Original Research Article

LESS GASTROINTESTINALSYMPTOMS IN INFANTS FED GOAT MILK-BASED INFANT FORMULA: A CROSS-SECTIONAL STUDY IN CHINA

Abstract

Objectives

Gastrointestinal (GI) symptoms affect approximately half of infants and can adversely impact infants' and parents' quality of life. In this cross-sectional study, infants fed goat milk-based infant formula (GMF) are compared toinfants fed cow's milk-based infant formula (CMF) regarding milk-related symptoms, eating behavior and their parents' quality of life (QOL).

Methods

Healthy Chinese infants aged <6 months, who were either exclusively GMF- (n=303) or CMF-fed (n=464), were included. Parents completed four questionnaires: Cow's Milk-related Symptom Score (CoMiSS®), Infant Gastrointestinal Symptom Questionnaire (IGSQ), World Health Organization Quality of Life (WHOQOL-BREF) questionnaire, and Baby Eating Behavior Questionnaire (BEBQ). Composite scores were compared between infants consuming GMF and CMF using Poisson regression or ANCOVA models.

Results

Infants, mean age 87.8 days, scored low on overallCoMiSS® (median 2, IQR 0-4) and IGSQ (median 16, IQR 14-20), indicating low occurrence of symptoms. The overall CoMiSS® was lower in GMF-fed infants compared to CMF-fed infants ($p<0.001$), specifically driven by crying ($p=0.006$), skin eczema ($p=0.014$) and urticaria ($p=0.039$). Parents of GMF-fed infants experienced better QOL regarding social relationships compared to parents of CMF-fed infants ($p=0.038$). Differences in eating behavior were seen in food responsiveness ($p=0.003$) and slowness in eating ($p=0.005$).No differences were seen on total IGSQ and total WHO-QOL.

Conclusions

Both infants consuming GMF and CMF showed normal scores on GI symptoms, eating behavior and their parents' quality of life. Infants consuming GMF experience less milk-related symptoms than infants consuming CMF, based on lower CoMiSS® scores.

Keywords: Infant Gastrointestinal Symptoms; Infants Eating Behavior; Parental Quality of Life;

Introduction

Adequate early life nutrition is essential for optimal health and growth of infants, as well as for their health later in life[1, 2]. Exclusive breastfeeding in the first six months of life is considered the most optimal source of nutrition for infants. Despite the World Health Organization (WHO) recommendations, more than 50% of infants globally are not exclusively breastfed during their first 6 months of life, and are therefore dependent on infant formula for their nutrition from early infancy [3]. To date, the majority of the infant formulas are cow'smilk-based, but there are alternatives. Goat milk has been approved as a protein source for infant formula in 2012 and has shown adequate growth in infants[4, 5].

Independent on the type of feeding, it is common for infants to experiencegastrointestinal (GI) discomfort such as flatulence, colic, unpleasant soft or hard stools and/orregurgitation during the first year of life[6].In a Chinese cross-sectional study, 43.8% of infants experienced colic in the first two months of life, the prevalence of regurgitation was 33.9% in infants aged 0-6 months [7].Even though GI symptoms commonly occur in healthy infants, some GI symptoms might be due to an allergicreaction to cow's milk protein. In Chinese infants the prevalence of cow's milk protein allergy (CMA) is 2.69%[8]. The Cow's Milk related Symptom Score (CoMiSS®) is an easy-to-use awareness tool, that can be used by caregivers or health care professionals to differentiate between normal milk-related symptoms and possible CMA symptoms[9].

Goat milk protein has shown in in-vitro models to be easier to digest than cow's milk protein [10-12]. The difference in digestibility may influence the occurrence of GI symptoms, but this is less studied in literature.Previous studies found that the occurrence of GI symptoms is strongly related to quality of life (QOL) of both theinfant and the parents [13, 14]. Potentially infants' eating behaviour could also be affected by protein digestibility. Faster digestion could be linked to less satiety and more frequent feeding demands. Therefore, parentalQOL and infant eating behavior were assessed as secondary outcomes.

The objective of this Chinese cross-sectional study was to determine the occurrence of milk-relatedGI symptoms and related health parameters of infants fed goat milk-based infant formula (GMF) compared to infants fed cow's milk-based infant formula (CMF).

Material & methods

Study design& participants

In this observational cross-sectional study, healthy Chinese infants,who exclusively consumedinfant formula for at least 14 consecutive days, were included. Eligible infants were born at term (gestational age between 37 -42 weeks), aged 14 days to 6 months old,their parents were≥18 years old and gave informed consent.Infants with a GI illness or malformation that could interfere with the study parameters were excluded, as well as children receiving medication for functional GI disorders.

Parentswere either invited by a medical doctor from one of the 18 participating hospitals (both CMF and GMF group) or invited via social media (GMF group). Hospitals were located in both rural and urban areas in various regions all over China.The GMF group consumed Kabrita® (Ausnutria, The Netherlands) or another commercially available GMF. The CMF was not specified, all commercially available CMF were allowed.The study protocol was approved by the Ethical Committee of the Nanjing Medical University in China, Registration number; (2021)588.

Outcome measures

The web-based questionnaire started with eligibility questions, which had to be completed beforethe main part of the questionnaire was started. In general the questionnaire consisted of 108 questions which could be completed within 20 min. In theonline questionnaire, a skipping pattern was used to skip irrelevant questions. In some hospitals apaper version of the questionnaire was used, in that case the eligibility questions wereassessed in more detail during data cleaning.

The primary outcome, milk-related symptoms, was assessed using two questionnaires;the Cow's Milk-related Symptoms Score (CoMiSS®) and the Infant Gastrointestinal Symptoms Questionnaire (IGSQ).Both questionnaires were shown to be valid and reliable when scored by parents[9, 15]

CoMiSS® was developed by an expert panel to assesssymptoms that could be CMArelated [16].This easy-to-use awareness tool can be used by caregivers or health care professionals to distinguish between normal milk-related symptoms and possible CMA symptoms, but it is not a diagnostic tool for CMA. CoMiSS® has been validated in a European population and was used in different countries, including China [17-19]. In a Chinese population,CoMiSS® had a sensitivity (87.5%) and specificity (78.6%),which were considered acceptable [17]. CoMiSS®, total score ranging 0-33, consists of five domains; crying, regurgitation, stools, skin (eczema & urticaria) and respiratory symptoms. Each domain has a maximum score of 6, except for respiratory symptoms which has a maximal score of 3. Crying was assessed as hours of crying per day without obvious cause; regurgitation was assessed in episodes and volume of regurgitation; stools were assessed using the Bristol Stool Scale; skin

symptoms were evaluated on presence of eczema on the head, neck and trunk, eczema on arms, hands, legs and feed, and urticaria;and respiratory symptoms were scored on severity. Scores of each item are added up to calculate overallCoMiSS®[16]. Infants with higher CoMiSS®experience more severe milk-related symptoms. Scores <6 indicate symptoms that are commonly present in health infants, it is unlikely that these infants suffer from CMA. OverallCoMiSS® ≥12is suggestive of CMA, further tests are required for diagnosis[16, 19, 20].

The Infant Gastrointestinal Symptom Questionnaire (IGSQ)was developed to interpret and communicate various signs of infants' GI discomfort to health care professionals[15]. IGSQ is a 13 item questionnaire, each item is scored on a scale of 1 to 5 and higher scores indicate more severe GI symptoms. IGSQ includes questions on stool, spitting up, crying, fussiness and flatulence. The majority of the questions focusses on frequency of a GI complaint [15].The IGSQ questionnaire was also validated for the Chinese infant population[15].

Parents'QOL was measured by WHO quality of life questionnaire (WHOQOL-BREF). This questionnaire is a 26-item version of the WHOQOL-100 and has fourdomains, environment, physical, psychological and social relationships. Each question is answered on a 5 point Likert scale, higher scores indicates a better QOL[21]. In China average QOL was reported as a total WHOQOL-BREF score of 64.5 and mean domainscores between 13.5 and 15.2 [22].

Baby Eating Behaviour Questionnaire (BEBQ) was used to assess the infants eating behaviour[23].BEBQ is a parent-reported questionnaire that contains 18 questions and is divided in four domains (enjoyment of food, food responsiveness, slowness in eating and satiety responsiveness). Each question is answered on a 5 point Likert scale and for each domain a mean score was calculated[24].

The questionnaire included questions onpotential confounders, like parental and infant demographics, birth data, and feeding regime.

Data analysis

Statistical analysis was performed using SAS 9.4 software.Means with standard deviations or medians with interquartile rangeswere calculated for continuous and quasi-continuous variables. Categorical data is presented in frequency tables using counts and percentages. Scores of questionnaires were calculated according to their specific instructions.Poisson regressionwith Kenward-Roger degrees of

freedom was used to analyze CoMiSS® and IGSQ scores. For BEBQ and WHOQOL ANCOVA with Kenward-Roger degrees of freedomwas used.

Potential confounding variables (covariates) were identified based on directed acyclic graphs (DAGs). The covariates that were included for analysis on the primary outcomewere age (days), mode of delivery (vaginal, scheduled caesarean, emergency caesarean), duration of feeding breast milk (months), attending daycare (yes, no), parental educational status (basic, high school, junior college/vocational, undergraduate, university or above), parental ethnicity (han, other), parental smoking (yes, no).The covariates that were included for analysis on the secondary outcomes areage, sex (boy, girl), birth weight (grams), mode of delivery, parental educational level and parental ethnicity. Missing values were not imputed and were omitted from the data analyses. P-values <0.05 were considered statistically significant.

Results

Study population characteristics

The study was conducted between July 2021 and December 2021 where data from 1939 infants was collected. After checking for inclusion criteria, complete and valid data of767infants,fed either GMF (n=303) or CMF (n=464), was included in the statistical analyses**(Figure 1)**. Based on the selected set of covariates, two subsets were created to analyze the outcomes. The primary outcome analyses were performed on a subset of 614 infants, as there were missing values for breast feeding duration (n=153), attending day care (n=13), parental educational status (n=1) and parental smoking (n=3). The secondary outcome analyses were performed on a subset of 762 infants, as there were missing values for birth weight (n=4) and parental educational status (n=1) **(Figure 1)**. Infants mean age was 87.8 (±46.1) days and 55.8% of them were boys. The two groups were comparable for all infant and parental characteristics (**Table 1)**.

Gastrointestinal symptoms

OverallCoMiSS® waslow (median 2, IQR 0-4), which indicates symptoms that are normally present in healthy infants.A larger portion of GMF-fed infants showed lower overall CoMiSS® compared to CMF-fed infants (**Figure 2**).

With adjustment for covariates, significant lower scores were found in overallCoMiSS® (ratio of geometric means=0.813, p<0.001) and the domains crying (ratio of geometric means=0.196,

p=0.006), skin eczema (ratio of geometric means=0.690, p=0.014) and skin urticaria (ratio of geometric means=0.486, p=0.039) in GMF-fed infants compared to CMF-fed infants. Lower scores indicate less milk-related symptoms.

The IGSQ scores were low in both the GMF (median 16 (IQR 14-20)) and the CMF group (median 16 (IQR 14-19). When comparing theoccurrence of GI symptomsbetween GMF- and CMF-fed infants no statistically significant difference was found in total IGSQ. In the IGSQ domain fussiness, GMF-fed infants scored higher compared to CMF-fed infants (ratio of geometric means=1.178, p=0.002). The other domains did not show statistically significant differences.

Quality of life

Overall parentalQOLwas high (median 72.7 (IQR 64.6-79.6)).Parents of infants in the GMF group scored significantly higher on the WHOQOL-BREF domain social relationships compared to parents of infants in the CMF group (estimate=0.423, p=0.038)**(Table 2)**. This indicates that parents of infants fed-GMF are more satisfied with their personal relationships, sex life and the support they receive from friends. Total WHOQOL-BREF and scores of the other 3 domains did not show significant differences between GMF and CMF infants.

Eating behavior

Differences in parent-reported eating behavior were seen in the domains food responsiveness and slowness in eating (**Table 3**). GMF infants scored higher on food responsiveness (estimate=0.157, p=0.003) and lower on slowness in eating (estimate= -0.159, p=0.005), indicating that GMF-infants eat faster than CMF-fed infants. The GMF group showed higher agreement to the food responsiveness statements, such as “my baby is happy to feed again if offered” and “my baby can easily take a feed within 30 min of the last one”.In the slowness in eating domain, parents of infants in the CMF group scored higher agreement with the question “My baby sucks more and more slowly during the course of a feed” than parents of infants in the GMF group.

Discussion

To our knowledge, this is the first real-life evidence cross-sectional observational study that investigatedmilk-related symptoms inGMF- and CMF-fed infants in China. All infants scored low on both CoMiSS® and IGSQ, whereasthe GMF-fed infants experienceless milk-related symptoms than

CMF-fed infants. GMF and CMF-fed infants were overall comparable in eating behavior and parental QOL.

Less occurrence of milk-related symptoms in GMF-fed infants can possibly be explained by the difference in protein digestion. There are differences in protein composition between goat and cow's milk. Compared to cow's milk, goat milk contains lower levels of α_{S1}-casein and higher levels of β-caseinwhich is the major protein in human milk [10, 25].The protein composition of goat milk causesthe formation of softer and smaller curds in the stomach[10, 25]. Thismay explain the faster digestion of goat milk protein compared to cow's milk protein that was seen in multiple*in vitro* studies[10-12, 26]. Infants might benefit from the fast digestion of GMF. Two case studies in infants reported GI benefits of feeding GMF when having GI issues [27, 28].

The easy digestibility of goat milk protein could be thought to lead to hunger feelings and less satiety. However, GMF-fed infants did not show higher scores on the crying domain of both CoMiSS® and IGSQ, and there was no difference in BEBQ domains general appetite and satiety responsiveness. GMF-fed infants did score higher on food responsiveness compared to CMF-fed infants. The same was seen in a double-blind randomized controlled trial thatcollected BEBQ data in GMF- and CMF-fed infants during aperiod of 28 days [29]. GMF-fed infants scored higher on food responsiveness and general appetitecompared to CMF-infants after the intervention period [29]. Human milk is known to be easier to digest than infant formula, and breast fed infants score higher on BEBQ food responsiveness compared to formula fed infants [23]. The faster digestibility and higher food responsiveness in GMF is also seen in human milk. This may suggest that GMF is more similar to human milk. Further research should investigate the potential benefits of GMF in GI symptoms and eating behavior.

This study included CoMiSS® and IGSQ, as both questionnaires score GI symptoms, similar differences were expected between the GMF and the CMF group. However, the difference between CMF and GMF were only statistically significant in overall CoMiSS® and not in overall IGSQ. This could be due to the different focus of the tools; IGSQ is specified on GI symptoms, while CoMiSS® focusses on milk-related symptoms, including skin and respiratory symptoms. GMF-fed infants scored significantly lower on CoMiSS® domains skin-eczema and skin-urticaria, the difference in overall CoMiSS® is likely to be caused by the difference in skin symptoms.

CoMiSS® was developed as a tool to create awareness for the difference between common symptoms and symptoms that could be CMA related.Due to the high degree of cross-reactivity between mammalian milk (such as sheep, goats, cows and horses) and the similar response to milk protein, it is likely that CoMiSS® is a suitable tool to score symptoms related to mammalian milk

other than cow's milk such as goat milk.Recently CoMiSS® was updated, but unfortunately the update was not available at the start of our study [30]. The main changes in the updated CoMiSS® are a decrease in cut-off value from ≥12 to ≥10 for suspicion of CMA and the Brussels Infant and Toddler Stool Scale (BITSS) was used instead of the Bristol Stool scale. As this study included only healthy infants, the change in cut-off value is not expected to influence the results. The BITSS is known to have a better assessment of the infants stool by parents, so this might have biased the results.

Parents of the GMF-fed infants experienced better QOL regarding social relationships compared to parents of the CMF-fed infants, although the total QOL scores were similar between the GMF and CMF infants. The impact of GI symptoms on QoL is poorly described in the literature, while investigating the association between GI symptoms and QOL is of importance. These symptoms might cause parental anxiousness leading to distress in the infant which will negatively impact the QOL of the family. Therefore, reducing GI symptoms should focus on improving the infants' symptoms as well as on improving QOL of the family [31].

Strengths and limitations

The main strength of the study is inclusion of a large study population providing real-world evidence. Four types of validated questionnaires were used to obtain a complete picture of the infants' GI health, respiratory and skin symptoms, parents' QOL and infants' eating behavior, including adjustment for many covariates.

The main limitation is that due to the cross-sectional design of the study, no causal inferences can be made between the consumption of GMF and the infants' health, eating behavior or parental QOL.Another limitation was the completeness of the responses, a largenumber of infants had to be excluded because of missing and/or invalid answers on one of the eligibility questions. Due to the use of a paper version of the questionnaires, data was collected and infants were excluded in the data cleaning phase based on exclusion criteria. For further research, innovative techniques should be used to lower the burden of the questionnaire and increase the quality of the data.

Future studies should include more objective measures, such as calprotectin, or health care professional-reported instead of parent-reported questionnaires. The use a prospective randomized controlled double blind design could help to demonstrate the potential health benefits of GMF in infants.

Conclusion

To conclude, infants consuming GMF or CMF showed normal scores on milk-related symptoms, eating behaviour and their parents'QOL. Infants consuming GMF have less milk-related symptoms, specifically crying and skin symptoms, than infants consuming CMF based on a lower CoMiSS®. Future studies on the effect of GMF on milk-related symptoms couldhave a randomized study design and includemore objective measures.

Tables & Figures

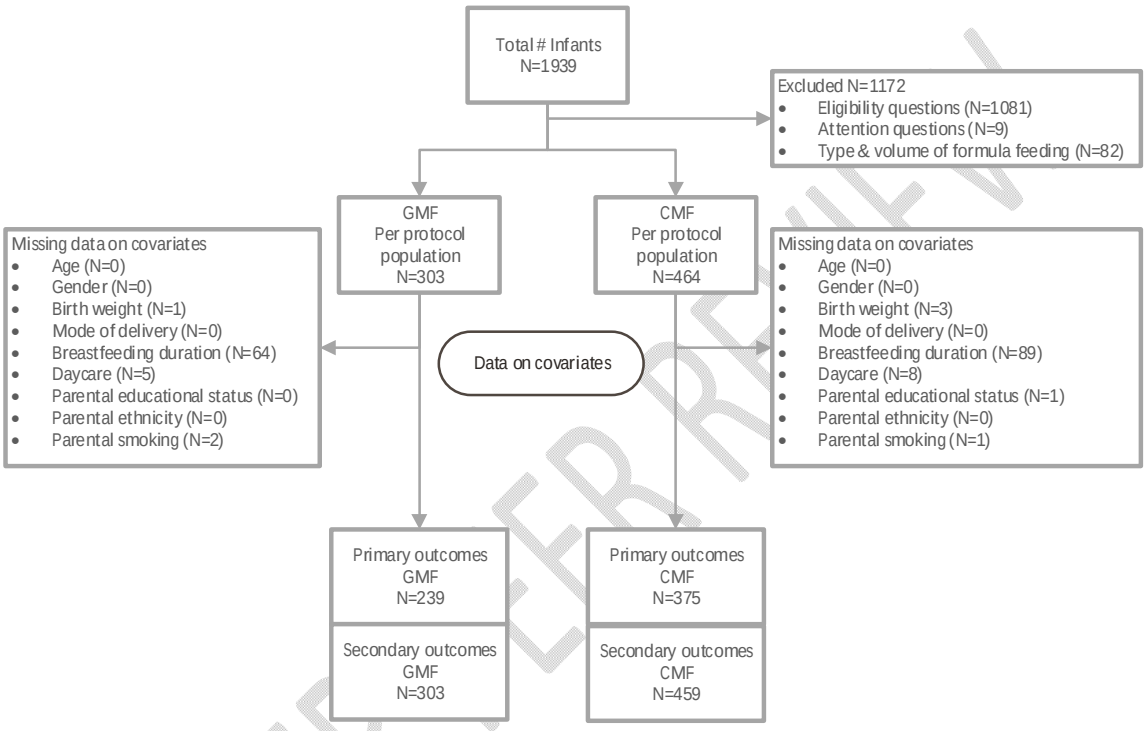

Figure 1. Flow chart

Table 1. Baseline characteristics of the Goat milk-based infant formula (GMF) and Cow's milk-based infant formula(CMF) group (n (%))

	Total	GMF (N= 303)	CMF (N=464)
Infant's characteristics			
Age, days (Mean (SD))	87.8 (46.1)	90.0 (46.6)	86.2 (45.9)
Birth weight, gram (Mean (SD))	3524.9 (953.3)	3624.5 (1030.1)	3459.6 (894.5)
Sex, boy	428 (55.8%)	164 (54.1%)	264 (56.9%)
Delivery			
Vaginally	427 (55.7%)	181 (59.7%)	246 (53%)
Caesarean scheduled	234 (30.5%)	93 (30.7%)	141 (30.4%)
Caesarean emergency	106 (13.8%)	29 (9.6%)	77 (16.6%)
Breastfeeding duration			
None	283 (46.1%)	120 (50.2%)	163 (43.5%)
First month (0-1 month)	107 (17.4%)	39 (16.3%)	68 (18.1%)
First 3 months (1-3 months)	144 (23.5%)	56 (23.4%)	88 (23.5%)
First 6 months (3-6 months)	80 (13.0%)	24 (10.0%)	56 (14.9%)
Missing		64	89
Attending day care	11 (1.4%)	6 (2.0%)	5 (1.1%)
Missing		5	8
Maternal demographic			
Highest completed education level			
Basic	65 (8.5%)	26 (8.6%)	39 (8.4%)
High School	119 (15.5%)	53 (17.5%)	66 (14.2%)
Junior College/Vocational	132 (17.2%)	62 (20.5%)	70 (15.1%)
Undergraduate	349 (45.5%)	149 (49.2%)	200 (43.1%)
University or above	102 (13.3%)	13 (4.3%)	89 (19.2%)
Ethnicity			
Han	727 (94.8%)	285 (94%)	442 (95.2%)
Other	40 (5.2%)	18 (5.9%)	22 (4.8%)
Prenatal smoking	6 (0.8%)	4 (1.3%)	2 (0.4%)
Prenatal alcohol	3 (0.4%)	2 (0.7%)	1 (0.2%)
Postnatal smoking	13 (1.7%)	6 (2.0%)	7 (1.5%)

Postnatal alcohol	2 (0.3%)	1 (0.3%)	1 (0.2%)
Paternal demographic			
Highest completed education level			
Basic	79 (10.3%)	39 (12.9%)	40 (8.6%)
High School	122 (15.9%)	40 (13.2%)	82 (17.7%)
Junior College/Vocational	141 (18.4%)	59 (19.5%)	82 (17.7%)
Undergraduate	337 (43.9%)	151 (49.8%)	186 (40.1%)
University or above	87 (11.3%)	14 (4.6%)	73 (15.7%)
Ethnicity			
Han	733 (95.6%)	284 (93.7%)	449 (96.7%)
Other	34 (4.4%)	19 (6.3%)	15 (3.3%)
Smoking	323 (42.1%)	107 (35.3%)	216 (46.6%)

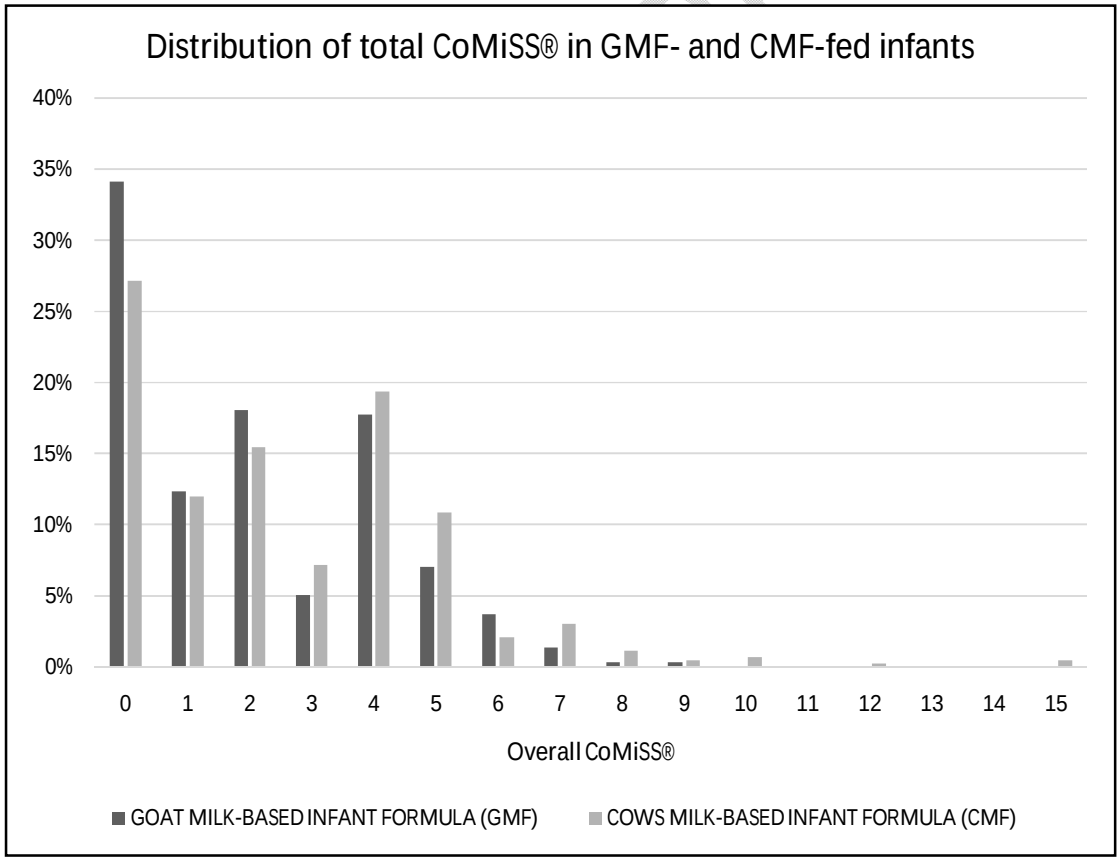

Figure 2 Distribution of overallCow's milk-related symptoms score(CoMiSS®) inGMF-and CMF-fed infants. There is a larger percentage of infants with lower CoMiSS® scores in the GMF group.

Table 2. World Health Organization Quality of Life **(**WHOQOL) (least squares means (95% CI))

	GMF (N=300)	CMF(N=458)	Estimate	95% CI	P-value
Environment score	15.0 (13.7-16.3)	14.7 (13.3-16.0)	0.297	-0.090, 0.685	0.132
Physical score	14.9 (13.7-16.1)	14.8 (13.6-16.0)	0.138	-0.221, 0.497	0.451
Psychological score	14.5 (13.1, 16.0)	14.3 (12.9, 15.8)	0.209	-0.123, 0.631	0.331
Social relationship score	15.6 (14.2, 16.9)	15.1 (13.8, 16.5)	0.423	0.024, 0.823	**0.038**
Total score	68.7 (61.4, 76.1)	67.1 (59.7, 74.5)	1.588	-0.606, 3.782	0.156

Results are obtained from an analysis of covariance model (ANCOVA) with treatment (Goat milk-based infant formula (GMF) or Cow's milk-based infant formula (CMF)) as a fixed effect, and paternal/maternal educational status, mode of delivery, paternal/maternal ethnicity, age, gender, and infant birth weight as covariates, with Kenward-Roger degrees of freedom.

Table 3. Baby Eating Behavior Questionnaire (BEBQ) (least squares means (95% CI))

	GMF (N=302)	CMF (N=455)	Estimate	95% CI	P-value
Enjoyment of food	4.2 (3.8, 4.5)	4.2 (3.9, 4.6)	-0.049	-0.153, 0.005	0.356
Food responsiveness	2.1 (1.8, 2.5)	2.0 (1.6, 2.3)	0.157	0.052, 0.263	**0.003**
Slowness in eating	2.0 (1.6, 2.3)	2.0 (1.7, 2.5)	-0.159	-0.270, -0.048	**0.005**
Satiety responsiveness	2.0 (1.6, 2.3)	2.0 (1.6, 2.3)	-0.001	-0.100, 0.098	0.982
General appetite	4.3 (3.8, 4.8)	4.2 (3.8, 4.7)	0.057	-0.080, 0.195	0.412

Results are obtained from an analysis of covariance model (ANCOVA) with treatment (Goat milk-based infant formula (GMF) or Cow's milk-based infant formula (CMF))as a fixed effect, and paternal/maternal educational status, mode of delivery, paternal/maternal ethnicity, age, gender, and infant birth weight as covariates with Kenward-Roger degrees of freedom.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

Term	Explanation
BEBQ	Baby Eating Behaviour Questionnaire

CMA	Cow's milk protein allergy
CMF	Cow's milk-based infant formula
CoMiSS®	Cow's Milk-related Symptom Score
IF	Infant Formula
IGSQ	Infant Gastrointestinal Symptom Questionnaire
GI	GastroIntestinal
GMF	Goat milk-based infant formula
WHO	World Health Organization
WHOQOL-BREF	World Health Organization Quality OfLife – short version
QOL	Quality of life

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