and arsenic. However, maternal mental health, known to influence fetal growth (Grigoriadis et al., 2013; Huybrechts et al., 2014), was not measured. Information regarding medication (including lithium and other psychotropic drugs) as well as any previous or current diseases was obtained through the interviews. Although no one reported either medication or diagnoses we cannot rule out the possibility of underreporting or recall bias.

The main limitation of the study is the lack of ultrasound measurements for all women. Missed measurements were mainly due to limited accessibility to the villages during the rain period (January–March), which made it impossible for us to reach some of the areas, especially Tolar Grande with known low lithium exposure (Concha et al., 2010). We didn't have the means to recruit a larger cohort in this first inventory study on environmental lithium exposure and early life effects, but further and larger cohort studies are indeed warranted. To note, we were not able to use serum lithium measurements as we found that the serum tubes for analysis of trace elements, including lithium (Vacuette®, Z Trace Elements Serum Clot Activator; Greiner bio-one, Kremsmünster, Austria), contained appreciable amounts of lithium (37 μg/L), invalidating our measurements (Lu et al., 2014). In a subsample we additionally measured concentrations in the plasma and found a correlation ($r_s$) of 0.99 with whole blood concentrations ($N = 20$; ratio plasma/whole blood = 1.37). Thus, we considered blood lithium to reflect the exposure equally well as plasma lithium. Importantly, the low atmospheric oxygen concentration at high altitudes causes particular stress on pregnancy and decreases the fertility rate. However, these effects are less common among indigenous people than those with Caucasian influence (Kametas et al., 2004; Soria et al., 2013; Vitzthum, 2013), and women in our study were mostly indigenous.

## 5. Conclusions

In conclusion, this study provides some indication that elevated environmental lithium exposure during pregnancy might be inversely associated with fetal size. Further studies are, however, necessary to confirm these findings and to understand the mechanisms involved. Such studies should also be performed on pregnant women in lithium therapy. The findings, if confirmed, have obvious public health relevance, but in any case there is a need for more measures of lithium in drinking water. It should be noted that the brands of bottled water with elevated lithium concentrations, similar to the highest in the present study, increase steadily.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2015.01.011.

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