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Randomized Control Trials

Whole goat milk versus cow milk formula and atopic dermatitis in infants: A randomized clinical trial

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S U M M A R Y

Background and aims: Atopic dermatitis (AD) poses a substantial burden on affected children and their families. The evidence of the role of feeding choices in infancy for AD development is limited.
Methods: This study is a two-arm, parallel, randomized, double-blind, controlled trial to assess the effect of infant feeding with whole goat milk formula (WGF) versus cow milk formula (CF) on AD development during the first year of life. Healthy term infants up to 3 months of age were enrolled in 6 Spanish and 4 Polish study centres, without AD risk selection. The primary outcome measure was AD diagnosed by study personnel at three study visits using the United Kingdom Working Party diagnostic criteria ($AD_{Primary}$). Reported doctor-diagnosed AD (AD_{Doctor}) was a secondary outcome. Cumulative incidence in the first year of life was calculated. Incidence rate ratios (IRR) were estimated by Poisson regression.

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Results: Data from 2132 infants were analyzed. 192 infants were diagnosed with $AD_{Primary}$ and 245 with AD_{Doctor}. The cumulative incidence rate of $AD_{Primary}$ for both groups was 11.6 per 100 person-years without difference between WGF and CF (IRR: 1.00; 95%CI: 0.75, 1.32; $p = 0.991$). In the per-protocol population, the incidence of AD_{Doctor} was lower in WGF than CF (IRR: 0.66; 95%CI: 0.49, 0.9; $p = 0.008$). In infants with parental history of AD, the protective effect of WGF was stronger: AD_{Doctor} IRR 0.36 (95%CI: 0.17, 0.76; $p = 0.007$).
Conclusion: This trial demonstrates that WGF can reduce the incidence of AD in formula-fed infants in the first year of life, especially in presence of parental history of AD.
Trial registration: ClinicalTrials.gov Identifier: NCT04599946. Submitted: 2020-10-05.

1. Introduction

Atopic dermatitis (AD), commonly referred to as eczema or atopic eczema, is a chronic, pruritic, and inflammatory skin disorder that affects children at a high rate [1]. Clinically, it presents with intense itching, recurrent eczematous skin lesions, and a relapsing-remitting disease course [2]. AD is most prevalent in childhood, with around 80% of symptom onset occurring within the first year of life [3]. In Europe, the average prevalence of AD is 14% [4]. AD not only predisposes to other inflammatory conditions such as food allergies, asthma, and allergic rhinoconjunctivitis [2], but it also impacts development, sleep and quality of life of the child and the whole family [5,6].

A family history of AD increases the risk of AD in offspring by 2–3 times [7,8]. In general, nutrition or dietary elimination has been shown to have limited effects on AD development [9–11]. Nevertheless, weak evidence shows an association of breastfeeding with a reduced risk of eczema in children up to 2 years of age [12]. When breastfeeding is not possible, infant formulas based on hydrolyzed cow milk protein have been investigated as a strategy to prevent allergic diseases, with reported benefits on AD in children with a family history of AD [13]. However, a Cochrane review from 2017 did not find conclusive evidence for a protective effect in healthy infants [14].

An Australian study, designed and powered to evaluate the suitability and safety of whole goat milk formula (WGF) in infants, found a one-third lower incidence of AD in a WGF compared to a cow milk formula (CF) group [15]. While the difference in this study with a relatively small sample size ($n = 301$) was not statistically significant, the potentially protective effect of WGF was considered plausible, as recent animal studies had indicated immunomodulatory properties of dietary components such as lipids in goat milk, including effects on inflammatory pathways associated with AD [16]. The casein structure and composition of milk proteins differ between WGF and CF. Both formula types contain the major milk allergen β-lactoglobulin, albeit in different amounts. In vitro and animal studies suggest that β-lactoglobulin may be digested more rapidly in WGF, potentially due to differences in casein composition and the formation of a softer gastric curd, which may enhance enzymatic accessibility [17–19]. This is supported by model studies demonstrating faster gastric hydrolysis of goat milk casein, which may reduce the allergenic potential of WGF [20,21]. Considering the established association between food sensitization, food allergy, and AD, this pathway represents a plausible mechanism linking formula composition to AD risk [22].

The primary objective of the Goat Infant Formula Feeding and Eczema (GIraFFE) study was to determine whether the cumulative incidence of AD in the first 12 months of life differs between infants fed WGF versus CF.

2. Methods

2.1. Study design

A summary of the study protocol was previously published [23]. Briefly, the GIraFFE study was designed as a two-arm, parallel, randomized, double-blind, controlled intervention trial conducted in 6 Spanish and 4 Polish study centres (Table S1). The study was coordinated, managed, and monitored by an academic institution (Ludwig-Maximilians-Universität Munich). The study population included healthy, term infants whose parents had chosen to initiate formula feeding for reasons unrelated to the trial, without any influence by the study staff on feeding choice. There was no selection based on an increased risk of AD. Infants were randomly assigned to receive either WGF or CF. Recruitment of infants started in January 2021 and ended in August 2023. Precautions were implemented to ensure that the recruitment process did not interfere with breastfeeding intention or practices.

The reporting of this study follows the Consolidated Standards of Reporting Trials (CONSORT) [24].

2.2. Study formula

WGF was based on whole goat milk, including goat milk fat (approximately 50% of total fat) with added vegetable oils, and retaining a whey:casein ratio of 20:80. CF was a standard cow milk formula based on skim cow milk and cow whey, comprising 5% of milk fat and 95% of fat from added vegetable oils, and a whey:casein ratio of 60:40. Energy content and nutrient composition of the formulas were almost identical (Table S2). Infant formulas were fed until 6 months of age; thereafter, follow-on formulas, again based on whole goat or cow milk, were offered in line with usual practice in Europe. All formulas complied with the European Union legislative standards on compositional and quality requirements of formulas for infants [25]. Parents were instructed to substitute all non-human milk feeds with the study formula.

2.3. Study population and procedures

Children were not included if they were older than 3 months, had consumed formula regularly for more than 4 weeks before inclusion, or had been diagnosed with AD or any other skin condition that could confound the diagnosis of AD, or were diagnosed with cow milk intolerance or allergy. The intervention period started with recruitment and ended with the 12-month visit. Face-to-face visits were scheduled at enrolment (baseline) and at infant ages of 4, 6, and 12 months, and telephone interviews at 8 and 10 months of age.

The primary outcome ($AD_{Primary}$) was AD diagnosed according to the United Kingdom Working Party (UKWP) [26] criteria, modified for infants in the first year of life, during the three face-to-face visits in the first year of life by trained study personnel. UKWP criteria were also assessed by telephone during planned telephone interviews and for planned study visits that were missed ($AD_{UKWP} = AD_{Primary}$ and/or parental reported AD based on UKWP criteria). Furthermore, parents reported at each contact whether a diagnosis of AD had been made by a medical doctor (AD_{Doctor}). AD_{Any} was defined as AD_{UKWP} and/or AD_{Doctor} (Table S3 and Table S4).

The severity of AD was rated using POEM (Patient-Oriented Eczema Measure) [27] and SCORAD (SCORing Atopic Dermatitis) [28]. Both measures were assessed only after an AD_{UKWP} diagnosis was made. SCORAD was assessed exclusively during study visits, while POEM was also collected during telephone interviews. The highest ever recorded score for each participant was used. SCORAD-scores were categorized and interpreted according to the SCORAD index [28]. POEM-scores were classified based on the banding proposed by Charman et al., 2013 [29].

Weight and recumbent length were measured twice consecutively at every visit with calibrated equipment, and the mean of both measurements was calculated. All anthropometric values will be expressed in z-scores according to the WHO growth standards [30]. Child and family characteristics were assessed at baseline. Parents were asked if they were ever diagnosed with AD by a medical doctor.

Adverse events (AEs) were categorized using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.1. For the analysis, multiple AEs belonging to one organ system were only counted once per individual. Relatedness of AEs to the study product was determined by the parents or study personnel, while relatedness of severe AEs (SAEs) was determined by the local principal investigator.

2.4. Sample size, analysis and statistical methods

A required sample size of 1722 infants was calculated based on an AD incidence of 15% and an assumed risk reduction of 30% [23]. A dropout of up to 25% was initially assumed, leading to a planned enrollment of 2296 infants. However, recruitment was stopped after reaching a total of 2132 infants since the observed dropout rate was lower than initially assumed.

The primary analysis was performed in the intention-to-treat population (ITT), including all randomized infants who consumed at least one feed of the study product. The per-protocol population (PP) comprised infants who additionally met the compliance criteria and attended all face-to-face visits up to 12 months of age, unless $AD_{Primary}$ occurred before. Compliance was defined by no formula-feeding interruption exceeding three consecutive days, and no introduction of solid foods before the age of 4 months.

Incidence rates (IRs) were calculated by dividing the number of AD cases by the total person-time at risk and were expressed per 100 person-years. Person-time at risk begins with enrolment and ends with either an AD diagnosis or the last performed contact for the respective outcome assessment. For doctor-diagnosed AD, person-years were calculated using the observation days up to the reported diagnosis date. Incidence rate ratios (IRRs) for AD were estimated using a mixed-effects Poisson regression with centre as a random intercept to account for intra-centre dependency. Person-time per subject was included as an offset term to account for individual time at risk. The primary outcome analysis included only the study product as a fixed effect. For secondary analysis, the model was adjusted for sex, country, and parental history of AD. For subgroup analysis, potential effect modification was assessed in the adjusted model by including interaction terms between the study product and either sex, country, parental AD, or age at enrolment (≤4 weeks; >4 weeks). The same subgroup analyses were also performed in the PP population. Differences by intervention groups in length- and weight-for-age z-scores at 12 months were assessed using linear regression, adjusting for baseline values of the respective anthropometric measure. All primary and secondary analyses were pre-specified in a statistical analysis plan (Supporting Information).

Statistical analyses were conducted using R (version 4.3.2 or above) and Stata 19.0. The *glmer* function from the lme4 package in R was used for the Poisson regression [31]. All tests were two-sided with a significance level of 5%. Confidence intervals (CIs) were two-sided and set at 95%. No imputation of missing values was performed.

2.5. Ethics

Written informed consent was obtained from all parents or caregivers before enrolment. Participants received the study product for free without compensation for participation. Ethical review was performed by the ethical committee of the LMU Hospital Munich, Germany, as well as the local ethical review boards of all participating study centres (Table S5).

3. Results

A total of 2132 infants were randomized, with 1065 assigned to WGF and 1067 to CF. 268 (12.6%) infants dropped out by 12 months of age, with the majority discontinuing before the 4-month visit (Fig. 1). Dropout rates differed between study groups: 15% in WGF and 10% in CF ($p < 0.001$). However, reasons for dropout were not significantly different between groups: 60 (22%) infants stopped participation due to a medical problem/AE, 112 (42%) withdrew, and 92 (34%) were lost to follow-up. Baseline characteristics of infants and their parents showed no major differences between formula groups (Table 1). Almost all infants had started formula feeding before being included in the study; only very few children (4%) were exclusively breastfed before the study formula was started, 61% had mixed feeding and 35% were exclusively formula-fed without any difference between study groups ($p = 0.8$). Most children receiving formula were fed with standard cow milk formula (89%), some with hydrolyzed cow milk formula (15%) or goat milk formula (4%). The types of formula used before the study formula was started did not differ between groups.

9.5% of infants had at least one parent with a history of doctor-diagnosed AD; about 13% of mothers had smoked during pregnancy. 1417 (66%) of infants were recruited in Spain and 715 (34%) in Poland, with a median of 210 (range 119–327) infants per centre. Baseline characteristics were different between countries in most variables assessed (Table S6). Polish infants were on average 21 days older at enrolment compared to Spanish infants. The prevalence of caesarean section was higher in Poland (53%) than in Spain (27%) ($p < 0.001$). Spanish parents reported more often to have AD (11%) or any other allergy (42%) than Polish parents (7% and 33%, respectively; $p = 0.011$ and < 0.001). 1473 (69%) of the randomized infants fulfilled the per-protocol criteria, 723 (68%) in WGF and 750 (70%) in CF ($p = 0.23$). The majority (93%) of infants not being per-protocol missed a visit (64%) and/or interrupted study formula intake for more than 3 consecutive days (78%). 9% (166/1864) of the infants who did not drop out stopped study product consumption before the end of the intervention phase (Fig. 1). Per-protocol infants were more likely to come from families with higher education but did not differ in parental AD (Table S7). Within the PP population baseline characteristics of infants and parents showed no major differences between formula groups (Table S8).

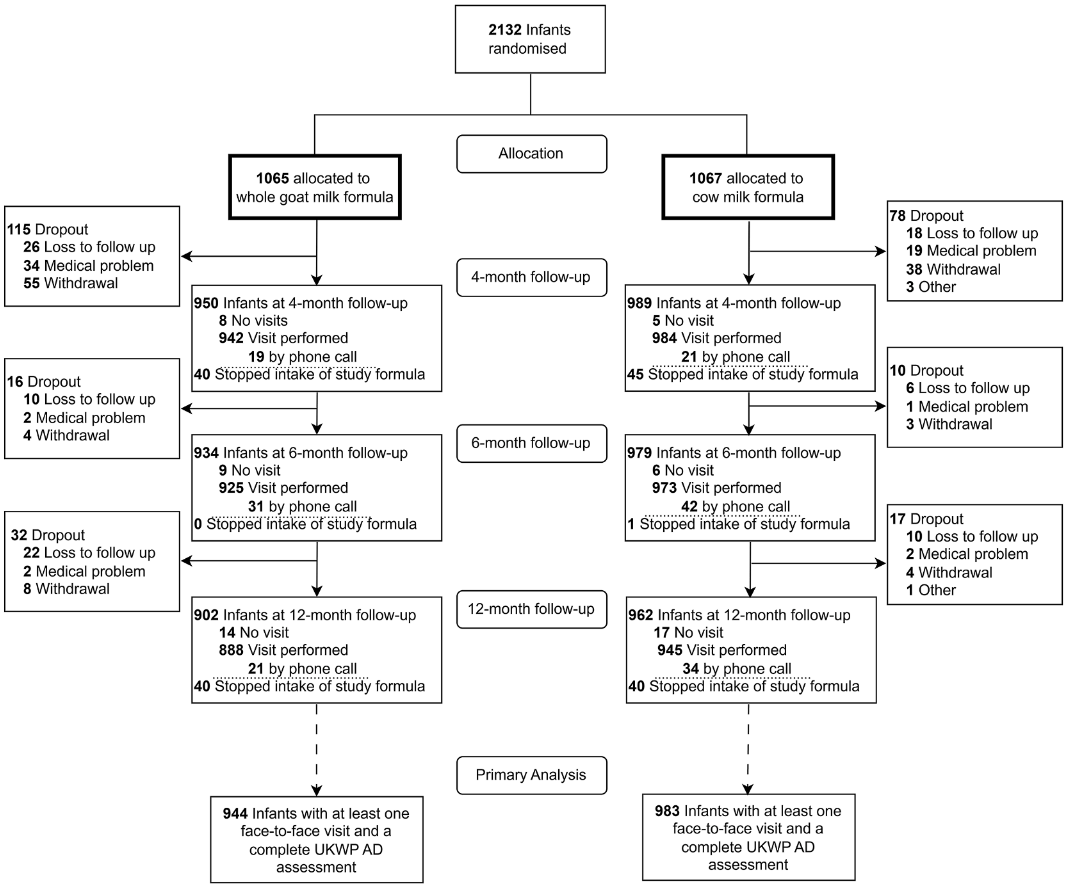

Fig. 1. Flow chart of the study population by formula group
Visit performed includes all infants who had face-to-face visits or telephone interviews at the corresponding time-point; No visit involves infants who did not attend the visit or telephone interview but continued participating in the study.

3.1. AD cases and incidence rates of AD

Overall, 327 infants were diagnosed with AD (AD_{Any}). Between 3.8% and 9.4% of infants were diagnosed with AD_{Any} at each visit per intervention group (Table 2). 36% of AD_{Any} cases had a doctor-diagnosis of AD, of which 52% (60/115) never reported an itchy skin condition. 69% of all $AD_{Primary}$ cases had visible eczema at diagnosis; for 34% of infants, visible AD was decisive (1 of only 3 fulfilled criteria) for the diagnosis of $AD_{Primary}$. The cumulative IR of $AD_{Primary}$ in the first year of life was 11.6 per 100 person-years (Table 2). While there was no difference in $AD_{Primary}$ between countries, the IR for AD_{Doctor} was significantly higher in Spain than in Poland (Table S9). The incidence of $AD_{Primary}$ was not different between WGF and CF (IRR: 1.00; 95%CI: 0.75, 1.32; $p = 0.991$, Fig. 2) in the ITT population but was lower for AD_{Doctor} in WGF (IRR: 0.79; 95%CI: 0.62, 1.02; $p = 0.073$), and was significantly lower for AD_{Doctor} in the PP population (IRR: 0.66; 95%CI: 0.49, 0.90; $p = 0.008$). Detailed data on all unadjusted and adjusted analyses are provided in Table S10.

The median SCORAD-score of infants with $AD_{Primary}$ was 14 (IQR: 6–26) in WGF and 16 (IQR: 5–27) in CF ($p = 0.77$). 30% of $AD_{Primary}$ cases were classified as moderate, and 3% as severe. In infants with a parental history of AD, 10% of $AD_{Primary}$ cases were classified as severe. The median POEM-scores were not statistically different between study groups (WGF: 9 (IQR: 5–13), CF: 8 (IQR: 5–12), $p = 0.37$), with 62% of AD cases classified as moderate-to-very-severe.

3.2. Subgroup analysis

The intervention effect on all AD outcomes differed significantly by parental history of AD (Fig. 3; Tables S11–13). A protective effect of WGF versus CF on all AD outcomes was observed among infants with parental history of AD: IRR for $AD_{Primary}$ 0.48 (95%CI: 0.22, 1.03; $p = 0.06$) and 0.36 (95%CI: 0.17, 0.76, $p = 0.007$) for AD_{Doctor} (Table S12). These effects were generally stronger in the PP population (Table S13). There was no indication that sex or age at enrolment modulated the intervention effect, and no consistent findings for a country difference (Table S12).

3.3. Safety and adverse events

Mean length at 12 months was 75.7 ± 2.9 cm and mean weight was 9.8 ± 1.1 kg without difference between WGF and CF in length-for-age or weight-for-age z-scores: −0.2 (95%CI: −0.11, 0.07), $p = 0.66$, and −0.05 (95%CI: −0.13, 0.03), $p = 0.24$, respectively.

A total of 2066 AEs were reported, 1048 in 1065 WGF infants, and 1018 in 1067 CF infants (IRR: 1.03, 95%CI: 0.95, 1.12; $p = 0.48$); types of AE were somewhat different ($p = 0.03$) with more gastrointestinal AEs in WGF (n = 237) than CF (n = 175), the majority of those reported as constipation (46%/39%, respectively). The proportion of infants with AEs rated as probably related or related to the study product was higher in the WGF group (13%) than in the CF group (9%). Consistently, the rate of AE considered related to the study product was higher in WGF than in CF (IRR:

Table 1
Characteristics of study participants allocated to the two intervention arms.

Variable	Whole goat milk formula (N = 1065) n (%)/Mean (±SD)[a]	Cow milk formula (N = 1067) n (%)/Mean (±SD)[a]
Child's sex		
Female	506 (47.5%)	506 (47.4%)
Male	559 (52.5%)	561 (52.6%)
Age at enrolment (days)	25.6 (21.9)	25.6 (22.3)
Birth weight (g)	3360 (410)	3376 (424)
Length at birth (cm)	51.7 (3.2)	51.7 (3.3)
Mode of delivery		
Caesarean section	362 (34.0%)	397 (37.2%)
Vaginal birth	703 (66.0%)	670 (62.8%)
Birth order		
1st child	517 (48.5%)	548 (51.4%)
2nd child	383 (36.0%)	364 (34.1%)
>2nd child	165 (15.5%)	155 (14.5%)
Antibiotic use during delivery	342 (32.1%)	344 (32.3%)
Other formula before inclusion[b]	1023 (96.1%)	1030 (96.5%)
Education level mother[c]		
High	619 (58.1%)	596 (55.9%)
Medium	339 (31.8%)	363 (34.0%)
Low	107 (10.0%)	108 (10.1%)
Education level father[c]		
High	458 (44.3%)	446 (43.1%)
Medium	449 (43.4%)	432 (41.7%)
Low	127 (12.3%)	158 (15.3%)
At least one parent atopic dermatitis	91 (8.8%)	106 (10.2%)
Both parents atopic dermatitis	2 (0.2%)	4 (0.4%)
At least one parent other allergy[d]	399 (38.4%)	417 (40.1%)
Both parents other allergy[d]	68 (6.4%)	60 (5.7%)
Maternal smoking during pregnancy	151 (14.2%)	125 (11.7%)
Mother currently smoking	155 (14.6%)	138 (12.9%)
Father currently smoking	327 (31.5%)	340 (32.6%)

[a] As appropriate; SD: Standard deviation.
[b] Other formula signifies feeding with other infant formula before inclusion. Mixed feeding (both breastmilk and other infant formula) before inclusion is also included in this variable.
[c] Maternal and paternal educational levels were classified according to the International Standard Classification of Education (ISCED): 0 = Early childhood education, 1 = Primary education, 2 = Lower secondary education, 3 = Upper secondary education, 4 = Post-secondary non-tertiary education, 5 = Short-cycle tertiary education, 6 = Bachelor's or equivalent, 7 = Master's or equivalent, 8 = Doctoral or equivalent with division into low [0–2], medium [3–4], high [5–8] [48].
[d] Other allergies encompass doctor-diagnosed asthma, allergic rhinitis (hay fever) or food allergies.

Table 2
Rate of new AD cases per time point with number of children with completed assessment and incidence rate (IR) in the first year of life by intervention group.

AD outcome and assessment time points (in months)	WGF % (n/N)/IR (n/person-years)	CF % (n/N)/IR (n/person-years)
$AD_{Primary}$		
4	3.5% (32/923)	2.2% (21/963)
6	3.1% (27/865)	4.1% (37/912)
12	4.3% (35/815)	4.7% (40/860)
IR	11.6 (94/808)	11.6 (98/848)
AD_{UKWP}		
4	3.4% (32/942)	2.2% (22/984)
6	3.1% (28/895)	3.9% (37/952)
12	5.3% (44/833)	5.5% (49/890)
IR	12.6 (104/826)	12.4 (108/868)
AD_{Doctor}		
4	4.0% (38/942)	4.6% (45/984)
6	2.9% (26/889)	2.8% (26/928)
12	5.2% (43/827)	7.7% (67/875)
IR	13.1 (107/814)	16.4 (138/843)
AD_{Any}		
4	5.8% (55/942)	5.4% (53/984)
6	3.8% (33/873)	5.1% (47/921)
12	7.3% (59/805)	9.4% (80/849)
IR	18.4 (147/798)	21.7 (180/829)

$AD_{Primary}$: AD diagnosed according to UKWP criteria in face-to-face visit; AD_{UKWP}: AD diagnosed according to UKWP criteria in face-to-face visit or parent-reported by phone; AD_{Doctor}: doctor-diagnosed AD; AD_{Any}: AD UKWP and/or AD Doctor.
AD, atopic dermatitis; WGF, whole goat milk formula; CF, cow milk formula; UKWP, United Kingdom working party; (n), new AD cases per time point; (N), observed number of infants per time point; (IR), incidence rate per 100 person-years.

1.41; 95%CI: 1.09, 1.85; p = 0.009). However, the type of study product-related AEs did not significantly differ between groups. SAEs were more frequently reported in WGF (n = 165) than CF (n = 118) (IRR: 1.40; 95%CI: 1.10, 1.77; p = 0.005). Only 7 SAEs were classified as at least probably related to the study product, with even distribution between groups. Parent-reported cow milk protein allergy, documented without predefined diagnostic criteria, was reported in 63 infants (3%), with no statistically significant difference between groups (WGF n = 38; CF n = 25).

4. Discussion

We did not observe any difference in incidence rates between WGF and CF for AD diagnosed by UKWP criteria in all infants. However, when reported doctor-diagnosed AD was analyzed, AD incidence in WGF was significantly lower in the PP population. Moreover, we observed a significantly lower AD incidence in WGF in the subgroup of infants with parental AD: doctor-diagnosed AD was reduced by 64% in WGF compared to CF. Observed effects were larger in the PP population, suggesting that better adherence to WGF feeding was associated with greater risk reduction.

We observed a limited intervention effect in normal-risk children, but a more pronounced protective effect in high-risk children. This is in line with observations from other nutrition intervention studies showing that there is limited evidence for an effect of dietary interventions or feeding choices on AD risk [11] or AD severity [9] in the general population. However, effects might be more pronounced in higher-risk populations, as a meta-analysis showed a modest protective effect of breastfeeding on reducing AD risk in infants at high risk only [7,32]. Also, probiotic supplementation may lower the risk for AD, especially in high-risk infants [9,33]. Furthermore, extensively and partially hydrolyzed compared to standard cow milk formulas have been discussed to potentially reduce the risk of developing AD only in high-risk infants, but the level of evidence has been rated as low [34,35].

Both formulas used in this study contain major milk allergens, notably the whey proteins β-lactoglobulin and α-lactalbumin [36]. However, their content is lower in WGF, as whey contributes only 20% to total protein in WGF compared to 60% in CF. Additionally, the content of αS1-casein is lower in WGF compared to CF, resulting in the formation of a softer curd [17]. *In vitro* experiments indicated this softer curd to be associated with enhanced hydrolysis of milk proteins during simulated gastric digestion [18]. It is tempting to speculate that the effect of WGF observed in infants with parental AD might be partly explained by an increased predisposition to allergic sensitization, which could make them more responsive to the potentially lower allergenicity of milk proteins in WGF. Moreover, the lipid profile of WGF includes not only triglycerides but also substantial amounts of polar lipids derived from the milk fat globule membrane, which possess potential bioactive properties. These lipids may influence the infant

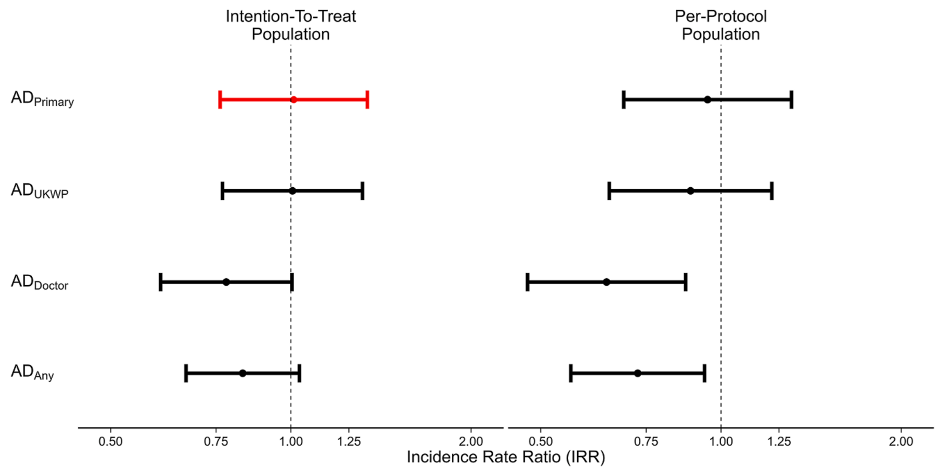

Fig. 2. Incidence rate ratios for AD (WGF/CF) in the intention-to-treat and per-protocol population according to the applied diagnostic criteria
Incidence rate ratio (IRR) based on Poisson model with study centre as a random effect. AD is defined by different assessment methods: *$AD_{Primary}$: AD diagnosed according to UKWP criteria in a face-to-face visit; AD_{UKWP}: AD diagnosed according to UKWP criteria in a face-to-face visit or by phone; AD_{Doctor}: reported doctor-diagnosed AD*; *AD_{Any}: AD_{UKWP}* and/or *AD_{Doctor}*
AD: Atopic Dermatitis; WGF: Whole Goat Milk Formula; CF: Cow Milk Formula; UKWP: United Kingdom Working Party.

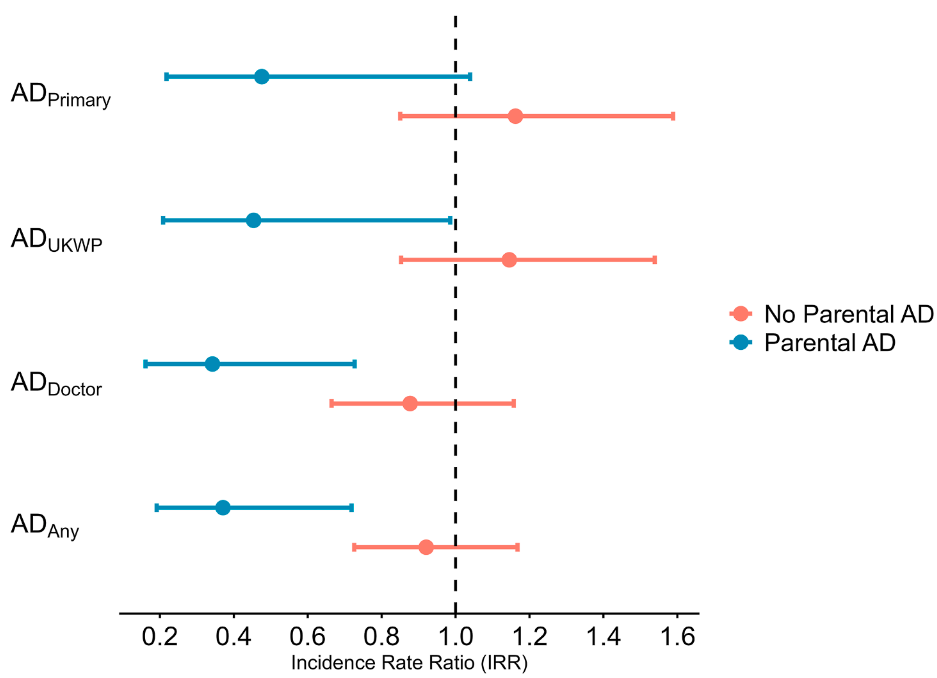

Fig. 3. Incidence rate ratio of WGF and CF in the subgroup of infants with parental AD
Incidence rate ratio (IRR) based on a Poisson model with study centre as a random effect in infants with a parental history of AD. AD is defined by different assessment methods: *$AD_{Primary}$: AD diagnosed according to UKWP criteria in a face-to-face visit; AD_{UKWP}: AD diagnosed according to UKWP criteria in a face-to-face visit or by phone; AD_{Doctor}: reported doctor-diagnosed AD; AD_{Any}: AD_{UKWP}* and/or *AD_{Doctor}*
AD: Atopic Dermatitis; WGF: Whole Goat Milk Formula; CF: Cow Milk Formula; UKWP: United Kingdom Working Party.

lipidome, including skin lipid composition, thereby providing an additional mechanism for AD risk reduction [37,38].

We used UKWP AD criteria for our primary outcome due to its high specificity. However, the objective assessment of itching as a prerequisite for UKWP-diagnosed AD is challenging in infants [39,40]. A systematic review reported reduced sensitivity of the UKWP criteria, particularly in populations with mild or early manifestations of atopic dermatitis [41]. This is in line with a more recent study that reported that only 30% of infants with clinical eczema fulfilled UKWP or the original Hanifin and Rajka (HR) criteria [39]. Nonetheless, the UKWP criteria were developed as a streamlined adaptation of the HR criteria to enhance practicability and standardization for large-scale epidemiological studies and remain the only diagnostic criteria validated in both hospital- and population-based settings [42]. Our findings on severity and overall AD incidences are consistent with previously reported prevalence data from Spain and Poland supporting the suitability of the UKWP criteria for the GIraFFE study [4,43]. The limitation of the itch criterion is somewhat confirmed in our cohort: nearly half of AD_{Doctor} had no reported history of itchy skin. Thus, also the discrepancy in incidence between AD_{UKWP} and AD_{Doctor} is in line with the lower sensitivity of UKWP criteria, indicating that AD_{Doctor} are more likely milder AD forms.

Dropout rates during the intervention phase were notably higher in WGF than CF. This differential attrition occurred predominantly within the first four months of life. Given that most infants were already introduced to formula before inclusion, most commonly cow milk-based, it appears possible that a switch to a formula with a different protein source may not have been as easily accepted by some infants. While reasons for stopping product consumption and the number of overall AEs were similar, AE categories showed a trend to somewhat higher rates of parent-reported constipation in WGF. Other comparative studies have not identified significant differences in gastrointestinal disorders or constipation between infants fed with WGF and CF [15,44,45]. Therefore, the underlying causes of these group differences remain unclear. Overall, levels of reported constipation in both groups were lower (8.2%) than the estimated worldwide prevalence of functional constipation in infants reported to be 15% [46] and therefore were within a normal range. In agreement with previous studies [15,47], the analysis of anthropometric data showed no differences between WGF and CF.

4.1. Strength and limitations

Strengths of our study include a RCT with a large sample size and high compliance, a low drop-out rate, similar intervention effects in two countries, and the inclusion of a large normal and healthy, formula-fed population, all pointing to the robustness of our findings and facilitating the generalizability of our results. We also included infants with two different AD definitions, one with highly specific criteria (UKWP), and one without criteria that were diagnosed by a medical doctor, increasing the sensitivity of the AD diagnosis. A more standardized, symptom-based and referral-based approach, instead of our fixed appointment study, might have increased the sensitivity of $AD_{Primary}$. Furthermore, an earlier start of the intervention with less pre-intervention cow milk formula intake would have been preferable. However, this is hardly possible for ethical reasons, as it would interfere with breastfeeding. In addition, it is highly likely that children will have consumed other dairy products during the intervention period. However, this applies to children in both the CF and WGF group. The limitations are unlikely to lead to a differential bias affecting observed intervention effects, rather they dilute potential effects.

5. Conclusion

WGF, compared to CF, did not reduce the incidence of AD defined by UKWP criteria in healthy, term infants. There was a protective effect on AD diagnosed by doctors in the PP population with a risk reduction of 34%. In infants with a parental history of AD, WGF significantly reduced the risk of developing AD_{Doctor} by 64%. This trial demonstrates that WGF can reduce the incidence of AD in formula-fed infants in the first year of life, especially in presence of parental history of AD.

Author contributions

BK, VG and LS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The study idea was developed by BK, the conception and design of the study were developed by BK, VG, HD, and UH. LS and VG produced the first draft of the manuscript and all co-authors HD, KG, UH, EW, BK, ME, CC, EC-G, JE, RG-M, JAGS, DG, CG-S, MJ, EJ-C, JK, AM, EP, IR-G, GR, BR, MSdP, MT-F, JW, and AW, critically reviewed the manuscript and approved the final version. RG-M, CC, MSdP, EJ-C, JW, BR, JE, and DG participated in the setup of the study.

Additional contributions

The members of the GIraFFE Study group contributed to the realization of the study. The GIraFFE Study group consists of the following members: Carme Rubio-Torrents, Natalia Ferré, Veronica Luque, Mariona Gispert (Tarragona/Reus); Encarnación López-Ruzafa, Melinda Moriczi (Almeria); Paula Grattarola, Cecilia Martínez- Costa (Valencia); María Luisa Álvarez, Cristina Guillén, Sheila García, Iris Iglesia (Zaragoza); Bibiana Chinea, Esperanza Escribano (Madrid); Elena Requena, Mireia Escudero-Marín, Rocío Bonillo-León, Francisco Contreras-Chova, Antonio Jerez-Calero Elena Requena Rodríguez(Granada); Alicja Syc, Aleksandra Żyła-Pawlak (Warsaw); Sabina Galiniak (Rzeszów); Aleksandra Lisowska, Klaudia Kotecka, Joanna Popek, Maria Chrobot, Natalia Jaworska, Ada Adamczak (Poznań); Fran Adamski (employee of DGC). Sophie Gallier, Colin Prosser, and Elizabeth Carpenter (former employees of DGC) contributed to the conception and design of the study.

Role of funder/sponsor

While the study concept was initiated and developed by the key principal investigator, the sponsor contributed to the design and conduct of the study and reviewed the statistical analysis plan and the manuscript. The sponsor had no role in data collection, data preparation, management, and analysis.

Disclaimer

The sponsor, the site principal investigators and the key principal investigator have agreed and fixed in the study protocol that the final decision-making power on the study rests with the trial steering committee, which includes the key principal investigator, all site principal investigators and the sponsor. The trial steering committee also takes decisions on further grant applications to fund additional analyses of data and biosamples generated in GIraFFE.

Data sharing statement

The study is still ongoing and the data has not been anonymized. There is no consent by participants for general data sharing. On special request and after establishing a data transfer agreement data sharing for specific purposes will be considered.

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Conflict of interest

EW is an employee of DGC (Dairy Goat Co-operative (NZ), Hamilton, New Zealand).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2026.106707.

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