Macronutrients during Pregnancy and Life-Threatening Respiratory Syncytial Virus Infections in Children

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Rationale: **Respiratory syncytial virus (RSV) is an important cause of hospitalization and death in infants worldwide. Most RSV deaths occur in developing countries, where burden and risk factors for life-threatening illness are unclear.**

Objectives: **We defined the burden of life-threatening (O_2 saturation [O_2 sat] $\leqslant$ 87%) and fatal RSV infection, and characterized risk factors for life-threatening disease in hospitalized children. Special emphasis was placed on studying the impact of dietary habits during pregnancy. We hypothesized that dietary preferences, differing from those of our remote ancestors, would negatively impact children's pulmonary health. For instance, a diet rich in carbohydrates is a signature of recent millennia and typical of low-income populations, heavily burdened by life-threatening RSV disease.**

Methods: **Prospective study in a catchment population of 56,560 children under 2 years of age during the RSV season in Argentina. All children with respiratory signs and O_2 sat less than 93% on admission were included.**

Measurements and Main Results: **Among 1,293 children with respiratory infections, 797 (61.6%) were infected with RSV: 106 of these had life-threatening disease; 1.9 per 1,000 children (95% confidence interval [CI], 1.5–2.2/1,000) under 24 months. A total of 22 hospitalized children died (9 RSV$^+$), 26 died at home due to acute respiratory infection (14 attributed to RSV); all were under 12 months old. The annual attributable mortality rate for RSV was 0.7 per 1,000 infants (95% CI, 0.4–1.1/1,000). Life-threatening disease was dose-dependently associated with carbohydrate ingestion during pregnancy (adjusted odds ratio from 3.29 [95% CI, 1.15–9.44] to 7.36 [95% CI, 2.41–22.5] versus the lowest quartile).**

Conclusions: **Life-threatening and fatal RSV infections are a heavy burden on infants in the developing world. Diets rich in carbohydrates during pregnancy are associated with these severe outcomes.**

Keywords: respiratory syncytial virus; bronchiolitis; fetal programming hypothesis; life-threatening illness; carbohydrates

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Respiratory syncytial virus (RSV) is an important cause of hospitalization and death in infants worldwide. Most RSV deaths occur in developing countries, where burden and risk factors for life-threatening illness are unclear.

What This Study Adds to the Field

Life-threatening and fatal RSV infections are a heavy burden on infants in the developing world. Diets rich in carbohydrates during pregnancy are associated with these severe outcomes.

Respiratory syncytial virus (RSV) is the most frequent agent of severe acute respiratory infection (ARI) in children younger than 2 years of age in the world (1, 2). An estimated 2.8–4.3 million children are hospitalized worldwide every year due to the virus (3). Most of these episodes resolve without major complications, but children with severe hypoxemia are at increased risk of death (4). Identification of these high-risk children is important for targeted primary preventive interventions. However, the characterization of children with life-threatening disease is incomplete. In fact, mortality rates due to RSV are difficult to ascertain, because children in developing countries—where 99% of fatal cases occur (3)—often die at home (5).

Identifying novel, modifiable risk factors for severe RSV disease is important. Although numerous determinants of hospitalization

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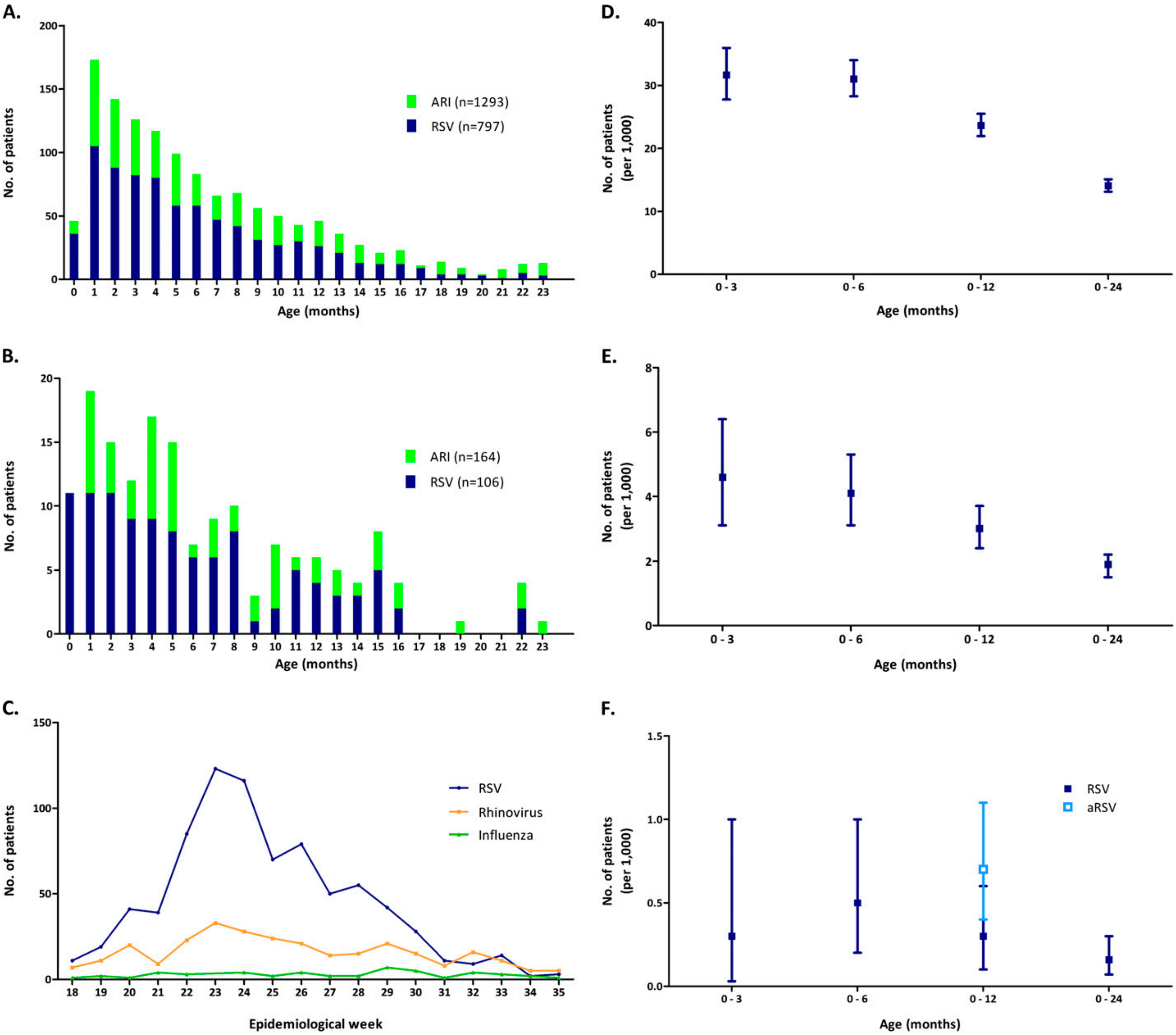

Figure 1. Burden of illness due to respiratory syncytial virus (RSV) in infants and children 0–24 months of age. (*A*) Number of hospitalized patients with acute respiratory infection (ARI; *blue* + *green*) or restricted to RSV infection (*green*) by month of age. (*B*) Number of hospitalized patients with O_2 saturation $\leqslant$ 87% due to ARI (*blue* + *green*) or restricted to RSV infection (*green*) by month of age. (*C*) Viral etiology of ARI in hospitalized patients during respiratory season. RSV (*blue*), human rhinoviruses (*orange*), influenza viruses (*green*). (*D*) Hospitalization rates due to RSV infection in infants and children 0–24 months of age, with 95% confidence interval (CI). (*E*) Rates of life-threatening disease due to RSV infection in infants and children 0–24 months of age, with 95% CI. (*F*) Mortality rates due to RSV infection (*blue squares*) in infants and children 0–24 months of age, and attributable mortality rates due to RSV (aRSV; *light blue open square*) for 0–12 months of age with 95% CI.

have been described (6–9), specific risk factors associated with life-threatening RSV disease are unknown. Well known postnatal risk factors for severe RSV disease include socioeconomic variables affecting families (e.g., poverty) and biological characteristics of children (e.g., prematurity) (6–9). Prenatal risk factors have received little attention to date, even though pregnancy is the dominant period of lung growth and immune development in life (10).

The "fetal programming hypothesis" postulates that events during pregnancy have long-term effects on the offspring's health during adulthood (11, 12). Well exemplified for lung diseases by the pernicious consequences of maternal smoking on lung development, the long-term impact of dietary choices during pregnancy have also attracted attention (11, 12). In fact, effects of maternal diet on fetal development may be influenced by evolutionary maladaptation of human genes exposed for millions of years to diets rich in fiber and protein, and only recently faced with 21st century diets rich in refined carbohydrates (13). A diet rich in carbohydrates is both a signature of recent millennia and typical of low-income populations (14), which are heavily affected by life-threatening ARI (3–9). However, whether exposure to excess carbohydrates during pregnancy influences susceptibility to lung disease in early childhood is unknown.

To characterize the burden of severe RSV infection, and to identify prenatal and postnatal risk factors for life-threatening disease during ARI, we conducted a large prospective

TABLE 1. EPIDEMIOLOGIC CHARACTERISTICS OF THE POPULATION

	ARI (*n* = *1293*)	RSV ARI (*n* = *797*)
Socioeconomic variables, *n* (%)		
House materials, tin/mud	293 (23.2)	190 (24.3)
Dirt floor	63 (5.0)	35 (4.5)
No sewage	811 (64.3)	501 (64.0)
Heating—unvented sources	75 (6.1)	47 (6.1)
Smoking at home	773 (61.8)	489 (62.7)
Maternal education*	174 (13.7)	96 (12.2)
Paternal education*	261 (16.6)	157 (17.0)
Malnutrition†		
Mild	218 (17.8)	127 (16.6)
Moderate to severe	58 (4.7)	26 (3.4)
Crowding	550 (44.5)	337 (44.1)
Household income‡	322 (24.9)	180 (22.6)
Pregnancy variables, *n* (%)		
Smoking during pregnancy	260 (20.6)	168 (21.5)
Maternal asthma	74 (5.9)	40 (5.1)
Carbohydrate intake§		
Quartile 1	375 (32.0)	221 (30.6)
Quartile 2	359 (30.7)	227 (31.4)
Quartile 3	174 (14.9)	107 (14.8)
Quartile 4	262 (22.4)	167 (23.1)
Fruits and vegetables intake‖ (high)	585 (46.2)	360 (45.9)
Protein intake¶		
Quartile 1	477 (37.9)	291 (37.3)
Quartile 2	328 (26.1)	201 (25.8)
Quartile 3	278 (22.1)	186 (23.8)
Quartile 4	175 (13.9)	102 (13.1)
Fat intake**		
Quartile 1	534 (42.6)	332 (42.9)
Quartile 2	282 (22.5)	181 (23.3)
Quartile 3	226 (18.0)	132 (17.0)
Quartile 4	212 (16.9)	130 (16.8)
Infant variables		
Age, mo, mean (range)	6.9 (0.1–24)	6.4 (0.3–24)
Birth weight, g, mean (range)	3,146 (800–5,750)	3,161 (800–5,750)
Prematurity, *n* (%)	172 (13.9)	103 (13.4)
Male, *n* (%)	678 (53.8)	431 (55.0)
Intrauterine growth retardation, *n* (%)	46 (3.9)	27 (3.7)
Breastfeeding, *n* (%)	941 (76.0)	587 (76.4)
Underlying chronic illness, *n* (%)	49 (4.0)	21 (2.8)

Definition of abbreviations: ARI = acute respiratory infection; RSV = respiratory syncytial virus.

* Maternal/paternal studies: incomplete primary school.

† Malnutrition: % of the infant's weight compared to that of a normal child (50th percentile of weight for age) of the same age according to WHO (37): 75–90% (mild), <75% (moderate to severe).

‡ Household income less than US$200 per month.

§ Carbohydrate-rich food groups: bread, pastries, sugar-sweetened beverages, sweetened infusions, pasta, rice, and potatoes.

‖ Fruits and vegetables high intake = 51–100% intake score versus reference group (0–50%).

¶ Protein-rich food groups: red meat, poultry, and fish.

** Fat-rich food groups: fried eggs, French fries, butter biscuits, oils, and snacks (e.g., chips).

evaluation of children younger than 2 years of age in Buenos Aires, Argentina.

METHODS

Population and Study Period

The Buenos Aires metropolitan statistical area and the neighboring city of La Plata have an estimated population of 361,000 infants and children younger than 2 years of age (15). Of these children, approximately 170,000 lack private medical insurance and receive free care at public hospitals (15, 16). In the metropolitan area, the southern region has the lowest socioeconomic indicators, and is home to 64,600 children younger than 2 years of age without private insurance (15, 16).

We conducted a prospective study in a catchment population of roughly 56,560 children younger than 2 years of age, who lacked private medical insurance in the southern region, and receive care from 12 public hospitals in Buenos Aires (three nonparticipating hospitals provide care for the remaining 8,040 children in the region, and present no significant differences with participating institutions) (15, 16). The study was conducted during the 2011 RSV season, lasting from detection by the hospitals of two positive cases of RSV ARI in 1 of the 12 institutions in 1 week until no RSV-positive cases were admitted to four institutions in 1 week. The study was approved by the institutional review boards at each participating institution, the state of Buenos Aires, and Vanderbilt University. Informed consent was obtained from all participating parents or guardians.

Eligible patients were infants and children younger than 2 years of age, admitted with a diagnosis of severe ARI, defined as the sudden onset of cough, wheezing, retractions and/or crackles with or without fever, and an oxygen saturation (O_2 sat) of less than 93% at rest when breathing room air (17). Infants and young children were considered to have extremely severe, life-threatening disease when presenting O_2 sat of 87% or less on admission (4, 18). Oxygen saturation cut-off for extreme severity was selected based on previous publications (4, 18) and to identify seriously ill children with hemoglobin saturations clearly below the flat portion of the oxyhemoglobin dissociation curve (most manufacturers of pulse oxymeters estimate measurement error at ±2%) (19). Admission to intensive care units, need for ventilatory support, or duration of hospitalization were not considered as outcomes, because, in the study setting, these services vary by individual medical practice, many participating hospitals lack intensive care units, and, consequently, have limited access to ventilators, and pediatricians—in regions with families at social risk—often need to prolong or shorten hospitalizations due to nonmedical reasons. We studied children younger than age 2 years because previous reports suggested that severe and fatal RSV ARI is negligible in children over 2 years of age (1–3). We focused our burden estimates on severe, life-threatening, and fatal RSV disease, because these cases represent the main costs for health care and the preventive target of future first-generation vaccines (20). As part of the study, all enrolled children were monitored daily during hospitalization using specifically designed forms until discharge.

In addition, a state program in our region systematically registered infant home deaths through questionnaires administered by trained professionals, based on a mortality classification system derived from the International Statistical Classification of Diseases and Related Health Problems, 10th revision, from the World Health Organization (21). Fatal cases were identified when families requested death certificates, mandatory for the performance of burials.

Epidemiological Data

Epidemiological and clinical data were obtained upon admission and through hospitalization using specifically designed questionnaires to determine risk factors associated with life-threatening disease. Traditional risk factors for hospitalization were evaluated in the study, and included sex, age, prematurity (<37-wk gestation at birth), mother with asthma (diagnosed by physician), lack of breastfeeding, and structural poverty (6–9). Structural poverty was assessed by collecting data on the following indicators: house and floor materials; presence of sewage; sources of heating; maternal and paternal education; crowding (>three persons/room); low household income (defined as a monthly income < US $200); malnutrition; and smoking at home.

Maternal diet during pregnancy was assessed using a food-frequency questionnaire modified from Willett and colleagues (22–24, 27, 28) using a comprehensive food list representative of the eating habits of the population under study, derived from the Argentinian Health and Nutrition Survey for pregnant women, and further categorized based on ingestion of macronutrients (e.g.: carbohydrates, proteins, fats) (23). The reference period included the dietary intake during the last trimester of pregnancy. This questionnaire version requests that respondents estimate their daily, weekly, monthly, and rarely/ever consumption frequencies of individual foods (e.g., bread) (24). Participants were categorized into quartiles based on their reported intake frequency, with the lowest quartile serving as reference group for each of the food categories. Given the 90-day period of reference and consequent concerns about portion size recall (36), our study did not collect information about daily portion sizes.

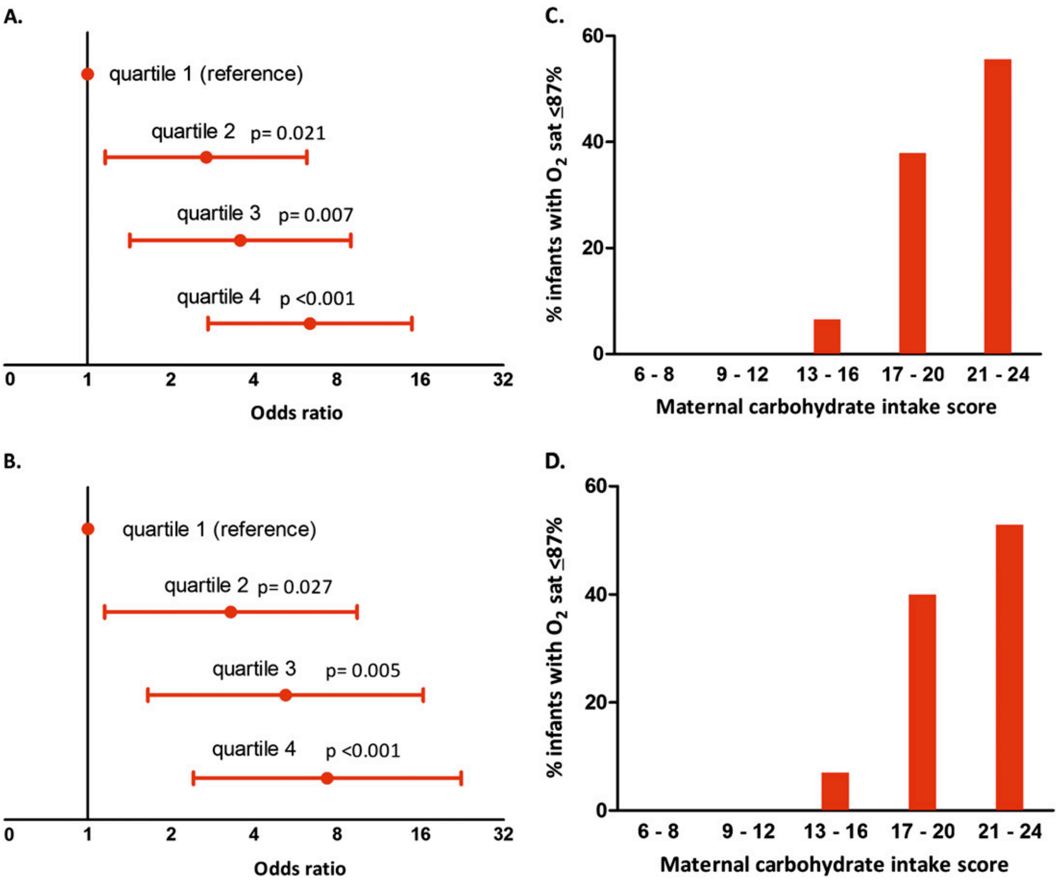

Figure 2. Carbohydrate intake during pregnancy and life-threatening acute respiratory infection (ARI) in children. (*A* and *B*) Adjusted odds ratio (OR) with 95% confidence interval (CI) for life-threatening disease (O_2 saturation [O_2 sat] $\leqslant$ 87%) in children with ARI (*A*) or restricted to respiratory syncytial virus (RSV) ARI (*B*) according to carbohydrate intake during the third trimester of pregnancy, categorized in quartiles for comparison. (*C* and *D*) Carbohydrate intake score and frequency of life-threatening disease. Briefly, six local food groups of high carbohydrate content (breads, pastries, sugar-sweetened beverages, sweetened infusions, pasta, rice, and potatoes) were scored by intake frequency yielding total scores between 6 and 24 points. Percent infants with life-threatening disease (O_2 sat $\leqslant$ 87%) due to ARI (*C*) and restricted to RSV infection (*D*) are displayed according to maternal carbohydrate intake score during the third trimester of pregnancy.

Viral Diagnosis

Nasal aspirates were obtained upon admission from all eligible children, and tested in duplicate by real-time RT-PCR for RSV, human rhinovirus (HRV), and influenza A viruses (2009 H1N1, seasonal H1N1 and H3N2) using methods described previously and described in the online supplement (25).

Statistical Analysis

Annual RSV incidence rates were calculated by dividing the number of children hospitalized with severe RSV ARI by the estimated census annual population in the catchment area. Chi-square and Student's *t* test were used to compare characteristics of children where appropriate. Multivariable logistic regression models identified risk factors for life-threatening disease among children hospitalized with severe ARI. Candidate covariates for this assessment were selected *a priori*. A second analysis included covariates in a stepwise forward logistic regression model that included covariates with a *P* value less than 0.20 in univariate analyses. Multivariate logistic regression models were tested for calibration (Hosmer-Lemeshow goodness of fit) and for discrimination using area under the receiver operating characteristics curve. A *P* value of less than 0.05 was considered statistically significant. All statistical analyses were performed using Stata 11.2 (StataCorp LP, College Station, TX).

RESULTS

During the season, 2,587 children younger than 2 years of age were hospitalized due to all causes. Of these, 1,338 (71%) families had a child with severe ARI and were invited to participate in the study; 1,293 (96.6%) accepted. Among hospitalized patients, RSV was detected in 797 (61.6%), HRV in 286 (22.1%), and influenza A viruses in 48 (3.7%; pH1N1 2009 = 4; influenza A H3N2 = 44) (Figure 1). Coinfections were identified in 153 patients: 140 (10.8%) with RSV and HRV, 7 (0.5%) with RSV and influenza, 3 with HRV and influenza, and 3 with all three viruses. Hospitalization rates for RSV were 23.7 per 1,000 children (95% confidence interval [CI], 22.6–25.5 per 1,000 children; Figure 1) younger than 12 months and 14.1 per 1,000 children (95% CI, 13.1–15.1 per 1,000 children) in children under 24 months. The majority of children admitted with all ARI (54.3%) and with RSV (56.3%) was younger than 6 months.

Poverty was widespread (Table 1). A total of 54% of children were males; breastfeeding was frequent at 76.0%. Pre-existent medical conditions were present in 49 admitted children (3.8%; some children had more than one condition), and included congenital heart disease (25; 1.9%), neurologic disorders (23; 1.8%), and immune deficiencies (13; 1.0%). During the last trimester of pregnancy, ingestion four or more times per week was frequent for bread (68.5%), sweetened infusions (71.4%), pasta and rice (51.7%), potatoes (47.6%), fruits (47.3%), sugar-sweetened beverages (44.7%), and red meat (34.9%).

Clinical Manifestations and Hospital Course

Among children with ARI, 164 (12.7%) had an O_2 sat of 87% or less on presentation to the hospital when breathing room air. A significant proportion of these infants were infected with RSV, with a rate of 3.0 per 1,000 children (95% CI, 2.4–3.7 per 1,000 children; Figure 1) for life-threatening illness in those 0–12 months of age (Figure 1). In addition, approximately 14.4% of children developed complications during their hospital stay. Most frequent complications included a clinical diagnosis of pneumonia (6.5%), atelectasis (2.5%), sepsis (0.6%), pleural effusions (0.3%), and pneumothoraxes (0.2%).

During our study, 22(1.7%) children died at the hospitals. All of them were younger than 1 year. A total of 14 of these infants died with bronchiolitis, 9 (41%) of them infected with RSV; two other infants died with pertussis-like symptoms, and six of primary pneumonia and sepsis. The mean age of the nine infants dying of RSV infection was 4.4 months (range, 0.86–10 mo). Five infants died of severe bronchiolitis (three of them with pneumothoraces), three died of bronchiolitis with secondary pneumonia, and one of apnea. The RSV annual mortality rate in 0- to 12-month-old hospitalized infants was 0.3 per 1,000 children (95% CI, 0.1–0.6 per 1,000 children).

A total of 26 additional infants died at home in the study region and received a postmortem diagnosis of ARI as the cause of death by verbal autopsy. We assumed that, as in hospital-based deaths, 41% of ARI-associated demises occurred in RSV-infected infants. In that case, the overall (hospital + home) annual attributable mortality rate for RSV was 0.7 per 1,000 infants (95% CI, 0.4–1.1 per 1,000 infants). Using these figures, we estimate that RSV accounted for 6% of infant deaths in Argentina in 2011 (national infant annual mortality rate = 11.9/1,000 infants) (26).

Risk Factors for Life-Threatening Disease

Among patients hospitalized with severe ARI, life-threatening disease (O_2 sat $\leq$ 87%) was associated with the type and frequency of macronutrients ingested by mothers during pregnancy. Specifically, frequent ingestion of carbohydrates exhibited a strong association with life-threatening disease, whereas fruits and vegetables conferred protection. A total of 55.6% of all infants born to mothers with the highest sugar-intake scores presented with O_2 sat of 87% or lower compared with a study population frequency of life-threatening hypoxemia of 12.7% (Figure 2). Multivariable logistic regression analysis confirmed a dose-dependent significant association between carbohydrate ingestion and life-threatening illness (Table 2; Figure 2). The only other factors associated with extremely severe disease were moderate to severe malnutrition and RSV infection; whereas breastfeeding conferred protection (Table 2). Results from a stepwise logistic regression analysis were consistent with findings from the main analysis (*see* the online supplement).

Restriction of the estimations to children with RT-PCR–confirmed RSV infection yielded similar results (Table 3). Maternal carbohydrate ingestion during the third trimester of pregnancy was again associated with an increased risk of life-threatening RSV disease. Moderate to severe malnutrition and crowding also increased the risk of life-threatening illness, whereas breastfeeding, maternal fat intake (quartile 4), and maternal

TABLE 2. RISK FACTORS FOR OXYGEN SATURATION OF 87% OR LESS IN CHILDREN HOSPITALIZED WITH ACUTE RESPIRATORY INFECTION

			Univariate Analysis			Multivariate Analysis		
	O_2 sat $\leq$ 87	O_2 sat > 87	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Socioeconomic variables, *n* (%)								
House materials tin/mud	35 (11.95)	258 (88.05)	1.072	0.71–1.61	0.73	0.587	0.29–1.20	0.15
Dirt floor	10 (15.87)	53 (84.13)	1.517	0.75–3.05	0.24	1.569	0.48–5.14	0.46
No sewage	52 (11.53)	399 (88.47)	0.969	0.67–1.39	0.87	0.739	0.43–1.28	0.28
Heating—unvented sources	14 (18.67)	61 (81.33)	1.846	1.00–3.40	0.05	1.940	0.80–4.72	0.15
Smoking at home	81 (10.48)	692 (89.52)	0.898	0.62–1.29	0.56	0.790	0.45–1.38	0.41
Maternal education	32 (18.39)	142 (81.61)	1.993	1.29–3.07	0.002	1.188	0.56–2.52	0.65
Paternal education	27 (10.47)	231 (89.53)	1.381	0.88–2.16	0.16	1.459	0.75–2.83	0.26
Malnutrition								
Mild	98 (10.32)	892 (89.58)	1.228	0.78–1.93	0.37	0.922	0.44–1.95	0.83
Moderate to severe	42 (15.22)	234 (84.78)	3.032	1.62–5.66	<0.001	3.464	1.19–10.1	0.02
Crowding	58 (10.55)	492 (89.45)	0.880	0.61–1.26	0.49	1.103	0.65–1.87	0.71
Household income	86 (10.34)	746 (89.66)	1.436	1.00–2.07	0.05	1.828	0.80–4.15	0.15
Pregnancy variables, *n* (%)								
Smoking during pregnancy	34 (13.08)	226 (86.92)	1.243	0.82–1.88	0.30	1.283	0.66–2.50	0.46
Maternal asthma	12 (16.22)	62 (83.78)	1.569	0.82–2.99	0.17	0.749	0.23–2.42	0.63
Carbohydrate intake								
Quartile 1	18 (4.80)	357 (95.20)	Ref.	—	—	Ref.	—	—
Quartile 2	37 (10.31)	322 (89.69)	2.279	1.27–4.08	0.006	2.689	1.16–6.22	0.02
Quartile 3	24 (13.79)	150 (86.21)	3.173	1.67–6.02	<0.001	3.575	1.42–8.98	0.007
Quartile 4	45 (17.18)	217 (82.82)	4.113	2.32–7.29	<0.001	6.384	2.73–14.9	<0.001
Fruits and vegetables intake (high)	46 (7.86)	539 (92.14)	0.508	0.35–0.73	<0.001	0.347	0.19–0.62	0.001
Protein intake								
Quartile 1	61 (12.79)	416 (87.21)	Ref.	—	—	Ref.	—	—
Quartile 2	40 (12.20)	288 (87.80)	0.947	0.62–1.45	0.80	0.847	0.45–1.58	0.60
Quartile 3	26 (9.35)	252 (90.65)	0.703	0.43–1.14	0.16	0.542	0.26–1.15	0.11
Quartile 4	14 (8.00)	161 (14.41)	0.593	0.32–1.09	0.09	0.833	0.33–2.14	0.71
Fat intake								
Quartile 1	48 (8.99)	486 (91.01)	Ref.	—	—	Ref.	—	—
Quartile 2	40 (14.18)	242 (85.82)	1.673	1.07–2.62	0.02	1.363	0.71–2.63	0.36
Quartile 3	30 (13.27)	196 (86.73)	1.550	0.95–2.51	0.08	1.128	0.54–2.35	0.75
Quartile 4	22 (10.38)	190 (89.62)	1.172	0.69–1.99	0.59	0.766	0.34–1.74	0.52
Infant variables								
Age, mo, mean (range)	7.37 (0.46–23.15)	6.86 (0.1–24)	1.018	0.98–1.05	0.28	1.025	0.98–1.07	0.29
Birth weight, kg, mean (range)	3.09 (0.80–4.90)	3.15 (0.80–5.75)	1.000	1.00–1.00	0.26	1.000	1.00–1.00	0.81
Prematurity, *n* (%)	21 (12.21)	151 (87.79)	1.107	0.67–1.82	0.69	0.793	0.30–2.07	0.64
Male, *n* (%)	71 (10.47)	607 (89.53)	0.817	0.58–1.16	0.25	0.695	0.41–1.18	0.18
Intrauterine growth retardation, *n* (%)	7 (15.22)	39 (84.78)	1.484	0.65–3.39	0.35	1.542	0.48–4.97	0.47
Breastfeeding, *n* (%)	90 (9.56)	851 (90.44)	0.535	0.37–0.78	0.001	0.447	0.25–0.81	0.008
Underlying chronic illness, *n* (%)	14 (28.57)	35 (71.43)	3.338	1.75–6.37	<0.001	2.00	0.74–6.50	0.15
RSV infection, *n* (%)	99 (12.53)	691 (87.47)	1.394	0.96–2.02	0.08	2.073	1.18–3.65	0.002

Definition of abbreviations: CI = confidence interval; O_2 sat = oxygen saturation; OR = odds ratio; RSV = respiratory syncytial virus.

TABLE 3. RISK FACTORS FOR OXYGEN SATURATION OF 87% OR LESS IN CHILDREN HOSPITALIZED WITH RESPIRATORY SYNCYTIAL VIRUS INFECTION

			Univariate Analysis			Multivariate Analysis		
	O_2 sat ≤ 87	O_2 sat > 87	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Socioeconomic variables, *n* (%)								
House materials tin/mud	23 (12.11)	167 (87.89)	0.935	0.57–1.54	0.79	0.727	0.30–1.74	0.47
Dirt floor	7 (20.00)	28 (80.00)	1.810	0.77–4.26	0.17	1.078	0.22–5.36	0.93
No sewage	35 (12.41)	247 (87.59)	1.015	0.65–1.58	0.95	0.659	0.32–1.35	0.25
Heating—unvented sources	9 (19.15)	38 (80.85)	1.695	0.79–3.62	0.17	0.937	0.23–3.75	0.93
Smoking at home	57 (11.66)	432 (88.34)	0.878	0.57–1.36	0.56	0.743	0.37–1.50	0.41
Maternal education	19 (19.79)	77 (80.21)	1.908	1.10–3.32	0.02	1.097	0.39–3.12	0.86
Paternal education	18 (11.54)	138 (88.46)	1.300	0.75–2.26	0.35	0.990	0.39–2.49	0.98
Malnutrition								
Mild	73 (11.93)	539 (88.07)	0.989	0.55–1.79	0.97	0.703	0.25–1.97	0.50
Moderate to severe	24 (15.69)	129 (84.31)	3.908	1.68–9.09	0.002	15.83	3.57–70.3	<0.001
Crowding	47 (13.95)	290 (86.05)	1.250	0.81–1.92	0.31	2.233	1.12–4.46	0.02
Household income	57 (11.63)	433 (88.37)	1.384	0.89–2.16	0.15	2.250	0.76–6.66	0.14
Pregnancy variables, *n* (%)								
Smoking during pregnancy	23 (13.69)	145 (86.31)	1.139	0.69–1.88	0.61	1.152	0.48–2.74	0.75
Maternal asthma	6 (15.00)	34 (85.00)	1.256	0.51–3.07	0.62	0.698	0.12–4.14	0.69
Carbohydrate intake								
Quartile 1	13 (5.88)	208 (94.12)	Ref.	—	Ref.	—	—	—
Quartile 2	27 (11.89)	200 (88.11)	2.160	1.08–4.30	0.03	3.290	1.15–9.44	0.03
Quartile 3	19 (17.76)	88 (82.24)	3.454	1.63–7.30	0.001	5.200	1.65–16.4	0.005
Quartile 4	26 (15.57)	141 (84.43)	2.950	1.47–5.94	0.002	7.357	2.41– 22.5	<0.001
Fruits and vegetables intake (high)	29 (8.06)	331 (91.94)	0.443	0.28–0.70	<0.001	0.263	0.12–0.57	0.001
Protein intake								
Quartile 1	42 (14.43)	249 (85.57)	Ref.	—	Ref.	—	—	—
Quartile 2	30 (14.93)	171 (85.07)	1.040	0.63–1.73	0.88	0.967	0.44–2.10	0.93
Quartile 3	15 (8.06)	171 (91.94)	0.520	0.28–0.97	0.04	0.393	0.14–1.13	0.08
Quartile 4	9 (8.82)	93 (91.18)	0.574	0.27–1.22	0.15	1.200	0.35–4.15	0.77
Fat intake								
Quartile 1	36 (10.84)	296 (89.16)	Ref.	—	Ref.	—	—	—
Quartile 2	30 (16.57)	151 (83.43)	1.633	0.97–2.75	0.07	0.853	0.37–1.95	0.71
Quartile 3	16 (12.12)	116 (87.88)	1.134	0.60–2.12	0.69	0.599	0.22–1.62	0.31
Quartile 4	13 (10.00)	117 (90.00)	0.913	0.47–1.78	0.79	0.300	0.10–0.92	0.04
Infant variables								
Age, mo, mean (range)	6.72 (0.46–22.8)	6.40 (0.30–24)	1.014	0.97–1.06	0.53	1.035	0.98–1.10	0.26
Birth weight, kg, mean (range)	3.15 (0.87–4.90)	3.16 (0.80–5.75)	1.000	1.00–1.00	0.88	1.000	1.00–1.00	0.98
Prematurity, *n* (%)	8 (7.77)	95 (92.23)	0.554	0.26–1.18	0.13	0.341	0.08–1.41	0.14
Male, *n* (%)	53 (12.30)	378 (87.70)	0.936	0.61–1.42	0.76	0.713	0.37–1.38	0.32
Intrauterine growth retardation, *n* (%)	3 (11.11)	24 (88.89)	0.892	0.26–3.02	0.85	1.351	0.19–9.39	0.76
Breastfeeding, *n* (%)	66 (11.24)	521 (88.76)	0.638	0.40–1.02	0.06	0.367	0.17–0.79	0.01
Underlying chronic illness, *n* (%)	5 (23.81)	16 (76.19)	2.211	0.79–6.18	0.13	4.19	0.65–30.1	0.09

Definition of abbreviations: CI = confidence interval; O_2 sat = oxygen saturation; OR = odds ratio.

ingestion of fruits and vegetables conferred protection (Table 3 and the online supplement).

DISCUSSION

In this article, we address important questions about burden of illness and susceptibility to life-threatening RSV infections. First, we estimate rates for extreme severity and mortality in a large prospective multicenter study in a socially disadvantaged region of the developing world. Our results suggest that RSV is a major cause of hospital and home deaths in infants, and that this problem demands new preventive strategies. Consequently, we identify among hospitalized children novel prenatal determinants of life-threatening illness: high maternal carbohydrate intake and low intake of fruits and vegetables during pregnancy.

Our study, in line with estimates from a recent meta-analysis (3), suggests that the burden of fatal RSV disease in infants is considerable. In fact, the gravitas of RSV for infants is well exemplified by noting that, in the same Buenos Aires metropolitan area, the burden of illness due to RSV in 2011 outweighed that of 2009 H1N1 influenza A virus during the pandemic year 14-fold in hospitalizations and fourfold in virus-confirmed deaths (29).

Severe disease appears to be significantly more common in developing countries than in industrialized nations. For example, population-based surveillance in children in three counties during 5 years in the United States reported an annual average rate of 17 RSV hospitalizations per 1,000 infants younger than 6 months of age (30). Moreover, no RSV-associated deaths were observed in the United States (30), whereas nine hospitalized infants died due to RSV in these low-income neighborhoods of Argentina in one winter. Notably, several infants with ARI died at home, indicating an important residual burden of illness outside the hospitals and highlighting the need for careful, systematic assessment of this outpatient population, even in middle-income countries.

The mechanisms behind the detrimental effects of carbohydrates in lung disease may be tied to the premise that humans are genetically adapted to a diet devoid of grains and refined sugars, which were incorporated in to modern nutrition only about 10,000 and a few hundred years ago, respectively (13). It also seems plausible that women, having eaten vegetables and fruits for millions of years, would have evolved to use elements in them—not refined sugars—for fetal lung growth and immune development. Although the mechanisms behind these associations require further study, and may extend to alterations in the maternal microbiome (31), delayed fetal lung maturity (32), and/or presence of antioxidants in fruits and vegetables (33), our data suggest that our observations could not be explained by differences in poverty, overweight at birth, foods rich in vitamin D or antioxidants (data not shown), or rapid weight gain in early life. Our analyses accounted for measurements of structural poverty and socioeconomic status, and were conducted among a relatively homogeneous, underserved population. Our findings, and the importance of prematurity in susceptibility to lung infections (6), suggest that the obstetrician may be as influential as the pediatrician in prevention of severe ARI in infancy.

Our study has limitations. The evaluation was conducted during a single season, and burden may differ in other years. However, nothing indicates that RSV was unusually severe in 2011, as rates derived from passive surveillance suggest that it has remained relatively stable for several years (34). In addition, an imperfect ascertainment of socioeconomic status could have resulted in residual confounding. In addition, food-frequency questionnaires—one of the methods of choice for ranking subjects based on "usual" intake—are retrospective tools relying on mothers' memories. We also assessed smoke exposures using questionnaires, and collected dietary information only for the third trimester of pregnancy. As for other environmental, genetic, or sociocultural interactions potentially affecting results, studying populations with strong preferences for carbohydrates in industrialized countries, or those with routine consumption of diets low in cereals and refined sugars in nonwesternized regions may be informative (35).

The study also has significant strengths. We used state-of-the art laboratory techniques to prospectively define the burden of disease in a large population from a developing country, and supplemented our study data with information from deaths at home, a scourge that developing country studies on ARI cannot ignore (5). Importantly, ours is the first large, population-based, prospective study to evaluate numerous candidate-dependent variables for life-threatening illness and identify novel modifiable risk factors for extremely severe disease. In fact, the dose-dependent association between a diet rich in carbohydrates during pregnancy and life-threatening ARI follows a logical hypothesis based on genetic maladaptation of humans to modern, 21st century diets (13). Whether other diseases of infancy are affected by food preferences in pregnancy deserves further investigation.

In summary, we show that RSV is a highly significant cause of life-threatening disease, and is frequently associated with infant deaths during the respiratory season. In addition, we show that a diet rich in carbohydrates and devoid of fruits and vegetables during pregnancy associates with these undesirable outcomes. If these observations are confirmed, public health strategies that modify the diet of women of childbearing age without compromising nutritional needs should be evaluated to decrease the burden of extremely severe ARI in young children.

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