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ORIGINAL ARTICLE

Cow's Milk Exposure and Asthma in a Newborn Cohort: Repeated Ascertainment Indicates Reverse Causation

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The effect of cow's milk consumption on childhood asthma has been debated for several years. This study attempts to provide further insight into this association through the use of a longitudinal study design. Newborns from parents with atopic history were recruited from Germany, Austria, and England ($n = 696$). For five repeated ascertainment, information was collected on cow's milk exposure, incidence of doctor-diagnosed asthma, and confounders. Generalized estimation equations, incorporating different models (concurrent, delayed, combined, and reverse causation), were used to determine this association. No association between cow's milk consumption and childhood asthma was found for the concurrent effects model (OR = 0.81, 95% confidence interval [CI]: 0.55, 1.20). In the delayed effects model, the direction of the association varied with time of follow-up. Thus, we stratified by period, which resulted in a significant protective delayed effect at 36 months (OR = 0.18, 95% CI = 0.06, 0.49). However, reverse causation negated this finding since the presence of asthma in prior months led to a reduction in further exposure to cow's milk (OR = 0.40, 95% CI = 0.16, 0.99). Hence, cow's milk consumption does not protect against childhood asthma. The apparent protection of cow's milk against asthma may result from parents of asthmatic children avoiding cow's milk, rather than actual prophylaxis.

Keywords asthma, cow's milk, children, reverse causation, epidemiology

INTRODUCTION

The prevalence of asthma and allergic disease has increased dramatically over the past two decades. The reasons for such an increase are unclear. Over this same period numerous reports have been published on the effect that cow's milk exposure can have on the prevalence of asthma in young children (1–14). The majority of these studies have suggested that cow's milk is a risk factor for the development of childhood asthma (1–7). However, the role of cow's milk on the development of asthma in children remains controversial. Some of the more recent studies have reported findings ranging from no effect of cow's milk consumption on asthma development to cow's milk exposure early in life being a protective factor against the development of childhood asthma (8–14).

The research described herein was stimulated by these controversial findings. The present study examines these associations in a cohort consisting of European newborns followed from birth to 3 years of age. Through the use of four modeling strategies (concurrent effect, 6-month delayed effect, combined effect, and reverse causation), and by taking into account the longitudinal nature of the data, our goal was to analyze the association between cow's milk consumption and the development of asthma. The concurrent effects model

was used to predict short-term effects of cow's milk on the development of childhood asthma by taking the cow's milk exposure during a given time interval (6 to 12 months) and relating it to the occurrence of asthma during the same period. The delayed model investigated the possibility of a postponed effect of cow's milk exposure on the occurrence of childhood asthma. For this model the cow's milk exposure from one period was related to the occurrence of asthma in the next survey period. The combined model investigated both the concurrent and delayed effects of cow's milk exposure simultaneously. Lastly, we used a reverse delayed model to investigate whether childhood asthma at one period could predict cow's milk exposure during the subsequent survey period. The idea of reverse causation stems from previous studies that investigated whether the reduction of exposure over time due to prior disease could generate a false protective association between outcome and exposure (15–17).

METHODS

Population

This cohort was assembled in 1997 and 1998 for the "Study on the Prevention of Allergy in Children in Europe" (SPACE) (18). The initial study was a multi-center, population-based, randomized controlled study of children at high risk of allergy. The research described here focuses on the newborn cohort, which was from Austria, Great Britain, and Germany. Before the initiation of the SPACE study, the local ethical committees at each of the study sites approved the working protocol of the research. During recruitment,

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informed consent was obtained from the parents of each newborn before data collection. Newborns were recruited for the SPACE study based on a positive history of atopy in their parents. A newborn was considered eligible for the study if one or both of the parents had either a positive skin prick test (SPT >3 mm) or specific serum immunoglobulin E (IgE > 0.7 PRU, SX1-Phadiotop, Kabi-Pharmacia, Sweden; or IgE >1.43 ML-Units/mL with the Magic-Lite method, ALK, Denmark and Ciba-Corning, Germany) for at least one allergen out of the panel of five aeroallergens tested (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, birch pollen, grass pollen, and cat dander). Specifics of the testing methods used above are described in detail elsewhere (18). These two sensitization testing methods were considered to be equivalent based on a study by Schuetze et al. (19). The only additional exclusion criteria that were used in our study were birth weights below 2,500 g and admission to a neonatal intensive care unit for longer than 7 days.

The parents of participating children were recruited before the birth of their child, thus eliminating the potential for recruitment biases after delivery. The enrollment process took place from April 1997 to June of 1998, yielding a total of 696 newborn participants who were then followed through August of 2001.

Exposure Ascertainment

Attempts were made to follow each of the newborn participants from birth to 36 months of age. Soon after the birth of a child, a short questionnaire was completed by the parents to ascertain information regarding their newborn, such as gender, birth weight, and current health status. At each of the 6-, 12-, 18-, 24-, and 36-month follow-up contacts the parents of each offspring were instructed to complete a more in-depth questionnaire dealing with a variety of exposures that their child may have experienced since birth regarding the living environment and feeding habits. Specific questions dealt with issues of passive smoking, doctor's diagnosis of lower respiratory tract infections (LRTI: yes-no), and consumption of different types of infant food (yes-no, start date, end date), such as breast milk, regular infant formula, hypoallergenic formula, and cow's milk. "In addition, we also reconstructed the history of pet exposure using information collected after birth and in five follow-up investigations. At birth we ask whether the parents had pets and what kind of pets, followed by the question of whether they ever had a pet in the house. In each consecutive investigation, we inquired whether they had obtained a new pet since the last survey. If yes, we then asked what kind of pet? We also asked the following: whether the parent had given up a pet since the beginning of the study, what kind of pet, and whether the child was regularly exposed to pets elsewhere in the respective period and if so by what pet." The questionnaires were developed so that they would obtain exposure information (food, pets, respiratory tract infections) since the previous survey to develop a complete record of exposure throughout the first 3 years of life.

Our focus was cow's milk exposure since its role in the development of asthma in children is controversial. Although formula may be based on processed cow's milk, we chose not to lump cow's milk exposure and use of formula and

hypoallergenic formula together. The reason for this choice is that the exposure to foreign proteins is likely to vary.

Outcome Ascertainment

The outcome of interest was doctor-diagnosed asthma in children. Information on asthma and wheezing was provided by parents at four follow-ups (12, 18, 24, and 36 months). Each questionnaire asked for information on new onset of asthma, new diagnoses, and wheezing during the interval since the last survey.

Data Analyses

Due to the longitudinal nature of the data, generalized estimating equation (GEE) models were applied to estimate the potential effects of cow's milk consumption on the occurrence of childhood asthma. We used the GEE model that applied a logistic regression approach, which accounts for within-subject effects. Additionally, the GEE model was capable of dealing with intermittent missing values by incorporating the "all available pairs" method, which uses data from all of the non-missing pairs in the development of the final model, thus not excluding all observations from one study subject due to the presence of one missing value (20). For each GEE model, an autoregressive working correlation matrix was invoked because the correlation between the repeated exposure and outcome measurements was a function of time. Additionally, to determine if significant losses to follow-up occurred over the entire study period, a GEE model was developed to see if any of the predictors were able to significantly account for the losses to follow-up that occurred during each of the study periods. All statistical analyses were performed using SAS software, version 8.2, specifically SAS PROC GENMOD (21). Odds ratios with 95% confidence intervals were estimated.

Both time-independent (e.g., gender) and time-dependent confounders (e.g., parental smoking) were analyzed. Potential confounders were identified in previous studies of the cow's milk-asthma association. The initial confounders included in the models were gender, history of parental atopy, passive smoking exposure, presence of LRTI, maternal education, season of birth, country of residence, pet exposure, intervention status (mattress covers and education), exposure to breast milk, and regular infant and hypoallergenic formula use. Confounders were divided into categories: Parental atopy was trichotomized into maternal atopy, paternal atopy, and both parents atopic, with paternal atopy as the reference group. Maternal education was divided into ≤ 10 years, 11–12 years, ≥ 13 years, with ≤ 10 years as the reference category. For birth weight three categories were used ($< 3,000$, $\geq 3,000$ – $< 4,000$, $\geq 4,000$ g) and two categories for exposure to passive smoking (yes-no). If the child's diet included breast milk, cow's milk, regular infant formula, or hypoallergenic formula in the prior observation period, the child's exposure was classified as positive for that type of diet and negative otherwise.

Modeling was used to determine the most parsimonious set of explanatory variables for the cow's milk-asthma association. A confounder was eliminated from the explanatory model when changes in the exposure coefficient estimates from the model with and without the potential confounding

variable were less than 10%. The modeling procedure was applied for the concurrent effect, 6-month delayed effect, combined effect, and reverse causation models. Each of these models was also stratified by follow-up period to investigate whether heterogeneity of effects existed over the course of the entire follow-up period. In addition, we ran models with and without LRTI infection to test whether LRTI infection could act an intervening variable between the child's diet and asthma.

RESULTS

Population characteristics for the risk factors used in the GEE models are presented in Tables 1 and 2. Out of the 696 total newborn participants, 50.3% ($n = 350$) were male and 49.7% ($n = 346$) were female (Table 1). Most (70.0%) of the newborns had birth weights between 3,000 and 4,000 g. Half of the study participants (54.2%) came from mothers with 11 to 12 years of education.

Regarding the time-dependent covariates, approximately 20 to 25% of the parents exposed their children to passive smoking (Table 2). The presence of lower respiratory tract infections (LRTI) in the newborn participants was also fairly consistent throughout the study period, ranging from 2.0 to 5.0%. The overall proportion of pet exposure varied in the five follow-up periods between 24 and 34%; however, pet exposure changed in individual households. Additionally, no children were breastfed after 24 months of age, with 12.2 decreasing to 3.2% of the newborns receiving breast milk in the first 24 months of age. The proportion of breastfeeding in this population of children of atopic parents is much lower than expected for this region of the world (22).

Cow's Milk Exposure up to Age 2

An infant was exposed to cow's milk in only 9.9% (69/696) of the study population by the 6-month follow-up (Figure 1); by 12 months 50.7% (15 + 338/696) had ever received cow's milk. After 12 months of age, the majority of the children continued to be exposed to cow's milk. In some children, after the initial exposure to cow's milk, consumption ceased, at least for a period of time (15 of 69 children after 6 months, and 45 of 338 after 12 months).

TABLE 1.—Study population characteristics.

Variable	Percentage ($n = 696$)
Gender	
Boy	50.3
Girl	49.7
Birth weight	
<3,000 g	19.4
≥3,000 g and <4,000 g	70.0
≥4,000 g	10.6
Season of birth	
Spring	26.9
Summer	28.7
Fall	22.1
Winter	22.3
History of parental atopy	
Maternal atopy	35.3
Paternal atopy	33.6
Both Parents atopic	31.1
Mother's education	
Normal (≤10 years)	22.8
Medium (11–12 years)	54.2
High (≥13 years)	23.0

TABLE 2.—Study population characteristics for repeated measurements.

Variable	6 months ($n = 696$) %	12 months ($n = 670$) %	18 months ($n = 625$) %	24 months ($n = 563$) %	36 months ($n = 553$) %
Passive smoking					
Yes	19.1	25.8	24.6	24.9	22.1
No	80.6	74.2	72.6	73.5	77.9
Missing	0.3	0.0	2.8	1.6	0.0
Lower respiratory tract infections					
Yes	2.0	3.6	5.0	7.1	3.8
No	92.1	94.6	91.5	87.6	93.7
Missing	5.9	1.8	3.5	5.3	2.5
Breastfeeding					
Yes	12.2	11.6	11.2	3.2	—
No	87.1	86.7	87.4	71.4	—
Missing	0.7	1.7	1.5	25.4	—
Regular infant formula					
Yes	40.1	50.6	29.1	13.5	—
No	46.4	45.7	68.5	58.6	—
Missing	13.5	3.7	2.4	27.9	—
Hypoallergenic formula					
Yes	34.6	35.1	14.7	6.4	—
No	47.6	52.4	69.6	65.5	—
Missing	17.8	12.5	15.7	28.1	—
Pet holding in the house					
Yes	32.3 [†]	33.9	24.6	24.3	27.3
No	67.5 [†]	66.1	74.7	73.9	72.5
Missing	0.1 [†]	0	0.6	1.8	0.2

Variables not ascertained at the 36-month follow-up period.

[†]For 6 months: determined at birth.

Occurrence of Asthma up to Age 3

When following the occurrence of asthma (Figure 2) the period prevalence varies from 2.2% at 6 months (15/696) to 4.0% (26/657) at 36 months. Figure 2 shows, for example, that of the 15 children who had doctor-diagnosed asthma at 12 months, 11 continued to have asthma at 18 months, and 4 were asthma-free, 3 of whom stayed asthma-free for the remainder of the study. A total of 36 children (5.6%) were diagnosed with asthma during the first 3 years of life, contributing 81 repeated observations of asthma (Figure 2).

Loss to Follow-Up

To investigate whether loss to follow-up was related to any of the predictors, we used a GEE model. Loss to follow-up was treated as a time-dependent outcome because some children re-entered the study after dropping out initially. Neither asthma nor any of the predictors ascertained in a preceding survey significantly accounted for the loss to follow-up (asthma: OR = 0.88, $p = 0.35$, 95% CI: 0.42, 1.63; cow's milk: OR = 1.18, $p = 0.80$, 95% CI: 0.72, 3.25).

Effect of Cow's Milk Exposure on Asthma Occurrence

The asthma concurrent effects model showed no association between cow's milk consumption and the prevalence of asthma (OR = 0.81, 95% CI: 0.55, 1.20, Table 3). However, the presence of LRTI was related to a significantly increased risk of asthma (OR = 4.06, 95% CI: 1.71, 9.68). Again, in the delayed effects model, cow's milk exposure was not associated with childhood asthma, whereas LRTI constituted a significant risk factor (Table 3). When combining both concurrent and delayed effects, similar results were obtained (data not shown). Also, excluding LRTI from the model did not change the odds ratios (Table 3). We additionally controlled for pet exposure. In the concurrent effect model, pet exposure

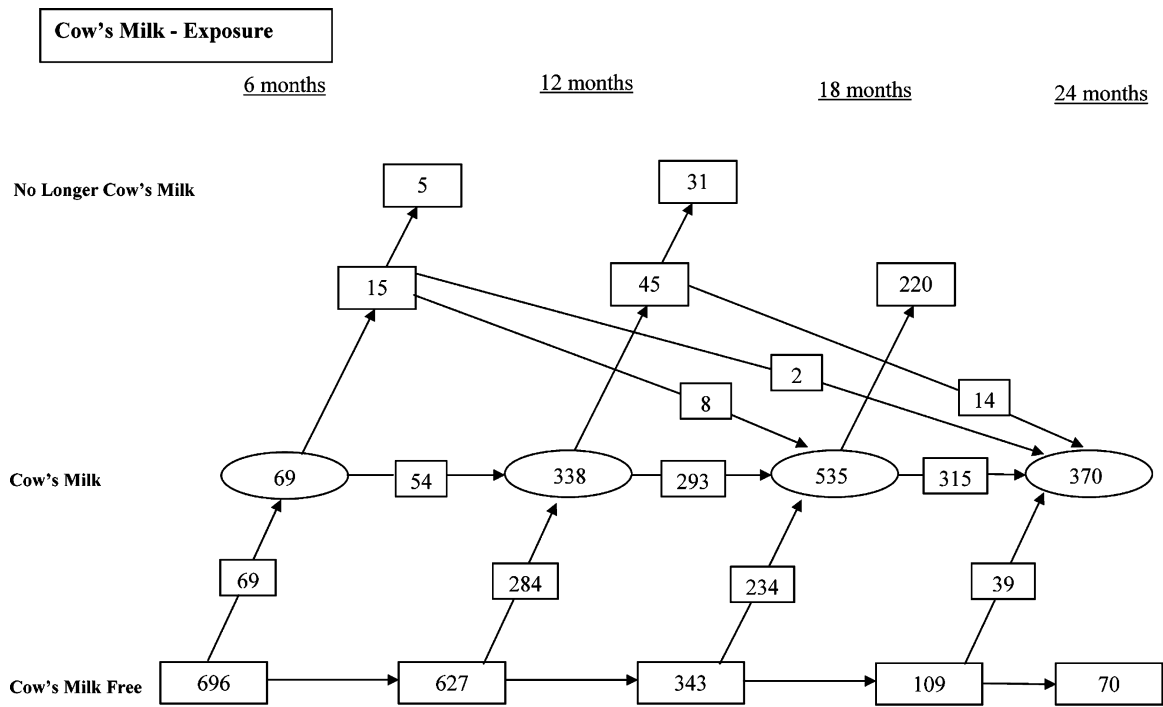


FIGURE 1.—Occurrence of cow's milk consumption in the SPACE study population over the entire study period. The bottom boxes signify the number of participants that were unexposed after each follow-up period. The middle ovals represent the participants who have the exposure at each follow-up. The upper boxes represent participants that had cow's milk exposure at one period then either never had it again or were exposed again in a future follow-up period.

was a significant risk factor for occurrence of asthma (OR = 1.80, 95% CI: 1.04, 3.11). However, the adverse effect disappeared in the delayed model (Table 3). Owing to variation in the direction of the associations with time of follow-up, the delayed model for asthma was strati-

fied by survey period. The stratification indicated that a delayed effect of cow's milk exposure, while controlling for confounders, was not a risk for asthma development at 12 and 18 months. However, at 24 and 36 months cow's milk exposure showed a protective effect, with this effect becoming

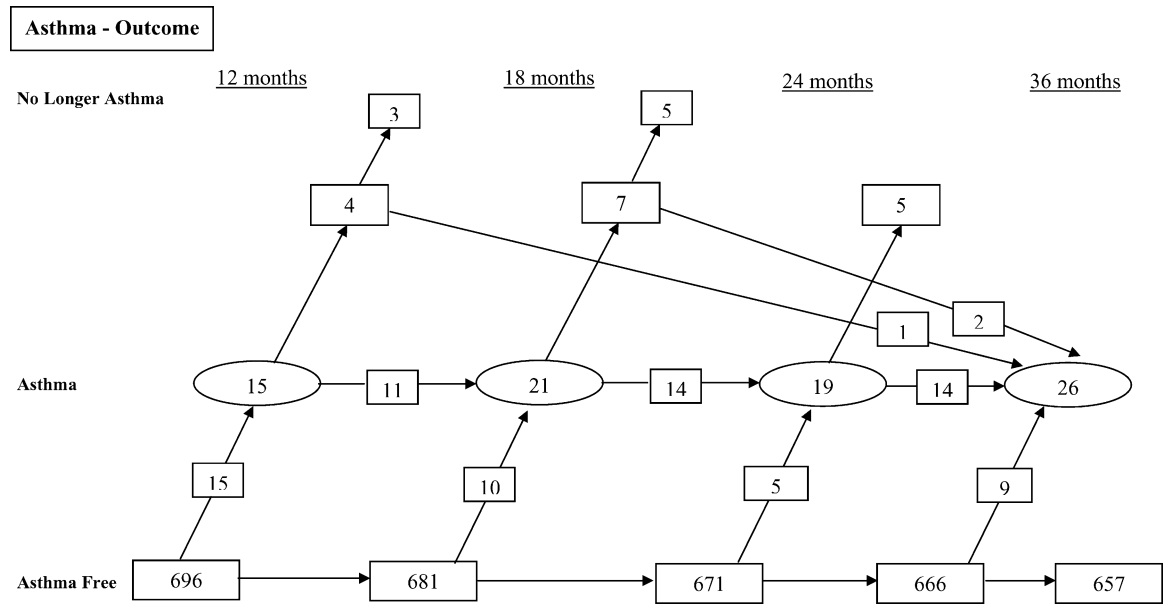


FIGURE 2.—Occurrence of asthma in the SPACE study population over the entire study period. The bottom boxes signify the number of children who were asthma-free after each follow-up period. The middle ovals represent the children who have asthma at each follow-up. The upper boxes represent children who no longer have asthma but may subsequently have a recurrence.

TABLE 3.—Results of the concurrent and delayed effects models for asthma.

Risk factor	Models with lower respiratory tract infections included [†]				Models without lower respiratory tract infections [†]			
	Concurrent effects model (<i>n</i> = 2,242 observations from 696 participants)		Delayed effects model (<i>n</i> = 2,149 observations from 696 participants)		Concurrent effects model (<i>n</i> = 2,137 observations from 672 participants)		Delayed effects model (<i>n</i> = 2,049 observations from 672 participants)	
	Odds ratio	95% CI	Odds Ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Cow's milk	0.81	(0.55, 1.20)	0.94	(0.64, 1.28)	0.75	(0.48, 1.17)	0.79	(0.56, 1.13)
Lower respiratory tract infections	4.06	(1.71, 9.68)	3.43	(1.36, 8.70)	—	—	—	—
Regular infant formula	0.67	(0.35, 1.30)	0.65	(0.33, 1.28)	0.50	(0.22, 1.14)	0.47	(0.21, 1.06)
Hypoallergenic formula	0.51	(0.29, 0.90)	0.50	(0.27, 0.92)	0.55	(0.29, 1.03)	0.47	(0.23, 0.99)
Pet exposure	1.80	(1.04, 3.11)	0.69	(0.39, 1.24)	1.83	(1.02, 3.31)	0.68	(0.36, 1.29)

[†]Controlling for gender, parental history of atopy, passive smoking exposure, country of residence, and maternal education.

statistically significant (OR = 0.18, 95% CI = 0.06, 0.49) at the 36-month follow-up period (Figure 3).

Effect of Asthma on Cow's Milk Exposure

A reverse causation model was developed to see whether asthma status in a preceding period changes cow's milk exposure in the next survey period. The model indicated that the presence of asthma was negatively associated with cow's milk exposure at the next follow-up period (OR = 0.40, 95% CI: 0.16, 0.99; Table 4), consistent with the notion that the presence of asthma in the child caused parents to stop providing cow's milk to their offspring. The reverse causation model was also stratified by survey period to determine if the direction of the associations varied with the time of follow-up, but no such variations were present (data not shown).

DISCUSSION

No significant effects of cow's milk exposure were found for asthma occurring in the same follow-up period. When investigating the delayed models stratified by follow-up period, it was discovered that cow's milk exposure at 6 and 12 months showed a nonsignificant trend towards more asthma 6 months later. In contrast, the findings for cow's milk exposure at 18 and 24 months suggested marginal protection for asthma at 24 and 36 months of age. However, a reverse causation model provided insight into why protective effects were obtained for the 24 to 36 month delayed effects model:

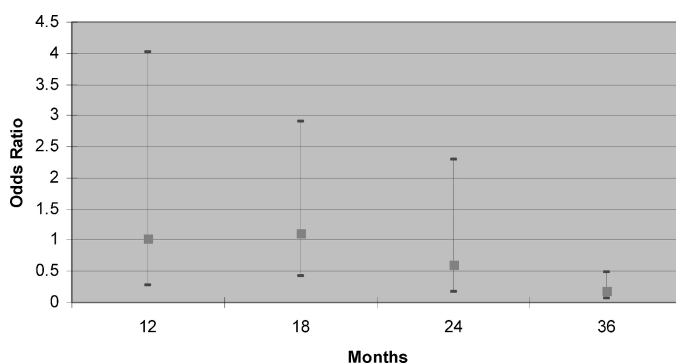


FIGURE 3.—Estimated odds ratios (with 95 percent confidence limits) for the delayed model regarding the effect of cow's milk consumption on the development of childhood asthma, stratified by survey period.

The analysis showed that prior asthma was significantly associated with a reduction in cow's milk consumption. For example, it is likely that parents stop feeding their children cow's milk after their child is diagnosed with asthma. As a consequence, children with asthma have less cow's milk consumption leading to the false impression that cow's milk protects against the development of asthma. These results could also be due to the fact that a physician's diagnosis of asthma may be accompanied by a recommendation to avoid certain foods, such as cow's milk, that could influence the further development of asthma (23).

Our results are based on parental reports of doctor-diagnosed asthma. Prior studies have shown that this approach to determining asthma is specific, but, for instance, compared to wheezing, less sensitive (24, 25). To investigate whether our findings would differ when using a more sensitive outcome, we also analyzed delayed effects and reverse causation using parental reports of wheezing. The results indicated that wheeze provided similar findings to that of the asthma modeling, but these results did not gain statistical significance. In addition, children with wheezing were more likely to be diagnosed with asthma compared to non-wheezers (at 12 months: prevalence ratio 13.37; 18 months: prevalence ratio 5.71; 24 months: prevalence ratio 7.63; 36 months: prevalence ratio 6.48). Hence, the two characterizations, asthma and wheezing, produce similar results. However, the doctor's intervention may explain the stronger effect of the reverse causation for asthma.

To investigate whether discontinuing participation may have introduced a bias, we analyzed whether asthma or cow's milk exposure ascertained in a preceding survey influenced parents to temporarily or permanently withdraw from the study. Neither variable was significantly associated with the observed loss to follow-up. Hence, it is unlikely that either

TABLE 4.—Reverse causation: asthma as predictor of cow's milk exposure in the next period (*n* = 1,735 observations from 696 participants).

Parameter	Odds ratio [†]	(95% CI)
Asthma		
Yes	0.40	(0.16, 0.99)
Parental atopy		
Mother atopic	1.18	(0.83, 1.66)
Both Parents atopic	1.18	(0.85, 1.62)
Mother's education		
High (≥ 13 years)	1.56	(1.01, 2.43)
Medium (11–12 years)	1.27	(0.89, 1.80)

[†]Controlling for country of residence.

non-participation in one survey or permanently leaving the study has changed the composition of the cohort in such a way that would have biased the reported associations between cow's milk and asthma.

Our decision not to collapse cow's milk, formula, and hypoallergic formula into one variable is supported by skin prick test results and determination of specific IgE conducted at 12 months of age (18). Use of any formula was related to a lower incidence of sensitization (4.4% [22/504] compared to 9.7% [11/113], $p = 0.02$). Conversely, cow's milk exposure showed no pattern of association: 6.2% [20/321] in children with exposure compared to 5.0% [14/280] without. All children sensitized to milk allergen were exposed to solid food before age 12 months.

Besides the cow's milk exposure variable, several of the other known risk factors for childhood asthma also showed significant associations in the repeated measurement models. For instance, having a history of atopy in both parents (as opposed to only one parent or no parents with a history of atopy) was associated with a 5- to 10-fold increase in the risk of childhood asthma over the first 3 years of life (data not shown). The presence of LRTI early in life was also related to a significant increase in the risk of childhood asthma (Table 3). In addition, whether the participant was part of the intervention group had no effect on the investigated associations and was eliminated in the modeling procedure. This finding supports a study by Horak et al. who also reported that the intervention status of the newborn cohort of the SPACE project had little or no effect on asthma or other allergic disease (26). Current pet exposure was associated with a higher occurrence of asthma in the repeated measurement models (Table 3). However, the adverse effect disappeared when we used pet exposure of the preceding investigation as a predictor. We also investigated the two more prevalent type of pets, namely dogs and cats. There were no substantial differences.

One limitation of this study is that participants received follow-up only until 3 years of age. It has long been known that the development of asthma may take longer than the first 3 years of life. Further, it has also been noted that even if asthma occurs in the first few years of life it does not necessarily follow that it will be present, for example, at 10 years of age or beyond (27). Another limitation is that within the individual follow-up periods of 6 to 12 months, no additional information was collected on when symptoms and diagnoses occurred for the first time.

In addition, we do not have information about day-care attendance in this group of children. However, due to paid maternal leave in most European countries, day-care attendance is infrequent in children below age 3. Further, there is no suspicion that day-care attendance would confound for the cow's milk—asthma association.

In each follow-up, the project collected specific information on the introduction of solid food such as baby rice, other cereals, hen's egg, pureed fruits or vegetables, instant baby food, and an open category for other food. For each item, we asked for child's age (month) of introduction. We combined this information into one variable "month of first solid food" (data not presented). This variable did not confound the cow's milk—asthma association.

The design of our study derives strength from the use of repeated measurements taken over the first 3 years of life, thus

enabling within-subject associations to be accounted for and increasing the power of the study results. Another strength of this study was that at least one of the parents of each participant had a history of atopy. This allowed us to investigate the effect of cow's milk consumption in a group that was already at high risk for the development of asthma.

With the availability of both repeated outcome and exposure measurements, our cohort design facilitated the investigation of the cow's milk-asthma association from exposure to outcome (forward causation), as well as from outcome to exposure (reverse causation). We believe that by being able to include a reverse causation analysis we have provided a more accurate explanation for the cow's milk-asthma association.

Our study indicates that reverse causation can adequately account for the cow's milk-asthma association. We are aware of biological mechanisms that have been proposed to explain this association. For example, some studies have proposed the direct and indirect effect of proteins and polyunsaturated fatty acids in cow's milk on the development of asthma (28–33). Since our findings indicate reverse causation, there is no need to invoke such biological explanations.

In conclusion, our study has revealed the possibility that time-dependent risk factors may produce false findings. Factors such as cow's milk exposure, pet keeping, and parental smoking can be influenced and changed, specifically, as a reaction to diseases, and thus may lead to a distortion in the assessment of behavior-related risks. Further, our results suggest that future studies need to consider the possibility of reverse causation and that this bias should be more carefully assessed in publications dealing with behavioral risk factors.

REFERENCES

1. Schonberger HJ, Maas T, Dompeling E, Pisters J, Sijbrandij J, van der Heide S, Knottnerus AJ, van Weel C, van Schayck OP. Environmental exposure reduction in high-risk newborns: where do we start? *Ann Allergy Asthma Immunol* 2003; 91:531–538.
2. Ram FS, Ducharme FM, Scarlett J. Cow's milk protein avoidance and development of childhood wheeze in children with a family history of atopy. *Cochrane Database Syst Rev* 2002;CD003795.
3. Chandra RK. Five-year follow-up of high-risk infants with family history of allergy who were exclusively breast-fed or fed partial whey hydrolysate, soy, and conventional cow's milk formulas. *J Pediatr Gastroenterol Nutr* 1997; 24:380–388.
4. Kaufman HS, Frick OL. The development of allergy in infants of allergic parents: a prospective study concerning the role of heredity. *Ann Allergy* 1976; 37:410–415.
5. Chandra RK. Prospective studies of the effect of breast feeding on incidence of infection and allergy. *Acta Paediatr Scand* 1979; 68:691–694.
6. Johnstone DE, Dutton AM. Dietary prophylaxis of allergic disease in children. *N Engl J Med* 1966; 274:715–719.
7. Glaser J, Johnstone DE. Prophylaxis of allergic disease in newborn. *JAMA* 1953; 153:620.
8. Van Asperen PP, Kemp AS, Mellis CM. Relationship of diet in the development of atopy in infancy. *Clin Allergy* 1984; 14:525–532.
9. Hattevig G, Kjellman B, Sigurs N, Björkstén B, Kjellman NI. Effect of maternal avoidance of eggs, cow's milk and fish during lactation upon allergic manifestations in infants. *Clin Exp Allergy* 1989; 19:27–32.
10. Poysa L, Korppi M, Remes K, Juntunen-Backman K. Atopy in childhood and diet in infancy. A nine-year follow-up study. I. Clinical manifestations. *Allergy Proc* 1991; 12:107–111.
11. Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study

- of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995; 95:1179–1190.
12. Lindfors ATB, Danielsson L, Enocksson E, Johansson SG, Westin S. Allergic symptoms up to 4–6 years of age in children given cow milk neonatally. *Br Med J* 1992; 47:207–211.
 13. Wijga AH, Smit HA, Kerkhof M, de Jongste JC, Gerritsen J, Neijens HJ, Boshuizen HC, Brunekreef B; PIAMA. Association of consumption of products containing milk fat with reduced asthma risk in pre-school children: the PIAMA birth cohort study. *Thorax* 2003; 58:567–572.
 14. Riedler J, Braun-Fahrlander C, Eder W, Schreuer M, Waser M, Maisch S, Carr D, Schierl R, Nowak D, von Mutius E; ALEX Study Team. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet* 2001; 358:1129–1133.
 15. Mattes J, Karmaus W. The use of antibiotics in the first year of life and development of asthma: which comes first? *Clin Exp Allergy* 1999; 29:729–732.
 16. Cullinan P, Harris J, Mills P, Moffat S, White C, Figg J, Moon A, Newman Taylor AJ. Early prescriptions of antibiotics and the risk of allergic disease in adults: a cohort study. *Thorax* 2004; 59:11–15.
 17. Greenland S, Brumback B. An overview of relations among causal modelling methods. *Int J Epidemiol* 2002; 31:1030–1037.
 18. Halmerbauer G, Gartner C, Schierl M, Arshad H, Dean T, Koller DY, Karmaus W, Kuehr J, Forster J, Urbanck R, Frischer T; SPACE Collaborative Study Team. Study on the Prevention of Allergy in Children in Europe (SPACE): allergic sensitization at 1 year of age in a controlled trial of allergen avoidance from birth. *Pediatr Allergy Immunol* 2003; 14:10–17.
 19. Schuetze G, Storm van's Gravesande K, Sparhold S, Frischer T, Kuehr J. Comparison between serial skin-prick tests and specific serum immunoglobulin E to mite allergens. *Pediatr Allergy Immunol* 1999; 10:138–142.
 20. Stokes ME, Davis CS, Koch GG. Categorical Data Analysis Using the SAS System. Cary, NC: SAS Institute 2004;413–424.
 21. SAS Institute. SAS/STAT Software. Cary, NC: SAS Institute, Inc., 2001.
 22. Grummer-Strawn LM, Mei Z. Does breastfeeding protect against pediatric overweight? Analysis of longitudinal data from the Centers for Disease Control and Prevention Pediatric Nutrition Surveillance System. *Pediatrics* 2004; 113:e81–86.
 23. American Academy of Pediatrics Committee on Nutrition: The use of whole cow's milk in infancy. *Pediatrics* 1992; 89:1105–1109.
 24. Henriksen AH, Holmen TL, Bjerner L. Gender differences in asthma prevalence may depend on how asthma is defined. *Respir Med* 2003; 97:491–497.
 25. von Mutius E, Fritzsche C, Weiland SK, Roll G, Magnussen H. Prevalence of asthma and allergic disorders among children in united Germany: a descriptive comparison. *Br Med J* 1992; 305:1395–1399.
 26. Horak F, Matthews S, Ihorst G, Arshad SH, Frischer T, Kuehr J, Schwieger A, Forster J; The SPACE Study Group. Effect of mite-impermeable mattress encasings and an educational package on the development of allergies in a multinational randomized, controlled birth-cohort study-24 months results of the Study of Prevention of Allergy in Children in Europe. *Clin Exp Allergy* 2004; 34:1220–1225.
 27. Kurukulaaratchy RJ, Fenn M, Matthews S, Arshad SH. Characterization of atopic and non-atopic wheeze in 10 year old children. *Thorax* 2004; 59:563–568.
 28. Asero R, Mistrello G, Roncarolo D, Amato S, Caldironi G, Barocci F, van Ree R. Immunological cross-reactivity between lipid transfer proteins from botanically unrelated plant-derived foods: a clinical study. *Allergy* 2002; 57:900–906.
 29. Azofra J, Lombardero M. Limpet anaphylaxis: cross-reactivity between limpet and house-dust mite *Dermatophagoides pteronyssinus*. *Allergy* 2003; 58:146–149.
 30. Ragno V, Giampietro PG, Bruno G, et al. Allergenicity of milk protein hydrolysate formulae in children with cow's milk allergy. *Eur J Pediatr* 1993; 152:760–762.
 31. Salem N, Simopoulos A, Galli C, Lagarde M, Knapp HR, eds. Fatty acids and lipids from cell biology to human disease. 1996; 31(suppl):S1–S326.
 32. Woods RK, Raven JM, Walters EH, Abramson MJ, Thien FC. Fatty acid levels and risk of asthma in young adults. *Thorax* 2004; 59:105–110.
 33. Zeyda M, Szekeres AB, Saemann MD, Geyereggar R, Stockinger H, Zlabinger GJ, Waldhausl W, Stulnig TM. Suppression of T cell signaling by polyunsaturated fatty acids: selectivity in inhibition of mitogen-activated protein kinase and nuclear factor activation. *J Immunol* 2003; 170:6033–6039.