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Burden of Prematurity-Associated Recurrent Wheezing: Caregiver Missed Work in the D-Wheeze Trial

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Abstract

Objective: This study describes the burden of prematurity-associated wheezing in black infants with respect to caregiver missed work.

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Author Contributions:

Ms. Ledingham conceptualized and designed the study, helped to interpret the data, drafted the initial manuscript, and reviewed and revised the manuscript.

Ms. Minich and Dr. Tatsuoka had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. They provided statistical analyses and data interpretation and reviewed and revised the manuscript for important intellectual content.

Dr. Ross participated in the concept, design and data acquisition of the original trial from which these data were obtained, data interpretation, and review and revision of the manuscript.

Dr. Kerns participated in data acquisition of the original trial from which these data were obtained, data interpretation, and review and revision of the manuscript.

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Dr. Zimmerman participated in the concept and design of the original trial from which these data were obtained and review and revision of the manuscript.

Dr. Hibbs had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. She conceptualized and designed the study, coordinated and supervised data collection, helped to interpret the data, reviewed and revised the manuscript, and obtained funding for this study.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Study Design: We analyzed data from the D-Wheeze trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01601847) identifier [NCT01601847](https://clinicaltrials.gov/ct2/show/study/NCT01601847)). Black infants between 28-0/7 to 36-6/7 weeks' gestational age at birth receiving <28 days of supplemental oxygen were enrolled. The primary outcome was missed work to care for the infant in the first year.

Results: 147/277 (53.1%) infants had caregivers who reported time off. In an adjusted model, vitamin D supplementation (OR 0.52 [95% CI 0.30 - 0.89]; P = 0.018), recurrent wheeze (OR 2.26 [95% CI, 1.15 - 4.44]; P = 0.018), and other children in the household <5 years old (OR 0.45 [95% CI 0.26 - 0.78]; p = 0.004) were significantly associated with caregiver missed work.

Conclusions: Black premature infants had a significant burden of caregiver missed work, emphasizing the impact of prematurity-associated wheezing.

Introduction:

Recurrent wheezing is a common complication of prematurity (1). Prematurity-associated wheezing is associated with increased risk of respiratory illness resulting in more frequent hospitalizations and visits to primary care and emergency departments (2). Prematurity and prematurity-associated wheezing disproportionately affect black infants, with an odds ratio of 1.6 having been previously described in the literature, leaving this population especially susceptible to the significant burden of respiratory illness (3).

Several studies have attempted to quantify the burden of respiratory illness in infants and children with respect to cost of repeat hospitalizations and prophylaxis or treatment (4, 5, 6). Caregiver missed days of work to care for a sick child represents an additional important burden that has primarily been described for asthma and viral illness (7, 8). One study has examined caregiver missed days of work due to respiratory illness in infants, finding that a diagnosis of bronchiolitis necessitating a visit to the emergency department is associated with 2 days of missed caregiver work (9). Additional studies, however, are needed to further determine the family burden of respiratory illness in preterm infants and specifically prematurity-associated wheezing.

Vitamin D has the potential to lessen the impact of prematurity-associated wheezing through modulation of pulmonary and immune systems. In the Wheezing in Black Preterm Infants: Impact of Vitamin D Supplementation Strategy (D-Wheeze) trial, sustained supplementation with 400 IU/day of cholecalciferol until 6 months of age adjusted for prematurity was associated with a decrease in recurrent wheezing in infancy in black preterm infants without bronchopulmonary dysplasia (10). The current study is a secondary analysis of the D-Wheeze trial. The associations between caregiver missed work and recurrent wheezing, as well as vitamin D supplementation strategy, are described. It was hypothesized that prematurity-associated wheezing and vitamin D supplementation strategy would be associated with caregiver missed work.

Patients and methods:

This secondary analysis of the D-Wheeze trial included all enrolled infants who were seen in follow-up. Original inclusion criteria and methods for the D-Wheeze trial are described in

detail elsewhere (10). Briefly, infants were enrolled between January 2013 and January 2016 at participating institutions in Cleveland, OH, Charleston, SC, and Bronx, NY if they were 28-0/7 to 36-6/7 weeks' gestational age at birth, the family identified the child as black or African American, and they received 28 days or less of supplemental oxygen. Once infants were consuming a minimum of 200 IU/day cholecalciferol from formula or human breast milk fortifier, they were randomized to either 400 IU/day of cholecalciferol until 6 months adjusted age (sustained supplementation) or placebo (diet-limited supplementation). Exclusively breastfed infants in both arms received 400 IU/day of cholecalciferol for the duration of the study, as it was determined they were receiving less than the recommended 200 IU/day of cholecalciferol. Standardized questionnaires were administered at study visits at 3, 6, 9, and 12 adjusted months of age. Questionnaires were developed using a modified International Study of Asthma and Allergies in Childhood questionnaire (11), which seeks to describe frequency and severity of wheezing episodes the child has had in the past year and has been shown to perform well in infants born preterm (12). In addition to assessing wheezing symptoms, respondents were asked how many days of work had been missed in order to care for the infant by the respondent, their partner or spouse, and other family or friends since the last contact with the study team, which was based on respondent recall. Respondents were asked to clarify whether missed days of work were related to respiratory or non-respiratory concerns. The study was approved by the institutional review board at each participating institution.

The primary outcome in the present study is caregiver missed work to care for the child. Caregivers included parents, partners, or other family or friends. Missed work only pertained to caregivers who were employed at the time of the study; the outcome does not include days spent caring for the sick infant by caregivers who were unemployed. We investigated the associations between the primary outcome and recurrent wheeze and vitamin D supplementation.

Statistical analysis

Standard summary statistics were used to describe baseline characteristics. We used logistic regression with generalized estimating equations (GEE) fit and exchangeable covariance among same family members in all analyses. Two-sided Type I error of 0.05 was adopted for all tests and 95% confidence intervals of odds ratios were estimated. In Table 1, to assess association, we conducted univariate logistic regression GEE analyses with caregiver reported time off (yes or no) as the outcome, and a range of baseline variables considered univariately as the respective covariate. For analysis of the primary outcome, we then conducted a multivariate logistic regression GEE analysis, again with caregiver reported time off as the outcome, and included as covariates significantly associated variables from Table 1, as well as recurrent wheezing status and vitamin D randomization group. All statistical analyses were conducted using SPSS version 24 (IBM Corp) or SAS for Windows 9.4 (SAS Institute Inc).

Results

Of the 300 infants enrolled in the original D-Wheeze study, 277 participants were seen in follow-up and responded to the questionnaire at any timepoint. The response rates at each timepoint were 277/283 at 3 months, 272/282 at 6 months, 267/281 at 9 months, and 264/281 at 12 months. Among the questionnaire respondents, 93.2% were mothers, 3.7% were fathers, and 3.1% were grandparents per self-report. The characteristics of these infants included in this study are shown in Table 1. Univariate logistic regression analyses using caregiver time off as the outcome and each of the characteristics in Table 1 as the covariate showed that multiple births, other children <5 years old in the household, and mother employed for >6 months were significantly different between infants whose caregivers did and did not miss days off work to care for them.

Of children for whom follow-up questionnaires were completed, 147 (53.1%) infants had caregivers who took time off to provide care. Among those who missed work, the median was four missed days (IQR 2.0 – 13 days). Of this time off, 16.9% was sick leave or maternity/paternity leave, 5.9% was personal time paid for by the employer, 3.5% was vacation time, 58.9% was time off with no pay, and 4.6% was in a self-employment situation. The remainder did not know the type of time off or reported multiple types. The percentage of caregivers who took time off at the 3, 6, 9, and 12-month points were 21.4%, 17.6%, 25.8%, and 23.9%, respectively.

Unadjusted univariate logistic GEE regression analyses showed no significant difference in healthcare utilization for *non-respiratory* complaints between infants whose caregivers who took time off and infants whose caregivers did not take time off (Table 2). This includes visits to the pediatrician's office, emergency department (ED), and hospitalizations. Conversely, there was a significant difference in the odds for *respiratory-related* ED and hospital visits between infants whose caregivers did and did not miss days of work, with infants whose caregivers did miss days of work having an increased likelihood of respiratory-related ED visits and hospitalizations. Respiratory-related pediatrician visits were not significantly different between the groups.

Both multiple births and other children <5 years old in the household were significantly associated with caregiver missed work (Table 1). That is, both multiple births and other children <5 years old were associated with fewer missed days of work to care for the infant. Since having other children <5 years of age in the household includes siblings from the same gestation, only the variable of other children <5 years was used in the planned logistic regression GEE analysis. Maternal employment at >2 follow-up timepoints was also significantly associated with caregiver missed work, but this was not included in the GEE analysis because maternal employment status only captures the availability of a single caregiver to care for the sick infant, when in reality there may be multiple caregivers available. In this model, recurrent wheezing, randomization to the sustained vitamin D strategy, and having another child <5 years of age in the house were all significantly associated with caregiver missed work (Table 3).

Of those infants in the sustained vitamin D supplementation group, 62/140 (44.3%) had caregivers who reported missed days of work at any time-point, compared to 85/137 (62.0%) in the diet-limited randomization group. Figure 1 shows the distribution of reported missed days of work between caregivers of infants in the sustained supplementation group and caregivers of infants in the diet-limited group.

Parent-reported recurrent wheezing was reported in 98/277 (35.3%) of infants. Of the caregivers of infants with recurrent wheezing, 63/98 (64.3%) reported missed work at any time, compared to 84/179 (46.9%) of caregivers of infants with no recurrent wheezing. Figure 2 shows the distribution of missed days of work between caregivers of infants with recurrent wheezing, compared to caregivers of infants who did not report recurrent wheezing. Table 4 shows the distribution of missed days of work compared to number of wheezing episodes in one year.

Discussion

This secondary analysis of the D-Wheeze trial demonstrates a distinct and important burden of caregiver missed work in this group of black preterm infants without bronchopulmonary dysplasia. Recurrent wheezing was significantly associated with caregivers reporting missed work, suggesting that prematurity-associated wheezing is an important contributor. In addition, caregivers of infants randomized to sustained vitamin D supplementation were less likely to report taking time off from work to care for the infants, suggesting that this supplementation strategy may ameliorate family burden as well as infant wheezing.

Our findings support the hypothesized correlation between recurrent wheeze and caregivers reporting increased missed work. This correlation is strengthened by our finding that as number of wheezing episodes increases, the median number of missed days of work increases as well. Conversely, caregivers who did not need to take time off work to care for their infant likely had an infant who did not experience recurrent wheezing (Table 4). Additionally, we found that infants with caregivers who did take time off work to care for the infant had a significant increase in respiratory-related ED visits and hospitalizations, while non-respiratory pediatrician visits, ED visits, and hospitalizations did not significantly differ between the groups. These data suggest that caregiver time off was directly impacted by respiratory complaints, rather than other medically attended illnesses. We suspect that respiratory-related pediatrician visits did not differ significantly between the groups because black individuals have been shown to consistently utilize emergency departments and hospital outpatient centers over primary care facilities such as pediatrician's office (13).

From a clinical standpoint, our findings can be used to guide expectations of caregivers of premature infants. From a societal perspective, these findings underscore the impact of this common prematurity-associated morbidity. Other studies have reported 20 missed days of work for every 100 children with influenza (8) and 275 missed days of work in 313 children with viral illness in one year (6). Bronchiolitis, one of the most common viral respiratory tract infections in infants, accounted for 2 caregiver missed days of work during the bronchiolitis season from November to March (9), compared to our finding of 4 caregiver missed days of work due to prematurity-associated wheezing throughout the entire year.

Finally, this association also supports the construct validity of the wheezing question, which was based on the ISAAC questionnaire and was previously shown to be associated with medically attended illness and to have good test-retest validity in the population of infants born preterm (12, 14).

It is difficult to compare burden of missed work due to respiratory illness in premature and full-term infants because caregiver missed work in full-term infants has not yet been described in the literature. We suspect, however, that the burden is greater in premature infants for several reasons. First, preterm infants have a significantly higher risk of experiencing respiratory symptoms, with 32% of early preterm infants, 22% of moderate preterm infants, and only 13% of full-term infants experiencing respiratory symptoms during their first year of life in one study (15). Second, although both preterm and full-term infants experience a burden of respiratory disease, caregivers of premature infants experience greater productivity losses than caregivers of full-term infants when caring for an infant with RSV: lost productivity for caregivers of premature infants was an estimated \$3873.38 compared to \$1920.88 for caregivers of full-term infants (16). The caregiver burden faced by our cohort of premature infants is therefore likely to be greater than the burden of recurrent wheezing faced by full-term infants.

Sustained vitamin D supplementation was associated with fewer caregivers reporting taking time off to care for the infant, compared to diet-limited supplementation. The original D-Wheeze study demonstrated that sustained vitamin D supplementation is associated with a reduced risk of recurrent wheeze in black preterm infants (10). Therefore, we hypothesize that the primary mechanism of sustained vitamin D supplementation in reducing caregiver missed work is via the effect of vitamin D supplementation on reducing recurrent wheeze, but additional unmeasured impacts on infant health or caregivers' perceptions of their health cannot be ruled out.

In addition to family stress, caregiver missed work may represent meaningful lost income, as the majority of caregiver time off was unpaid. While this study did not directly calculate the economic losses associated with caregiver missed work, other studies would suggest this cost is notable. One study estimated that parental wage losses due to missed days of work is as great as 5,990 EUR in the first year of life for parents of extremely low birth weight premature infants (17), while another estimated that U.S. parental wage losses over a five-year period to care for children with asthma were as great as \$1.1 billion dollars (18). Both of these studies looked at caregivers of children with chronic conditions similar to prematurity-associated wheezing, so it is reasonable to assume the burden of caregiver missed days of work for prematurity-associated wheezing holds similar economic implications. For families from lower socioeconomic status especially, even only a few missed days of work could be very impactful. Future research should further quantify this burden.

Finally, we speculate the impact of prematurity-associated wheezing on caregiver work is likely even greater than reported here. Studies have shown that primary and intensive caregivers, i.e. providing >20 hours/week of childcare, are significantly more likely to be unemployed, more likely to cut back work hours, and more likely to quit a job due to

caregiving obligations than both non-intensive and non-caregivers (19, 20). This observation may explain our finding that caregivers with multiple births or multiple children under 5 are in fact less likely to take time off from work; these caregivers are less likely to be employed and less likely to work full time because multiple children increases the childcare burden. It is also possible that caregivers who reported taking significant time off work in the first three months of study enrollment subsequently needed to leave their employment situation to further care for their infant. In fact, our study noted a significant difference in employment status between mothers of infants whose caregivers did and did not take time off work, with infants whose caregivers did take time off having mothers who were more likely to be employed for >6 months. Although the mother represents just one caregiver, unemployment status of any caregiver obviates the need to take time off. Consequently, high rates of unemployment in the study population may artificially decrease the apparent family burden of prematurity-associated wheezing: while not employed, these caregivers still face significant productivity losses that contribute to the overall family burden of prematurity-associated wheezing. Future studies should work to better characterize the social networks of these families to understand how changing employment status in response to caregiving responsibilities affects caregiver missed days of work, as this represents another significant unmeasured family burden.

Limitations

The questions about caregiver time off have several limitations. First, the concept of missing work to care for a child versus choosing not to work for other reasons is subjective. Second, there is the possibility for inaccuracy in determining time off through self-report, both in determining number of days of missed work and in determining the reason for taking time off, such as time off due to infant wheezing or time off due to other medical concerns, such as vaccinations. Consequently, we could not assess data in roughly 10% of the infants due to contradictory information from the infant's caregivers regarding employment status and missed days of work. Nevertheless, despite some potential measurement bias in defining caregiver time off, which we worked to limit by excluding infants with contradictory data between caregivers, both recurrent wheezing and vitamin D supplementation were significantly associated with this outcome. Our analyses were not able to assess the burden faced by non-working caregivers or the burden of productivity losses during non-working hours, which may include reduced productivity due to the emotional or physical stress of caring for a sick infant. Similarly, we could not characterize the complex social networks of each family, which would help us better understand whether caregivers who did not take time off time work did so because they had access to more support. Furthermore, this study reported data on a very specific cohort – black infants without bronchopulmonary dysplasia – so the results may not be generalizable to other preterm populations, including black infants from higher socioeconomic classes than those of the infants included in our study. This study does demonstrate, however, that caregiver missed work can be significantly associated with both infant respiratory conditions and interventions, highlighting its importance as an outcome of interest in the medical care of preterm infants.

Conclusion

The families of black preterm infants without bronchopulmonary dysplasia enrolled in the D-Wheeze trial experienced a substantial impact of caregiver missed work, with 53.1% of caregivers reporting taking time off to care for their infants in the first year of life. An increased risk of missed work was associated with recurrent wheezing in the infants, suggesting that wheezing illnesses are important drivers of lost work time in this population. The number of caregivers reporting missed work was reduced with sustained vitamin D supplementation. Future research is needed to further describe this impact of illness and medical intervention in preterm infants on families.

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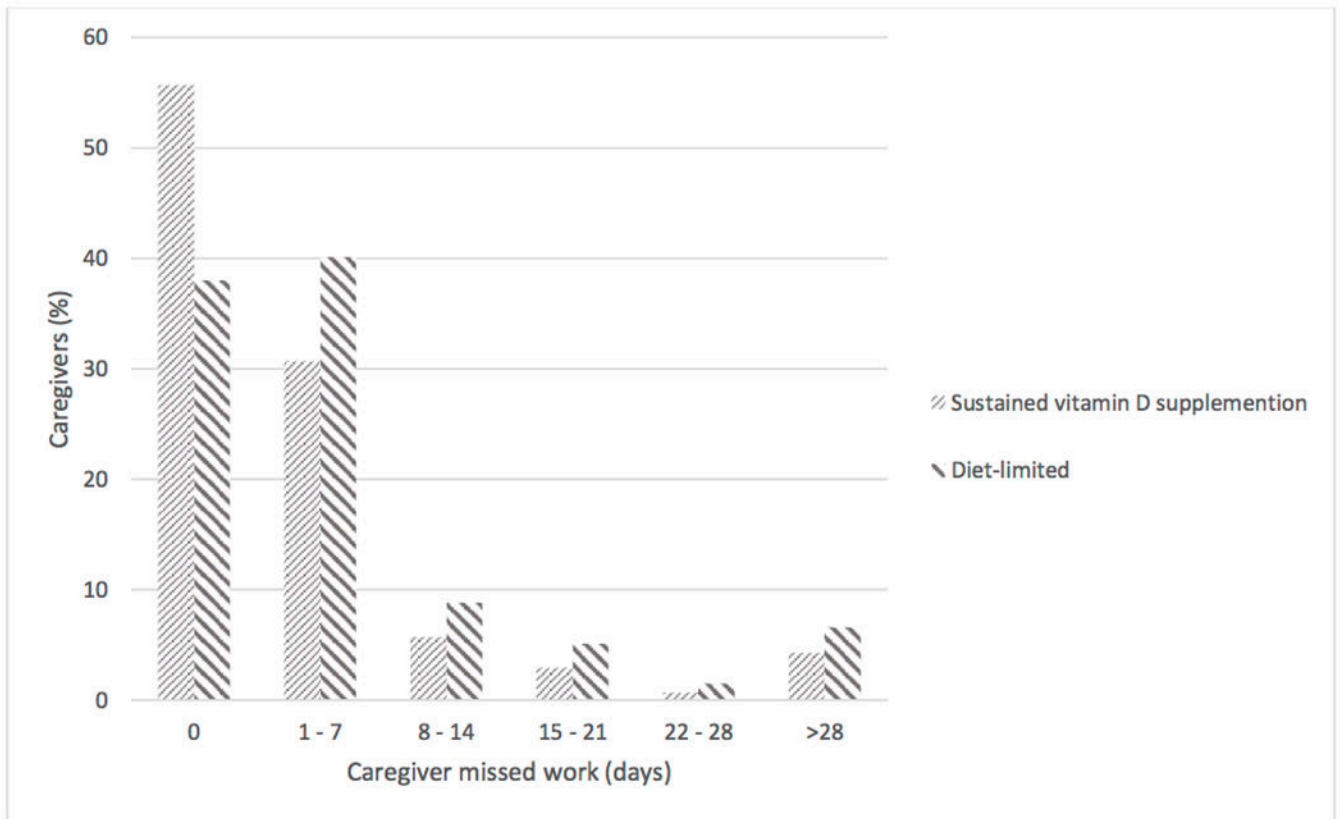


Figure 1. Percentage of caregivers of infants within the sustained vitamin D supplementation cohort (represented by thin lines) compared to percentage of caregivers of infants within the diet-limited vitamin D supplementation cohort (represented by thick lines) who missed the indicated days of work in one year to care for their child.

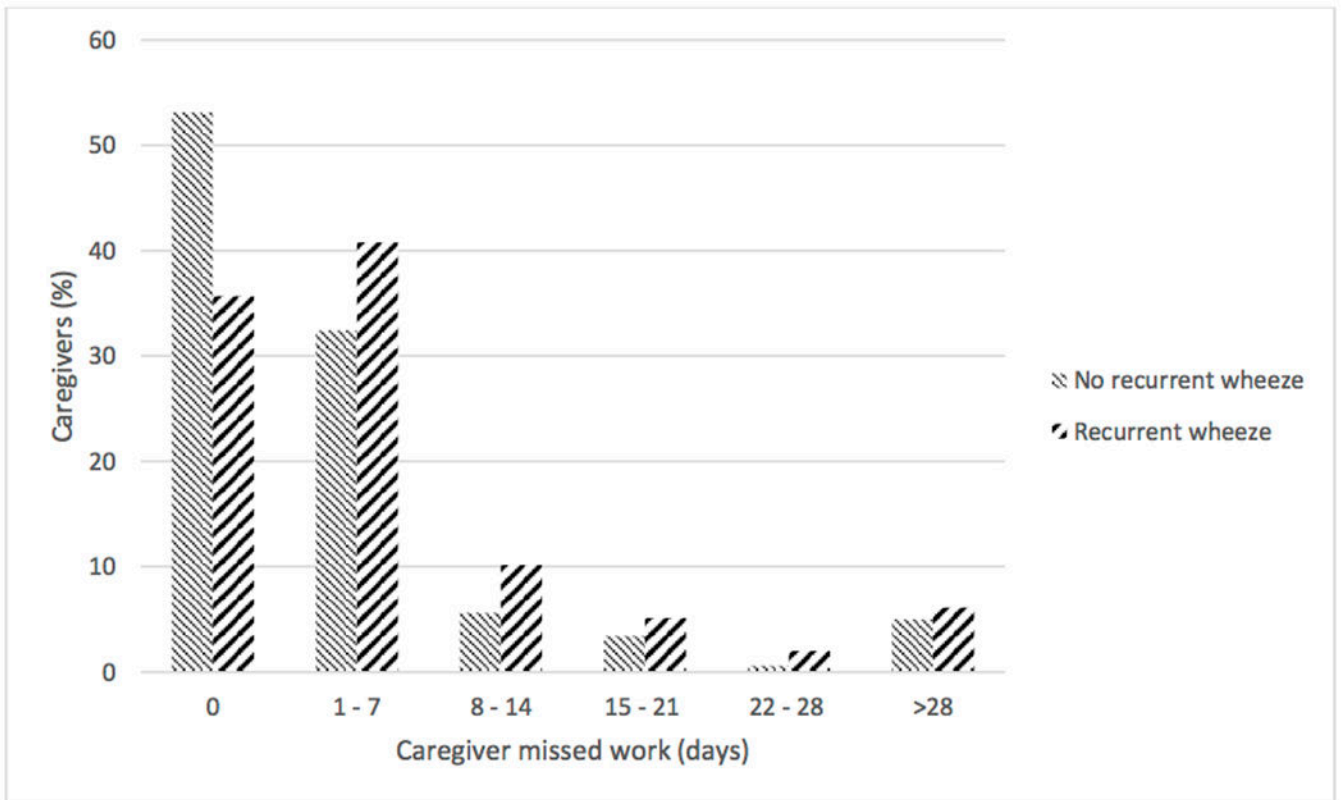


Figure 2. Percentage of caregivers of infants within the recurrent wheeze cohort (represented by thin lines) compared to percentage of caregivers of infants within the no recurrent wheeze cohort (represented by thick lines) who missed the indicated days of work in one year to care for their child.

Table 1.
Baseline characteristics.

Expressed as n/N (%) or Median (Interquartile Range).

Characteristic	Infants whose caregivers DID NOT miss days of work to care for infant	Infants whose caregivers DID miss days of work to care for infant	P-value
Infant	N= 130	N= 147	
Gestational age at birth, weeks	33.07 (31.96-35.29)	32.86 (31.43-34.86)	0.164
Gestational Age 28 to 33 weeks 34 to 36 weeks	77/130 (59.2%) 53/130 (40.8%)	97/147 (66.0%) 50/147 (34.0%)	0.363
Birth weight (kg)	1.89 (1.62-2.25)	1.80 (1.50-2.22)	0.310
Multiple birth	53/130 (40.8%)	36/147 (24.5%)	0.009
Male	61/130 (46.9%)	92/147 (62.6%)	0.342
Maternal age, years	27 (22-31)	24 (21-29)	0.140
Receiving maternal breast milk at randomization	89/130 (68.5%)	105/147 (71.4%)	0.405
Black race maternal	125/127 (98.4%)	140/145 (96.6%)	0.201
Black race paternal	129/130 (99.2%)	144/146 (98.6%)	0.676
Hispanic ethnicity maternal	8/129 (6.2%)	9/147 (6.1%)	0.505
Hispanic ethnicity paternal	7/130 (5.4%)	10/146 (6.8%)	0.525
Mother with greater than a high school degree	65/130 (50.0%)	71/147 (48.3%)	0.938
Father with greater than a high school degree	42/118 (35.6%)	45/135 (33.3%)	0.949
Mother employed for >6 months of the study	64/130 (49.2%)	100/146 (68.5)	0.001
Daycare planned	35/130 (26.9%)	45/147 (30.6%)	0.695
Other children <5 in the house	92/130 (70.8%)	76/147 (51.7%)	0.003
WIC enrollment ¹	124/127 (97.6%)	139/144 (96.5%)	0.653
Housing Status Owns or rents home Lives with family or friends or shelter	97/130 (74.6%) 33/130 (25.4%)	101/147 (68.7%) 46/147 (31.3%)	0.233
Insurance Status Private Insurance Public or No Insurance	13/130 (10.0%) 117/130 (90.0%)	16/147 (10.9%) 131/147 (89.1%)	0.952

Abbreviations: WIC, Women Infants and Children

¹WIC is a program that offers supplemental food, health care referrals, and nutrition education for low-income women and children

Table 2.
Comparison of healthcare utilization between infants whose caregivers did and did not take time off to care for the infant.

Expressed as n/N (%).

Characteristic	Infants whose caregivers DID NOT miss days of work to care for infant	Infants whose caregivers DID miss days of work to care for infant	P-value
Infant	N= 130	N= 147	
Any respiratory pediatrician visits	31/130 (23.8%)	65/147 (44.2%)	0.070
Any non-respiratory pediatrician visits	32/130 (24.6%)	53/147 (36.1%)	0.059
Any respiratory ED visits	50/130 (38.5%)	94/147 (63.9%)	0.000
Any non-respiratory ED visits	48/130 (36.9%)	82/147 (55.8%)	0.250
Any respiratory hospital visits	5/130 (3.8%)	33/147 (22.4%)	0.026
Any non-respiratory hospital visit	13/130 (10.0%)	28/147 (19.0%)	0.069

Table 3.

Association between caregiver missed work and recurrent wheezing, vitamin D supplementation strategy, and other children <5 in the household.

	Odds ratio	95% CI		P-value
		Lower	Upper	
Recurrent Wheeze	2.26	1.15	4.44	0.018
Sustained vitamin D supplementation	0.52	0.30	0.89	0.018
Other children <5 in the household	0.45	0.26	0.78	0.004

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Table 4.
Distribution of caregiver missed days of work in one year by frequency of wheezing episodes.

Expressed as Median (Interquartile Range).

	Number of Wheezing Episodes			
	0	1 - 2	3 - 5	> 5
Infant	N = 145	N = 64	N = 39	N = 29
Caregiver missed days of work	0 (0, 3)	1 (0, 4)	2 (0, 7)	6 (1,15)

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