

# Bimodal Effects of Obesity Ratio on Disease Duration of Respiratory Syncytial Virus Infection in Children

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## ABSTRACT

**Background:** Morbid obesity may be associated with hospitalization and possibly death from the 2009 pandemic H1N1 infection, suggesting a yet unknown association between obesity and the severity of viral infections. Thus, we examined association between obesity ratios and duration of disease in children with Respiratory Syncytial Virus (RSV) infection.

**Methods:** A retrospective survey of 243 children admitted for bronchitis, bronchiolitis, pneumonia, and those who tested positive for a RSV test, were observed from a single institute in Japan. Primary outcome was set as the total days of wheezing in both the outpatient clinic and during hospitalization. Secondary outcomes were as follows: 1) total days of fever ( $37.5^{\circ}\text{C}\leq$ ) during hospitalization, and 2) days of drip infusion during hospitalization.

**Results:** When the obesity ratio was 6 and less, days of wheezing showed significant negative association with obesity ratios. In contrast, when the obesity ratio was more than 6, days of wheezing, days of fever during admission and days of drip infusion showed significant positive association with obesity ratios.

**Conclusions:** These results suggest that disease duration of RSV infection may be prolonged not only in lean but also in obese children.

## KEY WORDS

body weight, obesity, Respiratory Syncytial Virus, RSV, wheeze

## INTRODUCTION

Numerous studies have reported associations between severe respiratory syncytial virus (RSV) bronchiolitis in infancy and recurrent wheezing and asthma in later childhood.<sup>1,2</sup> Pneumonia is the leading single cause of mortality in children aged less than 5 years old and RSV is one of the main pathogens associated with pneumonia, where lack of exclusive breastfeeding, under-nutrition, indoor air pollution, low birth weight and crowding are included among the risks of pneumonia death.<sup>3</sup> Even in developed countries, small children under 5 years old infected with RSV had the highest rate of emergency department visits and hospitalization, especially from November through April.<sup>4</sup> However, most children with RSV infection were previously healthy, suggesting that control strategies targeting only high-risk

children will have a limited effect on the total disease burden of RSV infection.<sup>5</sup>

Of interest, morbid obesity was pointed out to be associated with hospitalization and possibly death from the 2009 pandemic H1N1 infection,<sup>6,7</sup> suggesting that not only under-nutrition, but also over-nutrition may affect the severity of respiratory infection. Moreover, although lower birth weight is a well known risk factor for developing severe RSV infection,<sup>8</sup> obesity ratio at infection is not known as a risk. Therefore, we aimed to examine the association between obesity ratio and duration of disease, targeting children admitted for RSV infection, by conducting a retrospective survey in a single institute in Japan.

## METHODS

### STUDY DESIGN AND POPULATION

We conducted a retrospective survey of consecutive

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pediatric patients younger than 7 years old from 1988 to 2004, who were admitted for diagnosis of bronchitis, bronchiolitis or pneumonia and RSV infection that was confirmed by rapid diagnostic test (Abbott TEST-PAK RSV assay, Abbott Laboratories, North Chicago, III, USA), which is a rapid and reliable enzyme immunoassay for the direct detection of RSV antigen in nasopharyngeal swab specimens with high accuracy: Sensitivity: 89%; specificity: 96%, positive predictive value: 96%; negative predictive value: 89%<sup>9</sup>; between January 1, 2000 and December 31, 2008 at a single tertiary and community hospital: the Fuji Chuo Hospital. Moreover, four patients who showed more than 30 days of wheezing: consecutive infection with RSV, influenza A and influenza B: congenital malformation and asthma: Down syndrome: co-infection with adenovirus were excluded. As a result, 243 patients were included in this study.

## OUTCOME MEASURE

Primary outcome was set as the total days of wheezing in both the outpatient clinic and during hospitalization. Secondary outcomes were as follows: 1) days of fever ( $37.5^{\circ}\text{C} \leq$ ) during hospitalization, and 2) days of drip infusion during hospitalization. All patients had continuous drip infusion and three times infusion of antibiotics.

## VARIABLES

Obesity ratio was calculated as [(observed body weight - standard body weight of age and gender) / standard body weight of age and gender  $\times$  100].

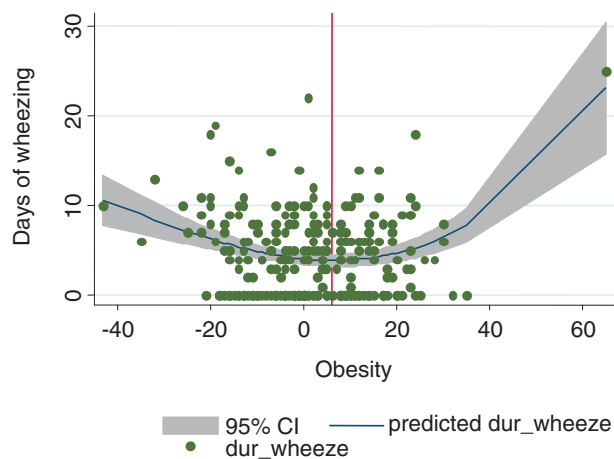
## STATISTICS

Linear regression models were computed with coefficient, its 95% confidence intervals (CI) and p-values. The associations between obesity ratio and outcome measures were adjusted with age, gender, gestational weeks, low birth weight, birth month, family history of asthma, past history of wheezes and atopic dermatitis. All statistical analyses were performed using STATA 11.0 (STATA Corp., College Station, TX, USA).  $P < 0.05$  was considered statistically significant.

## RESULTS

The mean age of all 243 children with RSV infection was  $2.6 \pm 1.3$  years (range, 1 to 6 years). Subjects included 131 (54%) boys and 112 (46%) girls.

Association between total days of wheezing and obesity ratios was drawn by the two-way fractional-polynomial prediction plots (Fig. 1). From the plots, the nadir of the curve for obesity ratio and total days of wheezing was found at an obesity ratio of 6. So, by stratifying the obesity ratio at 6, a linear regression model adjusted for age, gender, gestational weeks, low birth weight, birth month, family history of asthma, past history of wheezes and atopic dermatitis was computed (Table 1). When the obesity ratio was



**Fig. 1** Association between total days of wheezing and obesity ratios was drawn by the two-way fractional-polynomial prediction plots.

6 and less, days of wheezing showed significant negative association with obesity ratios. In contrast, when the obesity ratio was more than 6, days of wheezing showed significant positive association with obesity ratios.

Similarly, secondary outcomes: days of fever ( $37.5^{\circ}\text{C} \leq$ ) during hospitalization (Fig. 2, Table 1) and days of drip infusion during hospitalization (Fig. 3, Table 1) were analyzed. When the obesity ratio was 6 and less, days of fever did not show significant association with obesity ratios. In contrast, when the obesity ratio was more than 6, days of fever showed significant association with obesity ratios. When the obesity ratio was 6 and less, days of drip infusion did not show significant negative association with obesity ratios. In contrast, when the obesity ratio was more than 6, days of drip infusion showed significant positive association with obesity ratios.

## DISCUSSION

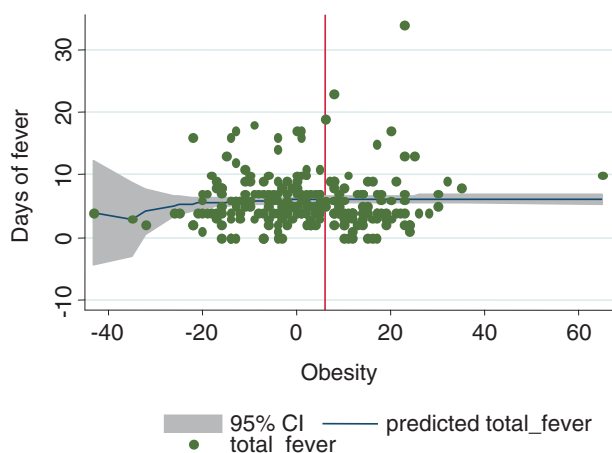
In this study, the nadir of the curves for obesity ratio and severity of RSV infection represented by days of wheezing, fever and drip infusion was found when the obesity ratio was 6. Similarly, there was a nadir of body-mass index (BMI) in the curve for BMI and mortality: Mortality was higher in both lean and obese populations whereas it was lower in-between groups.<sup>10</sup> There was a J-shaped curve in the incidence of infections recorded by BMI with a nadir.<sup>11</sup> In a cohort of American Indian children, rates of premature death from endogenous causes in the highest quartile of BMI were more than double those among children in the lowest BMI quartile during a median follow-up period of 24 years,<sup>12-14</sup> suggesting obesity in children may be hazardous for health.

In children with higher obesity ratios, the disease tended to be prolonged. In the 2009 pandemic H1N1 infection, obesity was a risk factor for developing a

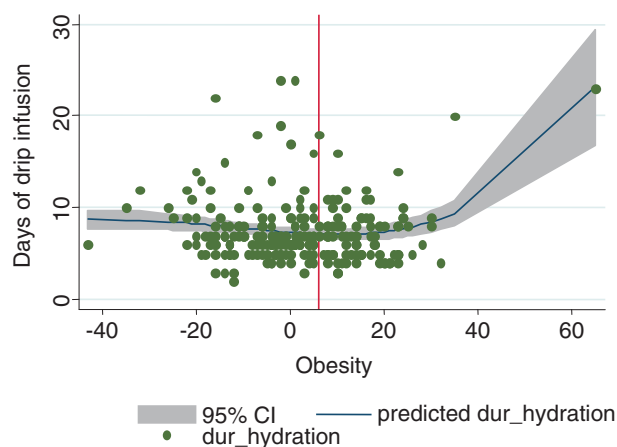
**Table 1** Associations between outcomes and obesity ratio †

Outcome	Obesity ratio ≤6 Coefficient (95%CI)	P-value	Obesity ratio 6 < Coefficient (95%CI)	P-value
Wheezing	-0.13 (-0.21 to -0.05)	0.001	0.19 (0.06 to 0.31)	0.004
Fever after admission	-0.00 (-0.03 to 0.03)	0.81	0.07 (0.01 to 0.14)	0.021
Drip infusion	-0.03 (-0.10 to -0.04)	0.40	0.15 (0.07 to 0.24)	0.001

† The associations were adjusted with age, gender, gestational weeks, low birth weight, birth month, family history of asthma, past history of wheezes and atopic dermatitis.



**Fig. 2** Association between total days of fever (37.5°C≤) after hospitalization and obesity ratios was drawn by the two-way fractional-polynomial prediction plots.



**Fig. 3** Association between days of drip infusion during hospitalization and obesity ratios was drawn by the two-way fractional-polynomial prediction plots.

severe case,<sup>6,7</sup> of which mechanisms remained unknown. However, a currently favored paradigm is that obesity induces cellular stress that initiates and perpetuates a chronic inflammation.<sup>15</sup> There are several articles suggesting impaired or aberrant immune responses in obese populations: Natural killer cell levels were significantly decreased in obese subjects compared to lean controls<sup>16,17</sup> and in animal models: In diet induced obese mice with H1N1 influenza challenge, production of gamma-interferon and number of influenza-specific memory T cells were significantly reduced and 25% died compared with 0% mortality in controls.<sup>18</sup>

The results should be interpreted in the context of the study limitations. Primary outcome measure was days of wheezing, which might include observation bias. On the other hand, only patients suspected with RSV infection by doctors were included in the study, which might include selection bias. On the other hand, due to the retrospective nature of the study, we could collect only basic clinical information that might include recall bias in such wheezes and fever in the outpatient clinic setting.

In conclusions, when the obesity ratio was 6 and less, days of wheezing, showed significant negative association with obesity ratios. In contrast, when the obesity ratio was more than 6, days of wheezing, days

of fever during hospitalization and days of drip infusion showed significant positive association with obesity ratios. These results suggest that disease duration of RSV infection may be prolonged not only in lean but also in obese children.

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