Infant mortality and morbidity associated with preterm and small-for-gestational-age births in Southern Mozambique: A retrospective cohort study

Alberto L. García-Basteiro1,2,3*, Llorenç Quintó2, Eusebio Macete1, Azucena Bardají1,2, Raquel González1,2, Arsenio Nhacolo1, Betuel Sigauque1, Charfudin Sacoor1, Maria Rupérez1,2,4, Elisa Sicuri1,2,5, Quique Bassat1,2, Esperança Sevene1, Clara Menéndez1,2,4

1 Centro de Investigación em Saude de Manhiça, Manhiça, Maputo Province, Mozambique, 2 ISGlobal, Barcelona Ctr. Int. Health Res. Hospital Clínic—Universitat de Barcelona, Barcelona, Spain, 3 Amsterdam Institute for Global Health and Development, Academic Medical Centre, Amsterdam, The Netherlands, 4 Consorcio de Investigación Biomédica en Red de Epidemiología y Salud Pública, Barcelona, Spain, 5 School of Public Health, Imperial College London, London, United Kingdom

* alberto.garcia-basteiro@manhiça.net

Abstract

Background

Preterm and small for gestational age (SGA) births have been associated with adverse outcomes during the first stages of life. We evaluated the morbidity and mortality associated with preterm and SGA births during the first year of life in a rural area of Southern Mozambique.

Methods

This is a retrospective cohort study using previously collected data from children born at the Manhiça District Hospital in two different periods (2003–2005 and 2010–2012). Newborns were classified as being preterm and/or SGA or as babies not fulfilling any of the previous conditions (term non-SGA). All children were followed up for a year for morbidity and mortality outcomes.

Results

A total of 5574 live babies were included in the analysis. The prevalence of preterm delivery was 6.2% (345/5574); the prevalence of SGA was 14.0% (776/5542) and 2.2% (114/5542) of the children presented both conditions. During the neonatal period, preterm delivery and SGA were associated with 13 (HR: 13.0, 95% CI 4.0–42.2) and 5 times (HR: 4.5, 95% CI: 1.6–12.6) higher mortality compared to term non SGA babies. Risk of hospitalization was only increased when both conditions were present (IRR: 3.5, 95%CI: 1.5–8.1). Mortality is also increased during the entire first year, although at a lower rate.
Conclusions

Neonatal and infant mortality rates are remarkably high among preterm and SGA babies in southern Mozambique. These increased rates are concentrated within the neonatal period. Prompt identification of these conditions is needed to implement interventions aimed at increasing survival of these high-risk newborns.

Introduction

Preterm birth is the world’s leading cause of death in children under five years[1]. It has been estimated that each year, 11% of all deliveries in the world are premature, and one million out of six million child deaths are due to complications of prematurity[2,3]. Small for gestational age (SGA) births, are also a prevalent condition among newborns from low and middle income countries (up to 27% of all deliveries are SGA), with higher prevalence in South East Asia and Sahelian countries[4]. Preterm and SGA births are associated with adverse health consequences, including increased neonatal and infant mortality, childhood malnutrition, visual and hearing problems, and adulthood metabolic disease[5,6].

Both preterm birth and SGA are intrinsically associated with low birth weight and are not mutually exclusive. On the one hand, preterm birth is associated with multiple maternal and/or foetal conditions, including maternal and neonatal infections, vascular disease, uterine overdistension, pre-eclampsia/eclampsia or intrauterine growth restriction (IUGR)[7]. On the other hand, SGA is frequently associated with disorders such as foetal genetic/chromosomal defects or also to IUGR[8]. The latter is associated with factors that prevent normal circulation across the placenta causing poor nutrient and oxygen supply to the foetus, including maternal undernutrition, anemia, malaria, HIV and other acute or chronic infections[9]. Alternatively, SGA can result from an incorrect assessment of gestational age or a constitutionally–albeit not necessarily pathological- small size. However, since preterm and SGA babies are at risk of presenting different health problems they are associated with different morbidity and mortality risks[10]. Compared to SGA, preterm babies have been associated with higher risk of death during infancy, but lower risk of morbidity and better growth patterns during the first two years of life[10].

Despite the relative high prevalence and adverse outcomes associated with preterm births and SGA in low-income settings, very few studies have assessed their impact on neonatal and infant mortality and morbidity in sub Saharan Africa. Only one longitudinal study conducted in Malawi showed that preterm birth was associated with a greater risk of death as well as growth and development disabilities[11]. Understanding the true impact of these two common conditions is essential to improve pregnancy management and prevent their consequences in low income settings. Importantly, those regions with high rates of preterm births and low birth weight, mainly South East Asia and Africa, are also those with most fragile and underfinanced health programs, increasing the difficulties to tackle this health problem[12]. The main objective of this study was to evaluate the morbidity and mortality associated with preterm and SGA births during infancy in a rural area of Southern Mozambique.

Methods

Study setting

The study was conducted at the Centro de Investigação em Saúde da Manhiça (CISM) in the District of Manhiça, a malaria endemic semi-rural area in Southern Mozambique. The CISM
is adjacent to the Manhiça District Hospital (MDH) and runs a demographic surveillance system (DSS) covering 90,000 inhabitants in 2010 in what constitutes the study area. A passive case detection system is also running at the HDM that covers all paediatric outpatient visits and admissions. More than 80% of the deliveries in the district are institutional[13]. The prevalence of HIV infection detected through the antenatal clinic (ANC) has steadily increased in recent years, ranging from 23.6% in 2003–2004[13] to 29.4% in 2010[14]. Infant and neonatal mortality rates varied from 83.9 and 26 in 2004 to 63.0 and 24.0 per 1000 live births in 2010 (Nhacolo A., Charfudin et al personal communication)[15]. Other health and demographic characteristics of the population of the district have been described elsewhere[16].

**Study design**

This is a retrospective cohort study of collected data from children born at the MDH in two different time periods; period 1: from August 2003 to April 2005 and period 2: from March 2010 to March 2012. During these periods, gestational age was routinely captured for all births taking place at the MDH, due to the coexistence of research studies which required the assessment of gestational age. Infants were classified as being preterm and/or SGA, or as babies not fulfilling any of the previous conditions (term, non-SGA). All babies were followed up for a year for morbidity and mortality outcomes using the hospital passive case detection system and the DSS. Inclusion criteria for this analysis included living in the study area, being a live birth, being institutionally delivered, and having the gestational age and weight assessed at birth.

Gestational age was evaluated using two different methods based on postnatal examination of the newborn, namely, the Dubowitz test[17] (period 1) and the Ballard score[18] (period 2). Both methods are based on clinical assessment that includes neurological criteria on the infant’s maturity and other external physical criteria. Both methods are widely used in low-income countries, where ultrasound examination is not readily available. Dubowitz and Ballard’s tests were used in Manhiça due to the requirements of two different clinical trials evaluating antimalarials for prevention of malaria in pregnancy, which took place in those previously mentioned time periods[13,19,20]. Relevant socio-economic and demographic characteristics of the households of children included in the study are also recorded through the DSS.

**Case definitions and statistical methods**

Neonatal mortality was defined as the death of a live born baby within the first 28 complete days after birth, and infant mortality as deaths occurring during the first 12 months of life. The post-neonatal period was defined as that comprised after day 28 and the last day of the first year of life (included). Preterm birth was defined as that occurring before the completion of 37 weeks of pregnancy. Low birth weight was defined as less than 2500 grams at birth[21]. Small-for-gestational-age (SGA) was defined as birth weight below the 10th percentile for babies of the same gestational age[5]. Since no reference birthweight charts per percentile are available for the Mozambican population, we used as reference birthweights from a recent large study in HIV negative babies from Botswana[22].

Only live born babies (single and multiple deliveries) were included in this analysis. Incidence of outpatient visits or hospitalizations and mortality rates were calculated using time at risk from date of birth until date at one year of age, death or withdrawal. Mortality rates are expressed per 1000 children years at risk (CYAR). Association between risk factors and occurrence of any of the conditions at delivery was evaluated using univariate and multivariable logistic regression models. Hazard Ratio (HR) of mortality among different cohorts was evaluated using Cox Regression Models adjusted for child sex, HIV status of the mother, number of
previous pregnancies, maternal age, period and socio economic status (SES). Incidence rate ratio (IRR) of outpatient clinic visits or hospitalizations was assessed using negative binomial regression due to the possibility of several episodes during the study period. Variables for the multivariate analysis in the logistic, Cox, and negative binomial regression models were selected using the forward-stepwise approach with a p-value lower than 0.1 (obtained through likelihood ratio test). Multivariable models were estimated by a complete case analysis with missing values removed. P values lower than 0.05 were considered statistically significant.

SES was calculated using Principal Component Analysis (PCA) following the methodology described elsewhere[23]. The families of the children were grouped into quintiles based on the SES rank.

All data were captured in handwritten CRFs and then double entered by data clerks into the OpenClinica software. Data analysis was performed using Stata 13 (Stata Corporation, College Station, TX, USA). Microsoft Excel (Microsoft Office Package 13) was used for building graphs and tables.

**Ethical considerations**

This study is a retrospective analysis of previously collected information. Many participants were part of two research studies, whose protocols and informed consents were reviewed and approved by the National Ethics Board in Mozambique and the Ethics Committee from the Hospital Clinic of Barcelona (Spain)[13,19,20]. This specific study was approved by the Ethics Committee Hospital Clinic of Barcelona (Spain). Mothers/caregivers of children participating in the research studies signed a written informed consent form prior to enrolment. The study was conducted following the principles of the Declaration of Helsinki. The funding sources had no role in any step of the study, including the decision to submit the paper for publication.

**Results**

**Prevalence of low birth weight, preterm delivery and SGA**

A total of 5574 live babies with available data on gestational age were included in the analysis (3189 in period 1 and 2385 in period 2). Around 51.4% (2853/5554) of the babies were male and 29.0% (656/2265) were born to HIV infected mothers. Among all children included 26.6% (1397/5256) were born to primigravidae, and 23.2% (1219/5256 to women with more than 4 previous pregnancies.

The prevalence of low birth weight (<2500 g) in our sample was 10.3% (572/5570), that of very low birth weight (<1500 g) was 0.5% (29/5570), and the proportion of preterm delivery was 6.2% (345/5574). The prevalence of SGA was 14.0% (776/5542); among the SGA, 11.9% (662/5542) were at term SGA, while 2.1% (114/5542) of them fulfilled both definitions of preterm and SGA simultaneously. Nearly 4% [3.7% (205/5542)] of the infants were preterm but not SGA. Baseline characteristics of the study participants are depicted in Table 1.

Being multigravidae and older age were each associated with lower likelihood of SGA. If the mother had more than four previous pregnancies the odds of being SGA was 52% lower compared to the odds of primigravidae women (OR: 0.48, 95% CI: 0.25–0.90). Female sex and maternal HIV infection were also associated with being SGA (OR: 1.42 95% CI: 1.05–1.91 and OR: 1.78, 95% CI: 1.27–2.50, respectively). Likewise, the same variables were associated with preterm delivery, although without statistical significance in the multivariable model. Tables 2 and 3 show the results of the univariate and multivariable logistic regression analysis after adjusting for potential confounders.
Table 1. Baseline characteristics of participants included in the analysis. Columns are not mutually exclusive.

|                          | Total live births* | Preterm n (%) | Total live births* | SGA n (%) | Total live births | Non preterm–non SGA n(%) | Total live births | Preterm & SGA n(%) |
|--------------------------|--------------------|---------------|--------------------|-----------|-------------------|--------------------------|------------------|-------------------|
| **Total**                | 5574              | 345 (6.2)     | 5542              | 776       | (14.0)            | 5542                     | 4561 (82.3)     | 5542              | 114 (2.2%)        |
| **Previous pregnancies** |                    |               |                    |           |                   |                          |                  |                   |                   |
| Primigravidae            | 1397              | 107 (7.7)     | 1390              | 295       | (21.2)            | 1390                     | 1035 (74.5)     | 1390              | 41 (3.0)          |
| 1–4 previous pregnancies | 2640              | 147 (5.6)     | 2603              | 309       | (11.8)            | 2623                     | 2221 (84.7)     | 2623              | 41 (1.6)          |
| >4                       | 1219              | 59 (4.9)      | 1213              | 132       | (10.0)            | 1213                     | 1051 (86.4)     | 1213              | 23 (1.9)          |
| **Mother’s age**         |                    |               |                    |           |                   |                          |                  |                   |                   |
| <20                      | 1385              | 116 (8.4)     | 1373              | 300       | (21.8)            | 1373                     | 1007 (73.3)     | 1026              | 40 (2.9)          |
| 20–34                    | 3290              | 166 (5.1)     | 3277              | 369       | (11.3)            | 3277                     | 2804 (85.6)     | 2466              | 52 (1.6)          |
| >35                      | 587               | 28 (4.8)      | 582               | 68        | (11.7)            | 582                      | 503 (86.4)      | 483               | 12 (2.1)          |
| **Gestational age**      |                    |               |                    |           |                   |                          |                  |                   |                   |
| <37                      | 345               | NA            | 319               | 114       | (35.8)            | 319                      | NA              | 319               | 114(35.8)         |
| 37–42                    | 5222              | NA            | 5216              | 661       | (12.7)            | 5216                     | 4555 (87.3)     | 5216              | NA                |
| >42                      | 7                 | NA            | 7                 | 1         | (14.3)            | 7                        | 6 (82.3)        | 7                 | NA                |
| **Birthweight (mean)**   |                    |               |                    |           |                   |                          |                  |                   |                   |
| <1500                    | 29                | 20 (69.9)     | 24                | 24        | (100.0)           | 24                       | 0 (0.0)         | 24                | 15 (62.5)         |
| 1500–2500                | 572               | 201 (35.2)    | 565               | 461       | (81.6)            | 565                      | 9 (1.6)         | 565               | 99 (17.6)         |
| >2500                    | 4969              | 123 (2.48)    | 4951              | 291       | (5.9)             | 4951                     | 4550 (91.9)     | 4951              | 0 (0.0)           |
| **Newborn Sex**          |                    |               |                    |           |                   |                          |                  |                   |                   |
| Male                     | 2853              | 158 (5.54)    | 2833              | 342       | (12.1)            | 2833                     | 2408 (85.0)     | 2833              | 58 (2.1)          |
| Female                   | 2701              | 184 (6.81)    | 2689              | 431       | (16.0)            | 2689                     | 2137 (79.5)     | 2689              | 54 (2.1)          |
| **Period**               |                    |               |                    |           |                   |                          |                  |                   |                   |
| > 2003–2006              | 3189              | 187 (5.9)     | 3167              | 497       | (15.7)            | 3167                     | 2563(80.9)      | 3167              | 60 (1.9)          |
| < 2009–2012              | 2385              | 158 (6.6)     | 2375              | 279       | (11.8)            | 2375                     | 377(84.1)       | 2375              | 54 (2.3)          |
| **Study participant**    |                    |               |                    |           |                   |                          |                  |                   |                   |
| No                       | 3156              | 205 (6.5)     | 3135              | 437       | (13.9)            | 3135                     | 2571 (82.0)     | 3135              | 60 (1.9)          |
| Yes                      | 2418              | 140 (5.8)     | 2407              | 339       | (14.1)            | 2407                     | 1990 (82.7)     | 2407              | 54 (2.2)          |
| **Mother’s HIV status**  |                    |               |                    |           |                   |                          |                  |                   |                   |
| Uninfected               | 1609              | 97 (6.0)      | 1605              | 218       | (13.6)            | 1605                     | 1337 (83.3)     | 1605              | 43(2.7)           |
| Infected                 | 656               | 38 (5.8)      | 651               | 94        | (14.4)            | 651                      | 532 (81.7)      | 651               | 11 (1.7)          |
| **SES**                  |                    |               |                    |           |                   |                          |                  |                   |                   |
| Poorest                  | 508               | 26 (5.1)      | 508               | 67        | (13.2)            | 508                      | 426 (83.9)      | 508               | 11 (2.2)          |
| 2nd quintile             | 495               | 30 (6.1)      | 492               | 60        | (12.2)            | 492                      | 413 (83.9)      | 492               | 8 (1.6)           |
| 3rd quintile             | 514               | 31 (6.1)      | 511               | 72        | (14.1)            | 511                      | 419 (82.0)      | 511               | 9 (1.8)           |

(Continued)
Mortality associated with preterm delivery and SGA during infancy

The overall neonatal mortality rate associated with preterm delivery (not SGA) was 599.3 (95% CI 224.9–1596.7) per 1000 CYAR and the infant mortality rate was 79.2 per 1000 CYAR (95% CI 35.6–176.3). Among preterm newborns regardless of the SGA status, the rates were 980.2 (95% CI 542.8–1769.9) and 136.1 (95% CI 84.6–218.9), respectively. The overall neonatal mortality rate among term SGA newborns was 289.0 (95% CI 137.8–606.1) and the infant mortality rate was 55.1 (95% CI 33.2–91.4). Among SGA newborns regardless of preterm delivery, the mortality rates were 427.5 (95% CI 242.8–752.7) and 76.6 per 1000 CYAR (95% CI 51.3–114.2) for the neonatal and first year of life period. The presence of both conditions (SGA and preterm birth) boosted both neonatal and infant mortality rates to 1299.8 (95% 541.0–3122.9) and 218.3 (95% CI: 113.6–419.5) per 1000 CYAR, respectively (Table 4). No relevant differences on mortality rates were observed by sex of the infant.

Cox regression analysis adjusted for relevant variables is presented in Table 4. Both preterm birth and SGA conditions were independently associated with a higher hazard of dying during the neonatal period and infancy. During the first 28 days, preterm-non SGA delivery was associated with 13 times higher mortality rate (per unit time) compared to term deliveries not SGA (HR: 13.0, 95% CI 4.0–42.2), and term SGA was associated with about 5 times higher mortality rate (per unit time) when compared to the at term-non SGA group (hazard ratio 4.5 (95% CI: 1.6–12.6). The hazard of dying in the neonatal period for both preterm and SGA was higher when coexisting with each other. Mortality rates were still increased in the postneonatal period although of less magnitude, leading to lower hazard ratios associated to preterm and SGA compared to term-non-SGA babies. The hazard of dying the first year of life for both preterm and SGA was higher when coexisting with each other.

Morbidity associated with preterm delivery and SGA during infancy

The incidence rate (IR) of outpatient clinic attendance was similar for the cohort of preterm-non SGA babies compared to that of babies born at term non-SGA, both in the neonatal and in the post-neonatal period (IRR 1.4, 95% CI: 0.9–2.4 and IRR: 1.0, 95% CI: 0.8–1.3 respectively). Likewise, there were no differences on outpatient attendances among term SGA newborns compared to those born at term non-SGA (Table 5). Most outpatient diagnoses in SGA and preterm infants were related to respiratory infections (29.2% and 20.1% respectively) followed by skin and conjunctivitis related visits (23.6% and 16.7%, respectively). However, no differences in the proportion of these diagnoses were observed in comparison to the at term non-SGA group.

With regard to neonatal hospitalizations, these were more frequent only in babies with both conditions (IRR 3.5; 95% CI 1.5–8.1) compared to the term non-SGA group. The rate of hospitalizations was also increased during the entire first year of life in preterm (IRR: 1.7: 95% CI: 1.0–2.9) and preterm and SGA babies (IRR: 2.5; 95% CI: 1.4–4.5) (Table 6).
Discussion

This is one of the few studies carried out in sub-Saharan Africa evaluating the impact of both prematurity and small for gestational age births on mortality and morbidity during the first year of life. Information available on the health impact of these two conditions mostly focus on the neonatal period and derives from high or middle income countries. These findings show that neonatal and infant mortality rates are remarkably higher during the neonatal and post-neonatal periods in both preterm and SGA babies compared to babies born at term and non SGA. However, preterm birth is associated with even higher neonatal and infant mortality, almost two fold, compared to SGA without prematurity. This information is fundamental to guide preventive and management measures.

The analysis has been done using different statistical models in order to allow for different but important interpretation of the results, namely, the evaluation of preterm and SGA births.

Table 2. Univariate and multivariable analysis of factors associated with preterm birth.

| Factor                      | Total | Preterm | Univariate Analysis | Multivariate analysis |
|-----------------------------|-------|---------|---------------------|-----------------------|
|                             | n (% )| uOR (95% CI) | p value* | aOR (95% CI) | p value^ |
| Newborn Sex                 |       |         |                     |                       |
| Male                        | 2491  | 83 (3.3) | 1.00                | <0.001                | 1.70 (0.98–2.95) | 0.055   |
| Female                      | 2258  | 121 (5.4) | 1.64 (1.23–2.18)   |                       | 1.00 (0.98–2.95) |
| Previous pregnancies        |       |         |                     |                       |
| Primigravidae               | 1095  | 60 (5.5) | 1.00                | 0.006                 | 1.00 (0.98–2.95) | 0.66    |
| 1–4 previous pregnancies    | 2314  | 93 (4.0) | 0.72 (0.52–1.01)   | 0.76 (0.34–1.71)      |                       |
| >4                          | 1081  | 30 (2.8) | 0.49 (0.32–0.77)   | 0.60 (0.19–1.88)      |                       |
| Mother’s age                |       |         |                     |                       |
| <20                         | 1073  | 66 (6.2) | 1.00                | <0.001                | 1.00 (0.98–2.95) | 0.154   |
| 20–34                       | 2908  | 104 (3.6) | 0.57 (0.41–0.78)   | 0.46 (0.21–1.04)      |                       |
| >35                         | 514   | 11 (2.2) | 0.33 (0.17–0.64)   | 0.31 (0.05–1.77)      |                       |
| Period                      |       |         |                     |                       |
| > 2003–2006                 | 2670  | 107 (4.0) | 1.00                | 0.260                 | 1.00 (0.98–2.95) | 0.40    |
| < 2009–2012                 | 2096  | 98 (4.7) | 1.17 (0.89–1.55)   | 1.29 (0.71–2.35)      |                       |
| Study participant           |       |         |                     |                       |
| No                          | 2698  | 127 (4.7) | 1.00                | 0.112                 | #                    |
| Yes                         | 2068  | 78 (3.8) | 0.79 (0.59–1.06)   |                       |                       |
| Mother’s HIV status         |       |         |                     |                       |
| Uninfected                  | 1387  | 50 (3.6) | 1.00                | 0.367                 | 1.00 (0.98–2.95) | 0.073   |
| Infected                    | 557   | 25 (4.5) | 1.25 (0.76–2.05)   | 1.75 (0.95–3.21)      |                       |
| SES                         |       |         |                     |                       |
| Poorest                     | 394   | 13 (3.3) | 1.00                | 0.282                 | 1.00 (0.98–2.95) | 0.20    |
| 2nd quintile                | 454   | 21 (4.6) | 1.42 (0.70–2.88)   | 1.50 (0.64–3.49)      |                       |
| 3rd quintile                | 457   | 17 (3.7) | 0.13 (0.54–2.36)   | 1.04 (0.42–2.58)      |                       |
| 4th quintile                | 454   | 19 (4.2) | 1.28 (0.62–2.63)   | 1.60 (0.68–3.74)      |                       |
| Weathiest                   | 428   | 9 (2.1) | 0.62 (0.26–1.48)   | 0.55 (1.18–1.69)      |                       |

*p value calculated through Wald Tests.
^p value calculated through LR test.
# variable excluded in the model due to high collinearity with mother’s HIV status.
uOR = unadjusted odds ratio.
aOR = adjusted odds ratio.
doi:10.1371/journal.pone.0172533.t002
as independent conditions (model 1, main model), but also the evaluation of these conditions without considering the presence of the other (model 2 and 3). Prematurity was associated with almost a 13 and 4 fold-increased risk of dying during the neonatal and the postneonatal period, respectively. Small for gestational age on the other hand, was associated with a lower risk of death compared to preterm births in all models, in line with findings from other studies [10,24]. Since SGA definition is based on a statistical approach, babies with SGA might or might not be associated with a specific morbid condition during pregnancy, and they could be considered healthy children having no adverse consequences or complications during infancy [25].

Our results on mortality rates associated with preterm and SGA in the neonatal period are in line with those published in a recent pooled country analysis for low and middle income countries[26]. It has been reported that the mortality rate among preterm births is almost two...
fold increased during the second year of life [11]. These results confirm that the increased risk is mostly concentrated during the neonatal period as it has been described long time ago by Barros and colleagues [10]. In the analysis (model 1) for the post-neonatal period (data not shown) an increased mortality rate associated with preterm delivery or SGA is not observed. However, when analysing these conditions without taking into account the presence of the other (models 2 and 3), an increased mortality during the postneonatal period is observed (around three fold for preterm and 1.8 fold for SGA babies). This apparent discrepancy could be explained by the presence of confounding, that is, in the preterm group there are many SGA babies, distorting the independent association of prematurity with mortality. Likewise, the same confounded association would occur when estimating mortality among SGA babies.

Interestingly, the results on morbidity seem to be contradictory with the mortality findings. It seems that neither prematurity nor SGA births are associated independently with higher rates of hospitalization during the neonatal period compared to those term non-SGA. Model 1, only shows an increased risk of hospitalization when both are present (IRR 3.5, 95% CI: 1.5–8.1), but not when they are analysed separately. Moreover, we did not observe an increased
risk of outpatient attendances in the preterm or SGA cohort for any of the periods. This could be due to several reasons. First, small numbers of hospitalizations and outpatient visits in the preterm and SGA cohorts might have hindered the chances of finding this association if it does indeed exist. Second, morbidity due to mild conditions might be similar between the groups, and increased morbidity risk might only be associated with severe conditions, which might be best reflected when analysing hospitalization risk of both SGA and preterm delivery. Third, in this area of southern Mozambique many children are first taken to the traditional healer when they are sick. If the potential health problems associated with preterm and/or SGA are severe, children might not be taken to the formal health system before they die. Thus, morbidity surveillance based on outpatient or inpatient attendances might be an underestimate of the true morbidity burden associated with these conditions.

These findings underscore the need to identify these conditions early enough in order to implement interventions aimed at increasing the level of care, and ultimately survival. However, with currently available strategies, there is a broad room for improvement in the field of prevention, which should focus in targeting the known risk factors, including: preconception

### Table 5. Incidence Rates (IR) of outpatient visits per 1000 CYAR and Incidence Rate Ratios (IRR) of visiting the outpatient clinic during the neonatal period and first year of life of different cohorts analysed.

| MODEL 1 | Subjects | Outpatient visits | Time At Risk (CYAR) | IR (per 1000 CYAR) and 95% CI) | aIRR (95% CI) | p-value* |
|---------|----------|-------------------|---------------------|-------------------------------|--------------|---------|
| Neonatal Period | non Preterm & non SGA | 2336 | 447 | 193.9 | 2.3 (2.1–2.5) | 1 | 0.5895 |
|  | non Preterm & SGA | 296 | 56 | 24.2 | 2.3 (1.8–3.0) | 1.0 (0.7–1.4) | |
|  | Preterm & non SGA | 84 | 20 | 6.7 | 3.0 (1.9–4.6) | 1.4 (0.9–2.4) | |
|  | Preterm & SGA | 53 | 10 | 3.9 | 2.6 (1.4–4.8) | 1.1 (0.5–2.1) | |
| 0–12 month Period | non Preterm & non SGA | 2341 | 7462 | 2199.2 | 3.4 (3.3–3.5) | 1 | 0.6922 |
|  | non Preterm & SGA | 296 | 911 | 272.2 | 3.4 (3.1–3.6) | 0.9 (0.8–1.1) | |
|  | Preterm & non SGA | 84 | 251 | 75.8 | 3.3 (3.0–3.8) | 1.0 (0.8–1.3) | |
|  | Preterm & SGA | 53 | 155 | 41.2 | 3.8 (3.2–4.4) | 1.1 (0.8–1.4) | |

| MODEL 2 | Subjects | Outpatient visits | Time At Risk (CYAR) | IR (per 1000 CYAR) and 95% CI) | aIRR (95% CI) | p-value* |
|---------|----------|-------------------|---------------------|-------------------------------|--------------|---------|
| Neonatal Period | non Preterm | 2600 | 7876 | 2256.1 | 3.5 (3.4–3.6) | 1 | 0.6884 |
|  | Preterm | 134 | 411 | 113.7 | 3.6 (3.3–4.0) | 1.0 (0.9–1.2) | |
| 0–12 month Period | Non Preterm | 2640 | 8379 | 2474.4 | 3.4 (3.3–3.5) | 1 | 0.5676 |
|  | Preterm | 147 | 443 | 124.9 | 3.6 (3.2–3.9) | 1.1 (0.9–1.3) | |

| MODEL 3 | Subjects | Outpatient visits | Time At Risk (CYAR) | IR (per 1000 CYAR) and 95% CI) | aIRR (95% CI) | p-value* |
|---------|----------|-------------------|---------------------|-------------------------------|--------------|---------|
| Neonatal Period | Non SGA | 2420 | 467 | 200.6 | 2.3 (2.1–2.6) | 1 | 0.9032 |
|  | SGA | 349 | 66 | 28.1 | 2.4 (1.9–3.0) | 1.0 (0.7–1.3) | |
| 0–12 month Period | Non SGA | 2425 | 7713 | 2275.0 | 3.4 (3.3–3.5) | 1 | 0.5187 |
|  | SGA | 349 | 1066 | 313.5 | 3.4 (3.2–3.6) | 1.0 (0.9–1.1) | |

aIRR: adjusted Incidence Rate Ratio. Negative binomial regression model adjusted for: child sex, HIV status of the mother, number of previous pregnancies, mother age, period and socio economic status.

CYAR: children year at risk.

* P value obtained through Wald tests.

doi:10.1371/journal.pone.0172533.t005
counselling and family planning; health education programs aimed at prevention, early diagnosis and treatment of infections before and during pregnancy; increased control of conditions such as diabetes, hypertension, anaemia, before and during pregnancy; close monitoring of nutritional status and mental health of the mother, as well as implementation of best practices in assisted reproduction (which includes training to all health care workers involved)[27]. Although in our setting the rate of induced labour before week 37 is negligible, other settings should closely monitor and potentially reduced these practices, as well as rates of caesarean section.

This study has several limitations. First, gestational age was measured through indirect methods based on postnatal examination of the newborn (Dubowitz test, Ballard score). Although both methods have been validated and are broadly used in low income countries [28], the accuracy, agreement and reproducibility of these methods have been questioned[29]. The Dubowitz test might underestimate GA in SGA and term infants (<33 weeks)[30], although it could also overestimate GA in very preterm infants (<33 weeks)[31]. Some assessments have also questioned the accuracy of the Ballard score[29]. If any of the methods would underestimate

| Table 6. Incidence Rates (IR) of hospitalizations (per 1000 CYAR) and incidence rate ratios (IRR) of being hospitalized during the neonatal period and first year of life of different cohorts analysed. |
|---------------------------------|-----------------|--------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **MODEL 1**                     | **Subjects**    | **Hospitalizations** | **Time At Risk (CYAR)** | **IR (per 1000 CYAR) and 95% CI** | **IRR (95% CI)** | **p-value** |
| **Neonatal Period**             |                 |               |                   |                                |                  |                |
| non Preterm & non SGA           | 2336            | 113           | 193.9             | 0.6 (0.5–0.7)                  | 1                | 0.0324        |
| non Preterm & SGA               | 296             | 17            | 24.2              | 0.7 (0.4–1.1)                  | 1.0 (0.6–2.0)    |                |
| Preterm & non SGA               | 84              | 7             | 6.7               | 1.1 (1.2–4.5)                  | 1.6 (0.6–4.5)    |                |
| Preterm & SGA                   | 53              | 9             | 3.9               | 2.3 (1–2.8)                    | 3.5 (1.5–8.1)    |                |
| **0–12 month Period**           |                 |               |                   |                                |                  |                |
| non Preterm & non SGA           | 2341            | 507           | 2199.2            | 0.2 (0.2–0.3)                  | 1                | 0.0082        |
| non Preterm & SGA               | 296             | 74            | 272.2             | 0.3 (0.2–0.3)                  | 1.2 (0.8–1.6)    |                |
| Preterm & non SGA               | 84              | 20            | 75.8              | 0.3 (0.2–0.4)                  | 1.7 (1–2.9)      |                |
| Preterm & SGA                   | 53              | 22            | 41.2              | 0.5 (0.4–0.8)                  | 2.5 (1.4–4.5)    |                |
| **MODEL 2**                     |                 |               |                   |                                |                  |                |
| **Neonatal Period**             |                 |               |                   |                                |                  |                |
| non Preterm                     | 2635            | 132           | 218.4             | 0.6 (0.5–0.7)                  | 1                | 0.0176        |
| Preterm                         | 147             | 17            | 11.2              | 1.5 (0.9–2.4)                  | 2.2 (1.2–4.4)    |                |
| **0–12 month Period**           |                 |               |                   |                                |                  |                |
| non Preterm                     | 2640            | 583           | 2474.4            | 0.2 (0.2–0.3)                  | 1                | 0.0027        |
| Preterm                         | 147             | 45            | 124.9             | 0.4 (0.3–0.5)                  | 1.9 (1–3.2.9)    |                |
| **MODEL 3**                     |                 |               |                   |                                |                  |                |
| **Neonatal Period**             |                 |               |                   |                                |                  |                |
| Non SGA                         | 2420            | 120           | 200.6             | 0.6 (0.5–0.7)                  | 1                | 0.2767        |
| SGA                             | 349             | 26            | 28.1              | 0.9 (0.6–1.4)                  | 1.4 (0.8–2.3)    |                |
| **0–12 month Period**           |                 |               |                   |                                |                  |                |
| Non SGA                         | 2425            | 527           | 2275.0            | 0.2 (0.2–0.3)                  | 1                | 0.088         |
| SGA                             | 349             | 96            | 313.5             | 0.3 (0.3–0.4)                  | 1.3 (1.0–1.8)    |                |

allIR: adjusted Incidence Rate Ratio. Negative binomial regression model adjusted for: child sex, HIV status of the mother, number of previous pregnancies, mother age, period and socio economic status.

CYAR: children year at risk.
*p value obtained through Wald tests.

doi:10.1371/journal.pone.0172533.t006
the GA, the prevalence of preterm birth could be slightly overestimated and mortality and morbidity rates underestimated in comparison to the at-term non SGA group. In addition, in order to calculate gestational age, children had to survive the first hours of life and be hospital delivered, thus some deaths occurring before gestational age was assessed were not included. This would certainly underestimate the prevalence of prematurity and small for gestational age (but also the mortality risk associated with these conditions). Lastly, the fact that mothers have participated in a research study might have underestimated the true prevalence of preterm birth in this setting. It could be thought that this could have also positively contributed to better health outcomes in the first year of follow up. However, a majority of children with available prospective data belonged to the mentioned studies, thus, we believe our measures of effect are not biased in those born from study participants. If so, our findings would represent a conservative estimate of the true mortality and morbidity rates.

Conclusions
In conclusion, these results contribute to the evidence on the increased risk of mortality and morbidity associated with preterm and small for gestational age births in rural Africa. This increased risk is much higher for preterm births than for SGA without prematurity and appears to be concentrated within the neonatal period. Routine assessment of birth weight and gestational age at birth, and identification of these conditions should prompt interventions aimed at increasing the level of care among these high-risk newborns and improve survival.

Acknowledgments
We would like to thank all the children and mothers from the district of Manhiça. We also thank the health personnel of the Manhiça District Hospital, especially those at the maternity clinic, and the staff and colleagues from the Manhiça Health Research Centre (CISM) and Barcelona Institute for Global Health. We would like to thank the Spanish Epidemiology Society for the Enrique Nájera award to ALGB, which provided the framework and motivation to this piece of work.

Author Contributions
Conceptualization: CM E. Sicuri ALGB.
Data curation: LQ ALGB.
Formal analysis: ALGB LQ.
Funding acquisition: CM.
Investigation: EM AB RG BS MR E. Sevene.
Methodology: ALGB LQ AB RG.
Project administration: ALGB.
Resources: CM EM.
Supervision: CM E. Sevene.
Writing – original draft: ALGB.
Writing – review & editing: ALGB LQ EM AB RG AN BS CS MR E. Sicuri QB E. Sevene CM.
References

1. World Health Organization. Born too soon: the global action report on preterm birth [Internet]. 2012 [cited 8 Apr 2016]. Available: http://www.who.int/pmnch/media/news/2012/201204_borntoosoon-report.pdf

2. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2014; 385: 430–40. doi: 10.1016/S0140-6736(14)61698-6 PMID: 25280870

3. Harrison MS, Goldenberg RL. Global burden of prematurity. Semin Fetal Neonatal Med. 2015; 21: 74–9. doi: 10.1016/j.siny.2015.12.007 PMID: 26740166

4. Black RE. Global Prevalence of Small for Gestational Age Births. Nestlé Nutr Inst Work Ser. 2015; 81: 1–7.

5. Kozuki N, Katz J, Lee ACC, Vogel JP, Silveira MF, Sania A, et al. Short Maternal Stature Increases Risk of Small-for-Gestational-Age and Preterm Births in Low- and Middle-Income Countries: Individual Participant Data Meta-Analysis and Population Attributable Fraction. J Nutr. 2015; 145: 2542–50. doi: 10.3945/jn.115.216374 PMID: 26423738

6. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet (London, England). 2008; 371: 261–9.

7. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008; 371: 75–84. doi: 10.1016/S0140-6736(08)60074-4 PMID: 18177778

8. Sheridan C, Health R. Intrauterine growth restriction, diagnosis and management. Aust Fam Physician. 2005; 34: 717–723. PMID: 16184202

9. Bamberg C, Kalache KD. Prenatal diagnosis of fetal growth restriction. Semin Fetal Neonatal Med. 2004; 9: 387–94. doi: 10.1016/j.siny.2004.03.007 PMID: 15691774

10. Barros. Pediatrics. Comparison of causes and consequences of Prematurity. . .pdf.

11. Gladstone M, White S, Kafulafula G, Neilson JP, van den Broek N. Post-neonatal mortality, morbidity, and developmental outcome after ultrasound-dated preterm birth in rural malawi: A community-based cohort study. PLoS Med. 2011; 8: 1–11.

12. Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, et al. The worldwide incidence of pre-term birth: a systematic review of maternal mortality and morbidity. Bull World Health Organ. 2010; 88: 31–8. doi: 10.2471/BLT.08.062554 PMID: 20428351

13. Méndez C, Bardaji A, Sigaquue B, Sanz S, Aponte JJ, Mabunda S, et al. Malaria Prevention with IPTp during Pregnancy Reduces Neonatal Mortality. PLoS One. 2010; 5: e9438. doi: 10.1371/journal.pone.0009438 PMID: 20195472

14. González R, Munguambe K, Aponte J, Bavo C, Nhalungo D, Macete E, et al. High HIV prevalence in a southern semi-rural area of Mozambique: a community-based survey. HIV Med. 2012; 13: 581–8. doi: 10.1111/j.1468-1293.2012.01018.x PMID: 22500780

15. Nhacolo AQ, Nhalungo DA, Sacoor CN, Aponte JJ, Thompson R, Alonso P. Levels and trends of demographic indices in southern rural Mozambique: evidence from demographic surveillance in Manhiça district. BMC Public Health. 2006; 6: 291. doi: 10.1186/1471-2458-6-291 PMID: 17137494

16. Sacoor C, Nhacolo a., Nhalungo D, Aponte JJ, Bassat Q, Augusto O, et al. Profile: Manhiça Health Research Centre (Manhiça HDSS). Int J Epidemiol. 2013; 42: 1309–1318. doi: 10.1093/ije/dyt148 PMID: 24159076

17. Dubowitz LM, Dubowitz V, Goldberg C. Clinical assessment of gestational age in the newborn infant. J Pediatr. 1970; 77: 1–10. Available: http://www.ncbi.nlm.nih.gov/pubmed/5430794 PMID: 5430794

18. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walmsley BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr. 1991; 119: 417–23. Available: http://www.ncbi.nlm.nih.gov/pubmed/1880657 PMID: 1880657

19. González R, Desai M, Macete E, Ouma P, Kakolwa M a., Abdulla S, et al. Intermittent Preventive Treatment of Malaria in Pregnancy with Mefloquine in HIV-Infected Women Receiving Cotrimoxazole Prophylaxis: A Multicenter Randomized Placebo-Controlled Trial. PLoS Med. 2014; 11: e1001735. doi: 10.1371/journal.pmed.1001735 PMID: 25247995

20. González R, Mombo-Ngoma G, Ouédraogo S, Kakolwa M a., Abdulla S, Accrombessi M, et al. Intermittent Preventive Treatment of Malaria in Pregnancy with Mefloquine in HIV-Negative Women: A Multicentre Randomized Controlled Trial. PLoS Med. 2014; 11: e1001733. doi: 10.1371/journal.pmed.1001733 PMID: 25247709

21. WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO
as amended October 14, 1976. Acta Obstet Gynecol Scand. 1977; 56: 247–53. Available: http://www.ncbi.nlm.nih.gov/pubmed/560099 PMID: 560099

22. Matthews LT, Ribaudo HJ, Parekh NK, Chen JY, Binda K, Ogwu A, et al. Birth weight for gestational age norms for a large cohort of infants born to HIV-negative women in Botswana compared with norms for U.S-born black infants. BMC Pediatr. 2011; 11: 115. doi: 10.1186/1471-2431-11-115 PMID: 22176889

23. Vyas S, Kumaranyake L. Constructing socio-economic status indices: How to use principal components analysis. Health Policy Plan. 2006; 21: 459–468. doi: 10.1093/heapol/czl029 PMID: 17030551

24. Kc A, Wrammert J, Nelins V, Ewald U, Clark R, Malqvist M. Level of mortality risk for babies born preterm or with a small weight for gestation in a tertiary hospital of Nepal. BMC Public Health. BMC Public Health; 2015; 15: 877. doi: 10.1186/s12889-015-2232-1 PMID: 26359230

25. Onwuanaku C, Okolo SN, Ige KO, Okpe SE, Toma BO. The effects of birth weight and gender on neonatal mortality in north central Nigeria. BMC Res Notes. 2011; 4: 562.

26. Katz J, Lee ACC, Kozuki N, Lawn JE, Cousens S, Blencowe H, et al. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: A pooled country analysis. Lancet. 2013; 382: 417–425. doi: 10.1016/S0140-6736(13)60993-9 PMID: 23746775

27. Blencowe H, Cousens S, Chou D, Ostergaard M, Say L, Moller A-B, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health. 2013; 10 Suppl 1: S2.

28. Feresu SA, Gillespie BW, Sowers MF, Johnson TRB, Welch K, Harlow SD. Improving the assessment of gestational age in a Zimbabwean population. Int J Gynaecol Obstet. 2002; 78: 7–18. Available: http://www.ncbi.nlm.nih.gov/pubmed/12113965 PMID: 12113965

29. Wylie BJ, Kalili-Anjirah LH, Madanitsa M, Membe G, Nyirenda O, Mawindo P, et al. Gestational age assessment in malaria pregnancy cohorts: a prospective ultrasound demonstration project in Malawi. Malar J. 2013; 12: 183. doi: 10.1186/1475-2875-12-183 PMID: 23734718

30. Robillard PY, De Caunes F, Alexander GR, Sergent MP. Validity of postnatal assessments of gestational age in low birthweight infants from a Caribbean community. J Perinatol. 1992; 12: 115–9. Available: http://www.ncbi.nlm.nih.gov/pubmed/1522427 PMID: 1522427

31. Rosenberg RE, Ahmed ASMNU, Ahmed S, Saha SK, Chowdhury MAKA, Black RE, et al. Determining gestational age in a low-resource setting: validity of last menstrual period. J Health Popul Nutr. 2009; 27: 332–8. Available: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2761790&tool=pmcentrez&rendertype=abstract PMID: 19507748