Partially Hydrolyzed 100% Whey Protein Infant Formula and Reduced Risk of Atopic Dermatitis: A Meta-analysis

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ABSTRACT

Objective: A reduced risk of atopic dermatitis (AD) among healthy infants who received 100% whey protein partially hydrolyzed formula (PHF-W) compared with intact protein cow's milk formula (CMF), has been reported in several studies. To validate these observations and estimate the magnitude of this potential association with greater statistical precision, we conducted a meta-analysis of clinical trial and intervention studies.

Materials and Methods: A total of 18 articles representing 12 independent study populations met our inclusion criteria.

Results: A statistically significant 44% (summary relative risk estimate [SRRE] = 0.56, 95% confidence interval 0.40–0.77) reduced risk of atopic manifestations, which included AD, was found among infants receiving PHF-W compared with infants receiving CMF. In a subanalysis of 4 studies that reported results specifically for AD and that were considered of superior methodological quality, the incidence of AD was reduced by 55% (SRRE = 0.45, 95% confidence interval 0.30–0.70).

Conclusions: Regardless of study design, infant population, follow-up time, or study location, individual study findings were consistent because a reduced incidence of AD was reported in all of the reviewed studies. Exclusive breast-feeding should be encouraged as the standard for infant nutrition in the first months of life. For infants who are not exclusively breast-fed, feeding with PHF-W instead of CMF reduces the risk of AD in infants, particularly in infants with a family history of allergy.

Key Words: allergy, atopic dermatitis, infant formula, meta-analysis, nutrition

(*JPGN* 2010;50: 00–00)

Atopic dermatitis (AD), often referred to as eczema, is a chronic skin disease characterized by pruritic, inflamed skin (1–3). AD is the most common chronic skin disease in children because approximately 20% of the infants and young children experience symptoms of AD and >15 million people in the United States are estimated to be affected (1). The incidence of AD has steadily increased in the past 5 decades, particularly in developed countries (4).

Although the specific cause or causes of AD are unknown, a combination of genetic and environmental factors likely plays significant roles in the pathogenesis of disease. In a large multivariate regression analysis, Moore et al (2) examined several pre- and perinatal factors that may be associated with predicting AD during the first 6 months of life, and the authors found that family history of atopy, black and Asian race/ethnicity, male sex, and higher gestational age at birth were associated with increasing the risk of AD in the United States. Evidence regarding maternal diet during pregnancy and the subsequent development of atopic disease in infants has been equivocal (3).

Breast-feeding may confer a protective effect because studies have shown a reduced incidence of AD among infants who were exclusively breast-fed (3,5). In a recent meta-analysis of observational studies, breast-feeding was not significantly associated with a reduced risk of AD across all of the studies, although when infants who were breast-fed were compared with infants receiving conventional formula, a statistically significant 30% reduced risk of AD was observed (6). Although not all AD can be directly associated with specific allergens, the most common food allergens associated with AD are cow's milk proteins, which also constitute the most common protein source provided to infants who do not exclusively breast-feed. Several formulas have been developed and used for infants who are not exclusively breast-fed in an effort to decrease the risk of allergy associated with cow's milk protein. These formulations consist of protein that has been hydrolyzed by enzymatic or other means to decrease their potential for allergenicity.

Chemical and enzymatic hydrolysis reduce the molecular weight and the peptide size of cow's milk protein (7), thus potentially attenuating the allergenicity of the proteins. Hydrolyzed infant formulas have lower-molecular-weight proteins than cow's milk formula (CMF), and can decrease potentially sensitizing allergenic determinants. It has also been suggested that these proteins processed by the gut-associated lymphoid tissue may induce oral tolerance without sensitization (7). Some hydrolyzed formulas, particularly extensively hydrolyzed protein formulas, have been developed to manage cow's milk protein allergy and digestive disorders, and may also reduce allergy risk in healthy infants. However, their nutritional profile is not designed for use as a routine formula in healthy infants, limiting their application and broad use as a prevention strategy in the majority of the population. In contrast, partially hydrolyzed formulas have nutrient profiles intended for routine use in healthy infants, although an adequate comprehensive assessment of their efficacy in allergy risk reduction is lacking, and are thus the focus of this meta-analysis.

The potential benefit of a hydrolyzed formula in allergy prevention may be affected by 3 factors: protein source (eg, cow

Received July 27, 2009; accepted November 21, 2009.
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This work was partially funded by Nestlé (Dr Alexander only); however, Dr Alexander has no financial interests or economic incentives pertaining to Nestlé Corporation. Nestlé did not contribute to the data acquisition, writing, analysis, or interpretation of research findings. All of the data included in the present article were extracted from peer-reviewed published articles, and all of the analyses performed are transparent and reproducible. Dr Cabana received no financial support for his contribution to the writing and completion of the present article.
Copyright © 2010 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
DOI: 10.1097/MPG.0b013e3181cea52b

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casein, cow whey, or combinations thereof), method of hydrolysis (eg, type of enzyme(s) used, temperature, pH), and degree of hydrolysis. Therefore, the effect of such products can be adequately demonstrated only by randomized controlled clinical trials or well-conducted intervention follow-up studies with each specific formulation. Previous meta-analyses (8) and qualitative reviews (3) have conducted evaluations based on the combination of products with varying protein sources and/or methods of hydrolysis. Thus, interpreting results from these assessments is difficult and the results may not correctly estimate the potential effect of specific types of protein sources, degree, or methods of hydrolysis. Indeed, in a Cochrane Collaboration review of hydrolyzed formula and allergy prevention, a nonsignificant reduced incidence of eczema was reported in an analysis of 6 studies (8). To update the state of the science, we conducted a comprehensive meta-analysis of 18 publications representing 12 independent study populations to specifically estimate the magnitude of AD risk reduction among infants fed 100% whey protein partially hydrolyzed formula (PHF-W) compared with infants fed intact protein CMF.

MATERIALS AND METHODS

Study Identification

We conducted a literature search through April 2009 using the bibliographic database MEDLINE, specifying the following terms: [infant formula] and [allergy] or [allergic manifestations] or [atopic dermatitis] or [eczema]. In addition, the bibliographies of recent reviews and individual published articles were assessed to identify potentially relevant studies of infant formula and AD that were not identified through electronic searches. A supplemental search was conducted using Embase; however, no additional relevant studies were identified using this search engine.

Clinical and observational epidemiologic peer-reviewed studies that met the following criteria were included: compared healthy infants who received 100% PHF-W with infants who received intact protein cow's milk formula; reported results for AD (infant eczema) or an outcome that included AD (eg, variable labeled ''skin symptoms'' in infants that included AD); expressed results in the form of a risk estimate (eg, relative risk [RR], odds ratio [OR]) with an associated measure of variability (ie, confidence intervals [CIs]); or provided incidence data in a manner such that risk estimates and variability could be calculated. Studies that only reported findings for a general category of ''allergy'' or ''allergic manifestations'' were obtained, although we focused our analyses on the incidence of AD, as discussed below.

Of the studies identified as meeting the above criteria, 4 were excluded. One study did not specify the protein source used (9) and 1 study used a partially hydrolyzed casein/whey protein hydrolysate for which there were no other trials available, and thus provided insufficient data for a meta-analysis of this protein source (10). One study was excluded that restricted its analysis to preterm infants (11). One study (12) was excluded from our analyses based on unresolved concerns regarding data integrity. A total of 18 articles, representing clinical trial and intervention studies of 12 independent study populations and comprising approximately 1000 infants, were included in subsequent analyses (Table 1) (13–27). If multiple studies examined the same infant population, we extracted data from the most recent publication and/or the most comprehensive analysis.

Data Extraction and Classification of Studies

A heterogeneous group of feeding methods (eg, conventional formula, extensively and partially hydrolyzed formula, breastfeeding) and allergy-related outcomes (eg, AD, asthma, rhinitis) were evaluated both within and across the individual studies. Therefore, we extracted data specific to our primary evaluation, which was to examine the association between PHF-W and AD compared with intact protein CMF.

Estimates of risk (ie, RR and OR) and associated 95% CIs were extracted from the publications that represented distinct study populations. In most studies (13–21), RR estimates were not reported; however, incidence data were available that allowed for the calculation of risk estimates and CIs. De Seta et al (16) reported RRs and CIs in their study; we recalculated associations because the CIs reported in their publication were not symmetric around the RR. Chirico et al (15) reported 0 cases of eczema at 6 months among the PHF-W group and Vandenplas et al (21) reported 0 cases of atopic dermatological symptoms at 4 months among PHF-W-fed infants. In the study by D'Agata et al (22), only a bar chart of allergic symptoms was reported among the feeding categories, so we were unable to extract data from the present study. The present study was reviewed qualitatively but was not included in our meta-analysis.

We extracted data pertaining to multiple follow-up periods (if such data were available) to evaluate the temporal association between type of formula and AD. Specifically, incidence rates of AD at or near 6 months of age, 12 months of age, or periods >12 months of age were extracted and/or calculated. In addition, we modeled the risk of AD based on data extracted from follow-up periods that most closely captured the formula administration time frame, where applicable. For example, if infants were fed exclusively PHF-W for the first 4 months of life with dietary restrictions and fed without restrictions after 4 months of life, and associations for AD were reported for 6-, 12-, 18-, and 24-month intervals, then we included data for the 6-month association for this particular model. This analytical model was created to reduce the potential for bias or confounding by the introduction of foods that may be associated with atopic manifestations. Any bias that may result from the introduction of solid foods would likely be nondifferential (ie, bias associations closer to the null value of 1); thus, the magnitude and direction of summary associations after 6 months of age are clinically relevant. In addition, we created meta-analysis models that allowed us to generate associations after the first year and beyond. These models were constructed to evaluate the prolonged preventive effect of feeding with PHF-W.

After an extensive critical review of all of the studies that met our criteria for inclusion, we systematically identified 6 studies (13,14,18,23–25) representing 4 independent infant populations as being methodologically superior and more informative in evaluating the relation between infant formula (PHF-W vs intact protein CMF) and risk of AD. The studies were distinguished from the other studies in that they used established clinical criteria to define AD (1) and evaluated AD as an independent disease endpoint, exhibited better control of potential bias and confounding, presented transparent methodology, and compared the incidence of AD among infants fed PHF-W with infants fed intact protein CMF. We conducted a separate meta-analysis on these studies. In addition, we conducted a sensitivity analysis using only data from studies that incorporated random allocation of study formula into their design (13–16,18,19,23–25), although 1 study (26) was not included in this model because of limitations in a direct comparison between study formulas.

Statistical Analysis

We created meta-analysis models that included all of the studies that met our inclusion criteria and models that included the 6 studies identified as being the most appropriate for evaluating our hypothesis of interest. As mentioned above, we stratified our

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TABLE 1. Characteristics of reviewed studies that met inclusion criteria

References (location)	Study design	Study population	Any concomitant breast-feeding?*	Analytical group† (no. of infants)	Comparison group† (no. of infants)	Outcome definition†
Becker et al (26), Chan-Yeung et al 2000 (40) (Canada)	Randomized single-blind trial	Infants with at least 1 first-degree relative with asthma or 2 first-degree relatives with other IgE-mediated allergic disease	Yes	Infants randomly allocated to a multifaceted intervention program (avoidance of house dust mites, pet allergens, environmental tobacco smoke). Where breast-feeding was not possible, PHF-W was supplied. (n = 278)	Infants randomly allocated to a control group. Followed ''usual care.'' (n = 267)	Atopy: positive skin test reaction to 1 or more common inhalant or ingestant allergens
Chan et al (14) (Singapore)	Randomized single-blind trial	Infants whose mothers chose not to breast-feed and had a positive first-degree family history of allergic conditions	No	Infants randomly assigned to receive PHF-W exclusively for first 4 mo. After 4 mo, weaning diet with no restrictions, except for type of milk formula. (n = 53)	Infants randomly assigned to receive CMF exclusively for first 4 mo. After 4 mo, weaning diet with no restrictions, except for type of milk formula. (n = 57)	AD (eczema): eczematous eruption that was pruritic, typical morphology and distribution, tendency toward chronicity or recurrence
Chirico et al. (15) (Italy)	Randomized nonblind trial	Infants with at least the mother having a positive clinical history of atopic disease	No	PHF-W-fed infants at risk for atopy. Allergen avoidance program: dietary restriction, delayed weaning (at 6 mo), avoidance of passive smoking, pet and mite reduction, avoidance of nurseries. (n = 14)	CMF-fed infants at risk for atopy. Allergen avoidance program: dietary restriction, delayed weaning (at 6 mo), avoidance of passive smoking, pet and mite reduction, avoidance of nurseries. (n = 21)	Eczema: pruritic, chronic, or chronically relapsing dermatitis with typical features and distribution
D'Agata et al (22) (Italy)	Nonrandomized nonblind trial	Infants at risk for allergy (not clearly specified)	Not reported	Infants who received PHF-W for first 4 mo. (n = 50)	Infants who received CMF for first 4 mo. (n = 15)	Eczema: clinical examinations
De Seta et al (16) (Italy)	Randomized nonblind trial	Infants with a positive family history of atopy	No	Infants who were not breast-fed were randomly allocated to receive PHF-W for first 6 mo. Introduced to cow's milk after 6 mo. Other foods introduced at 6 mo. (n = 23)	Infants who were not breast-fed were randomly allocated to receive CMF for first 6 mo. Other foods introduced at 6 mo. (n = 39)	Eczema: diagnoses made in accordance with criteria of other researchers
Exl et al (17,31) (Switzerland)	Population-based follow-up study	Unselected population-based infants (not selected based on high-risk status)	Yes	Infants receiving PHF-W. Intervention and control groups combined. (n = 338)	Infants receiving CMF. Intervention and control groups combined. (n = 354)	Skin symptoms: parental monitoring, physicians' reports; international definitions for skin findings
Marini et al (18) (Italy)	Single-blind intervention study with random assignment	Infants with at least the mother having a positive clinical history of atopic disease	No	Infants randomly assigned to PHF-W. Exclusive formula for 5 mo, hypoallergenic foods 5–12 mo. All foods introduced at 12 mo. Environmental advice provided. (n = 41)	Infants randomly assigned to CMF. Exclusive formula for 5 mo, hypoallergenic foods 5–12 mo. All foods introduced at 12 mo. Environmental advice provided. (n = 43)	AD based on physical examination: scaly, erythematous, and itchy eczematous rash primarily on face and scalp, behind ears, and at flexural folds
Tsai et al (19) (Taiwan)	Randomized nonblind trial	Infants with a positive family history of allergy	Yes‡	Infants randomly allocated to receive PHF-W up to first 6 mo. These infants were breast-fed for the first 1–2 mo. (n = 15)	Infants randomly allocated to receive CMF exclusively since birth. (n = 18)	AD: physical examination (mild, moderate, severe)
Vandenplas et al (13,41) (Belgium)	Randomized double-blind clinical trial	Infants with a positive family history of atopic disease in at least 2 first-degree relatives	No	Nonbreast-fed infants randomly assigned to receive PHF-W for first 6 mo; unrestricted feeding thereafter. (n = 28)	Nonbreast-fed infants randomly assigned to receive CMF for first 6 mo; unrestricted feeding thereafter. (n = 30)	AD was diagnosed if an eczematous eruption was present with at least 3 of the 4 following criteria: pruritis, typical morphology and distribution, chronicity or recurrence of the symptoms, specific IgE at the time the rash was present
Vandenplas et al (21,42) (Belgium)	Follow-up study	Infants with a positive family history of atopy	No	Infants receiving PHF-W exclusively from birth to 4 mo. (n = 15)	Infants receiving CMF for 4 mo. (n = 15)	Dermatological symptoms: eczema, urticaria; recurrent symptoms
von Berg et al (23–25) (Germany)	Randomized double-blind intervention trial	Infants with a hereditary risk of atopy (at least 1 first-degree relative [parent or sibling] with an allergic disease)	Yes	Infants randomly assigned to receive PHF-W. Study formula provided until 6 mo of age. Strict dietary intervention period for at least 4 mo. (n = 241)	Infants randomly assigned to receive CMF. Study formula provided until 6 mo of age. Strict dietary intervention period for at least 4 mo. (n = 256)	AD based on modified diagnostic criteria: typical morphology, pruritus, tendency toward chronicity

(continued)

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TABLE 1. (*Continued*)

References (location)	Study design	Study population	Any concomitant breast-feeding?*	Analytical group† (no. of infants)	Comparison group‡ (no. of infants)	Outcome definition†
Willems et al (20) (Belgium)	Nonrandomized intervention trial	Infants at risk for atopy based on IgE screening at birth and family history of atopy	No	Infants who received PHF-W exclusively for the first 3 mo. Diet without restrictions after this time. (n = 30)	Infants who received CMF exclusively for the first 3 mo. Diet without restrictions after this time. (n = 37)	Allergic symptoms: eczema, asthma, and recurrent episodes of bronchitis, persistent rhinitis, persistent symptoms involving the GI tract, serious sleeping difficulties

AD = atopic dermatitis; CMF = cow's milk formula; GI = gastrointestinal; Ig = immunoglobulin; PHF-W = whey protein partially hydrolyzed formula. Summary of study characteristics included in meta-analysis.
* Pertains to whether there was any concomitant breast-feeding in either the analytical or control group for the data used in the analysis.
† The study-specific information was extracted to most closely reflect the primary study hypothesis; that is, comparing the incidence of AD among infants fed PHF-W with infants fed CMF.
‡ The comparison group was exclusively fed CMF.

analyses based on results reported at various follow-up periods throughout each study. Random effects models were used to calculate summary relative risk estimates (SRRE), 95% CIs, and corresponding *P* values for heterogeneity. This type of model assumes that the study-specific effect sizes come from a random distribution of effect sizes according to a specific mean and variance (27). The estimates of the individual studies were weighted based on the inverse of the variance, which is related to the sizes of the study populations. In our sensitivity analyses, the relative influence of each study on the model-specific SRRE was examined by generating an SRRE based on all of the studies in a particular model, followed by the removal of 1 study at a time to compare the overall SRRE with SRREs from models that had 1 study removed. This allowed us to determine the statistical robustness of each analytical model. All of the analyses were performed using Episheet (28), a spreadsheet-based analytical package designed for the analysis of epidemiologic data and Comprehensive Meta-analysis (29). The use of 2 independent analytical programs allowed for the validation of calculations.

Publication bias can affect meta-analysis findings if results from individual studies have been differentially published (eg, positive studies were more likely to be published than negative studies). We assessed publication bias by generating funnel plots for a visual examination, conducting correlation and regression tests for significance, and using a ''trim-and-fill'' procedure to evaluate symmetry around the summary effect (30).

RESULTS

The descriptive and qualitative characteristics of the studies included in the meta-analysis are presented in Table 1. The study designs consisted of clinical trials, both randomized and nonrandomized, and intervention-based follow-up studies. In all of the studies, except Exl et al (17,31), infants were identified as being high-risk status for allergy. The criteria used to designate infants as high risk for allergy were not consistent across studies because there is no universally accepted standardized method for such an appointment. In most studies, high-risk status was based largely on having a positive family history of allergy, which is the most commonly used tool for identifying an infant as having an increased atopic risk (7,32). The study population in Exl et al (17) was defined as an ''unselected population-based infant cohort.'' As mentioned, several atopic outcomes were reported across the individual studies; however, our analytical interest focused on AD. Thus, we extracted information specific to AD (infant eczema) or an outcome classification that included AD (eg, atopic manifestations with mention of AD). In most studies, AD was defined based on established clinical diagnostic criteria.

All of the studies identified for inclusion in this meta-analysis reported decreased risks of AD, or atopic outcomes that included AD, among infants fed PHF-W compared with infants fed intact protein CMF (Fig. 1). A statistically significant 45% (SRRE 0.55, 95% CI 0.40–0.76; *P* value for heterogeneity = 0.087) reduced risk of AD was found among infants receiving PHF-W compared with infants receiving intact protein CMF, based on the analysis of data from each study that most closely represented the formula intake period (Table 2). This result reflects a time period of 0 to 12 months, and in most studies, data were available before the introduction of solid foods. The removal of Becker et al (26), a study that did not explicitly discuss AD as being included in their outcome variable, from this meta-analysis model resulted in a stronger risk reduction (SRRE 0.48, 95% CI 0.38–0.60) and decreased the variability across studies (*P* value for heterogeneity = 0.459). The studies by Exl et al (17), Becker et al (26), von Berg et al (23), Tsai et al (19), and Chan et al (14)

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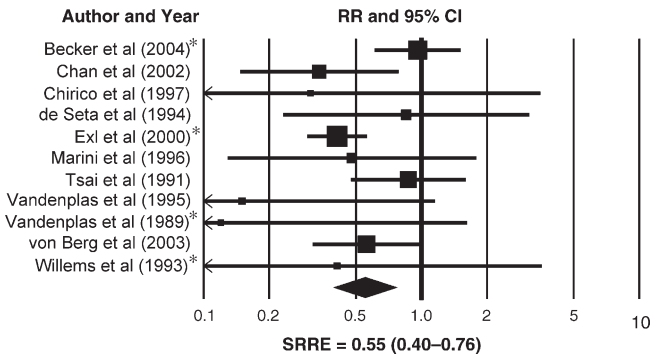

FIGURE 1. Meta-analysis results of all reviewed studies: risk of AD (PHF-W vs CMF). (Forest plot representation of meta-analysis; point estimates, confidence intervals, and summary relative risk estimate included.) ∗Results from individual studies that reported outcomes that included AD (eg, atopy, skin symptoms); all other studies specifically reported data for AD.

contributed a total of 83% of the relative weight in the all-studies meta-analysis model. Removing Exl et al (17), the study that contributed the most relative weight (23%), resulted in an attenuation of the RR estimate (SRRE 0.64, 95% CI 0.47–0.88); however, a statistically significant reduction in risk remained. Based on our influence and sensitivity analyses, removal of each of the other studies did not markedly alter the overall association because SRREs ranged from 0.52 to 0.59. Furthermore, all of the SRREs from models with 1 study removed were statistically significant, supporting the robustness of the overall findings. We conducted a sensitivity analysis consisting only of the studies that incorporated random allocation of study formula; results were similar to analyses of all of the study designs (SRRE 0.65, 95% CI 0.47–0.91; *P* value for heterogeneity = 0.257; SRRE with Becker et al (26) removed 0.58, 95% CI 0.41–0.80; *P* value for heterogeneity = 0.454).

A significant reduction in the incidence of AD (or outcome comprising AD) among infants who received PHF-W compared with infants who received CMF remained throughout all follow-up intervals, based on analyses of studies that provided results for extended time periods (Table 2). The strongest reduction in risk (59%) was found in the model based on studies reporting data after a 6-month follow-up period (SRRE 0.41, 95% CI 0.31–0.54). Reduced risks persisted in analyses of data at 1 year of age (SRRE 0.59, 95% CI 0.41–0.87) and in analyses that were extended up to age 3 (SRRE 0.76, 95% CI 0.57–1.00), indicating a true preventive effect of feeding with PHF-W, rather than delaying or postponing the development of AD.

The most informative meta-analysis model consisted of the 6 studies, representing 4 independent infant populations, that were determined to be of superior relevance to evaluate PHF-W and AD on the basis of reporting AD as an exclusive outcome, directly contrasting PHF-W and intact protein CMF, incorporating random allocation of study formula, and providing sufficient control of potential bias and confounding. A statistically significant 55% (SRRE 0.45, 95% CI 0.30–0.70) reduced risk of AD between 6 and 12 months of age was found in this model (Table 3). There was little variability across studies (*P* value for heterogeneity = 0.544), and a reduced risk of AD of at least 44% was reported in each study (Fig. 2). In the analysis based on data extending to 3 years of follow-up, a statistically significant decreased risk of AD among infants who received PHF-W was observed (SRRE 0.64, 95% CI 0.47–0.88), and there was little variability across studies in this extended follow-up period analysis (*P* value for heterogeneity = 0.604). Thus, these data support a prolonged preventive effect rather than a delay in the onset of development of AD.

In our assessment of publication bias among all of the studies (Fig. 3), we visually evaluated the symmetry around the summary effect sizes using funnel plots and found that the larger studies with less variability (near the top of the figure) were symmetrically distributed around the summary effect size, whereas the smaller studies with greater variability were generally distributed on 1 side of the mean effect size. This slight asymmetry among the smaller studies, however, was not indicative of publication bias based on our statistical assessments. Specifically, a quantitative evaluation using Begg and Mazumdar (33) rank correlation test and Egger et al regression method (34) was not supportive of publication bias, although the power of these tests is low unless there is significant bias or a substantial number of studies. An assessment using the trim-and-fill approach, an iterative method that adjusts for funnel plot asymmetry (30), did not significantly alter the summary estimates. The data point distribution was symmetrical for the meta-analysis model that included the top-tier studies. Overall, the findings from our meta-analysis were not likely influenced by publication bias.

DISCUSSION

Breast-feeding is the most effective and appropriate method to nourish infants, and exclusive breast-feeding is an effective way of minimizing risk for development of atopic disease (3). The use of cow's milk proteins for feeding healthy infants is also associated with an increased risk of atopic disease, particularly AD, which constitutes the most common allergic manifestation in infants. For infants who do not exclusively breast-feed, our analyses indicate that supplementation or exclusive use of a 100% PHF-W reduces the risk of AD, compared with feeding with intact protein CMF. Indeed, in all of the individual studies reviewed herein, a reduced incidence of AD (or outcome variable that included AD) was reported among infants who received PHF-W compared with infants who received intact protein CMF. In our meta-analysis incorporating data from all of the studies, we observed a statistically significant 45% reduction in risk among infants fed PHF-W. Moreover, throughout the 3 years of follow-up, the cumulative incidence of AD was markedly lower among infants receiving PHF-W.

As described previously, meta-analysis of data from the studies of more adequate methodological relevance to PHF-W and AD (13,14,18,23–25) demonstrated a statistically significant 55% decreased risk of AD through 6 to 12 months among infants who were fed with PHF-W. Even after 3 years of follow-up, a statistically significant 36% reduction in the incidence of AD remained, suggesting actual prevention rather than postponement of development of AD. These studies incorporated random allocation of infant formula, explicitly defined AD based on clinical criteria, evaluated AD as an independent disease outcome, directly compared the incidence of AD between infants receiving PHF-W and infants receiving intact protein CMF, adequately controlled for bias and potential confounding factors, and reported results in a readily interpretable fashion.

In addition to our quantitative assessment, we systematically evaluated the qualitative aspects and the methodology of each study included in our meta-analysis. Specifically, we critically examined the definition of high-risk status for allergy, loss to follow-up after randomization, duration of dietary interventions, scope and compliance with dietary restrictions, trial blinding procedures among study participants and researchers, clinical and diagnostic procedures, overall and within-group sample sizes, data analysis techniques, and control of potential bias and confounding. Despite

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TABLE 2. Meta-analysis results of reviewed studies: risk of AD* (PHF-W vs CMF)

	All studies		6 mo		12 mo		>12 mo	
References	RR† (95% CI)	Relative weight	RR (95% CI)	Relative weight	RR (95% CI)	Relative weight	RR (95% CI)	Relative weight
Becker et al (26)*	0.96 (0.61–1.50)	0.19	N/A	N/A	0.96 (0.61–1.50)	0.25	1.13 (0.68–1.91) [0–24 mo]	0.25
Chan et al (14)	0.34 (0.15–0.79)‡	0.10	0.34 (0.15–0.79)‡	0.11	0.36 (0.17–0.77)‡	0.15	0.65 (0.38–1.08)‡[0–30 mo]	0.27
Chirico et al (15)	0.31 (0.03–3.80)‡,§	0.02	N/A	N/A	N/A	N/A	N/A	N/A
de Seta et al (16)	0.85 (0.23–3.07)‡,‖	0.05	0.85 (0.23–3.07)‡,‖	0.05	N/A	N/A	1.02 (0.27–3.87)‡	0.04
Exl et al (17)*	0.41 (0.30–0.56)‡	0.23	0.41 (0.30–0.56)‡	0.82	N/A	N/A	N/A	N/A
Marini et al (18)	0.48 (0.13–1.78)‡	0.05	N/A	N/A	0.48 (0.13–1.78)‡	0.07	0.42 (0.14–1.26)‡ [0–36 mo]	0.06
Tsai et al (19)	0.87 (0.48–1.59)‡	0.15	N/A	N/A	0.87 (0.48–1.59)‡	0.19	N/A	N/A
Vandenplas et al (13)	0.15 (0.02–1.17)‡	0.02	0.15 (0.02–1.17)‡	0.02	0.46 (0.13–1.60)‡	0.07	1.07 (0.43–2.67)‡ [0–36 mo]	0.09
Vandenplas et al (21)*	0.12 (0.01–1.80)‡,§,#	0.01	N/A	N/A	N/A	N/A	N/A	N/A
von Berg et al (23,25)	0.56 (0.32–0.99)	0.16	N/A	N/A	0.56 (0.32–0.99)	0.20	0.60 (0.37–0.97) [0–36 mo]	0.29
Willems et al (20)*	0.41 (0.05–3.75)‡,¶	0.02	N/A	N/A	0.18 (0.04–0.72)‡	0.06	N/A	N/A
SRRE (95% CI)	0.55 (0.40–0.76)		0.41 (0.31–0.54)		0.59 (0.41–0.87)		0.76 (0.57–1.00)	
P value for heterogeneity	0.087		0.504		0.117		0.377	

AD = atopic dermatitis; CI = confidence interval; CMF = cow's milk formula; PHF-W = whey protein partially hydrolyzed formula; RR = relative risk; SRRE = summary relative risk estimates. Summary of meta-analysis findings; all of the studies included.

* Results from individual studies that reported associations for outcomes that included AD (eg, atopy, skin symptoms); all of the other studies specifically reported data for AD.

† Data were extracted from individual study follow-up periods that most closely captured the time frame for which infants received PHF-W and CMF (0–12 mo).

‡ Calculated with Episheet Statistical Software.

§ There were 0 cases of eczema in the PHF-W group. To calculate the RR with 95% confidence limits, 0.5 was added to the numerator.

¶ Association after 3 mo.

‖ Association based on incidence of eczema and cow's milk protein intolerance combined.

\# Association after 4 mo.

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TABLE 3. Meta-analysis of top-tier studies: risk of AD (PHF-W vs CMF)

	≤12 mo		≥30 mo	
References	RR* (95% CI)	Relative weight	RR (95% CI)	Relative weight
Chan et al (14)	0.34 (0.15–0.79)†	0.27	0.65 (0.38–1.08)† (0–30 mo)	0.37
Marini et al (18)	0.48 (0.13–1.78)†	0.11	0.42 (0.14–1.26)† (0–36 mo)	0.08
Vandenplas et al (13)	0.15 (0.02–1.17)†	0.04	1.07 (0.43–2.67)† (0–36 mo)	0.12
von Berg et al (23,25)	0.56 (0.32–0.99)	0.58	0.60 (0.37–0.97) (0–36 mo)	0.43
SRRE (95% CI)	0.45 (0.30–0.70)		0.64 (0.47–0.88)	
P value for heterogeneity	0.544		0.603	

AD = atopic dermatitis; CI = confidence interval; CMF = cow's milk formula; PHF-W = whey protein partially hydrolyzed formula; RR = relative risk; SRRE = summary relative risk estimate. Summary of meta-analysis findings for top-tier studies only.

* Data were extracted from individual study follow-up periods that most closely captured the time frame for which infants received PHF-W and CMF.

† Calculated with Episheet Statistical Software.

some differences in characteristics between studies, we believe that with appropriate study exclusions, combining data across studies in a meta-analysis design was justified scientifically. Furthermore, several studies exhibited uniform methodological traits, bolstering the rationale to evaluate quantitatively the results across individual studies. Our assessment of these studies is consistent with the findings of in-depth critical reviews, which appropriately separate and assess the effects of hydrolysates on atopic risk reduction (7,32). Indeed, in a recent publication of the American Academy of Pediatrics, it was stated, ''In studies of infants at high risk for atopy and who are not exclusively breastfed for 4 to 6 months, there is modest evidence that the onset of atopic disease may be delayed or prevented by the use of hydrolyzed formulas compared with formula made with intact cow milk protein, particularly for AD'' (3). However, the specific role of 100% PHF-W in AD risk reduction was not reported.

It should be emphasized that regardless of study design, infant population, sample size, follow-up time, or study location, individual study findings were consistent because a reduced incidence of AD was reported in all of the reviewed studies. Furthermore, the results from our meta-analysis do not appear to be affected by publication bias. It has been suggested that feeding with PHF-W may only serve to delay the onset of atopic manifestations such as eczema (35); however, the results from this meta-analysis support a prolonged reduction in the incidence of AD. Indeed, a statistically significant 36% decreased risk of AD was found in our meta-analysis of data that extended to 3 years of age (Table 3). In addition, von Berg et al (24) observed a statistically significant lower incidence of AD through 6 years of follow-up among infants randomly assigned to receive PHF-W compared with infants receiving intact protein CMF.

All of the studies except 1 analyzed in this meta-analysis included infants who were considered to be at high risk for atopy based on a positive family history of atopic disease. More than one third of all of the healthy infants in the general population would be considered to be at risk based on this criterion (36,37). The results of this meta-analysis may not be applicable to infants without a family history of atopy. However, results across all of the individual studies were relatively similar despite the fact that the definition of positive family history was variable, and despite the fact that there is no generally accepted or standardized method to obtain family history (38). In addition, although a family history of atopy may assist in identifying infants to be at an increased risk for atopic disease, most infants who develop AD do not have a positive family history. Family history has low sensitivity as a method to identify infants at risk for atopic disease (36,37), thus necessitating the consideration of atopic risk reduction strategies for the general population, such as the use of PHF-W.

Hydrolyzed formulas, particularly extensively hydrolyzed protein formulas, have been used therapeutically when infants exhibit protein-related intolerances and food allergies, and their salubrious effects in reducing the risk of atopic manifestations have increasingly been recognized. These extensively hydrolyzed

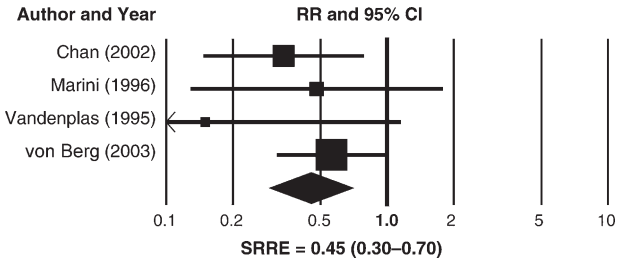

FIGURE 2. Meta-analysis of top-tier studies: risk of AD (PHF-W vs CMF). (Forest plot representation of meta-analysis; point estimates, confidence intervals, and summary relative risk estimate included.) All studies reported associations specifically for AD.

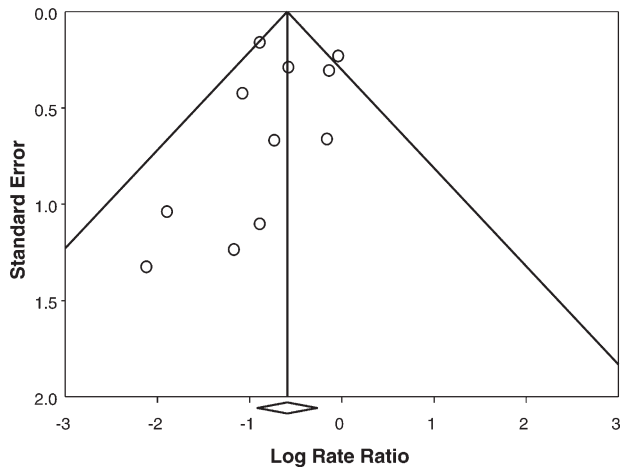

FIGURE 3. Funnel plot of all studies. (Funnel plot representing a visual assessment of potential publication bias.)

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formulas were developed with nutritional profiles adequate for the management of allergic and digestive disorders. Compared with routine-use formulas, commercially available extensive hydrolysates have higher protein content, contain medium-chain triglycerides, contain no lactose, and have higher osmolality and reduced palatability. This hinders their potential use as routine formulas for healthy infants. Partially hydrolyzed formulas overcome these limitations because they have been developed with nutritional profiles for routine use in healthy infants. In various countries, including the United States and Canada, PHF-W is classified and commercialized as a routine-use formula for healthy infants, and their cost is the same as other routine intact protein formulas. PHF-W has been safely used as a human milk alternative globally for decades in millions of infants, thus making it a desirable option for allergy risk reduction among infants who are not exclusively breast-fed.

The incidence of AD is increasing worldwide, with a particularly steep trend in rates observed in developed countries (1). It is estimated that 20% of the infants and young children in the United States may experience symptoms of AD (1). Preventing AD is of great public health importance because this disease is associated with infant discomfort, sleep disturbance, irregular feeding, familial stress, increased physician visits, and an economic burden to families and the health care system (1). Indeed, it has been projected that US health insurance companies may spend more than $1 billion/year on AD (1). Of particular concern is that AD has been shown to be associated with subsequent respiratory disease, namely the development of asthma and hay fever in later childhood or early adulthood (39).

CONCLUSIONS

In conclusion, the results from this meta-analysis indicate that healthy infants with a family history of allergy who are fed with 100% PHF-W have a reduced risk of AD compared with infants fed intact protein CMF. Exclusive breast-feeding should continue to be encouraged as a means of reducing atopic risk, as well as other health benefits. Given the rising incidence of atopic disease and inadequate means to predict individual risk, the use of PHF-W in the general population of infants who are not exclusively breast-fed should be considered a practical and potentially effective public health measure.

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