

Supplementary Materials (Otten et al. Nutrients 2023)

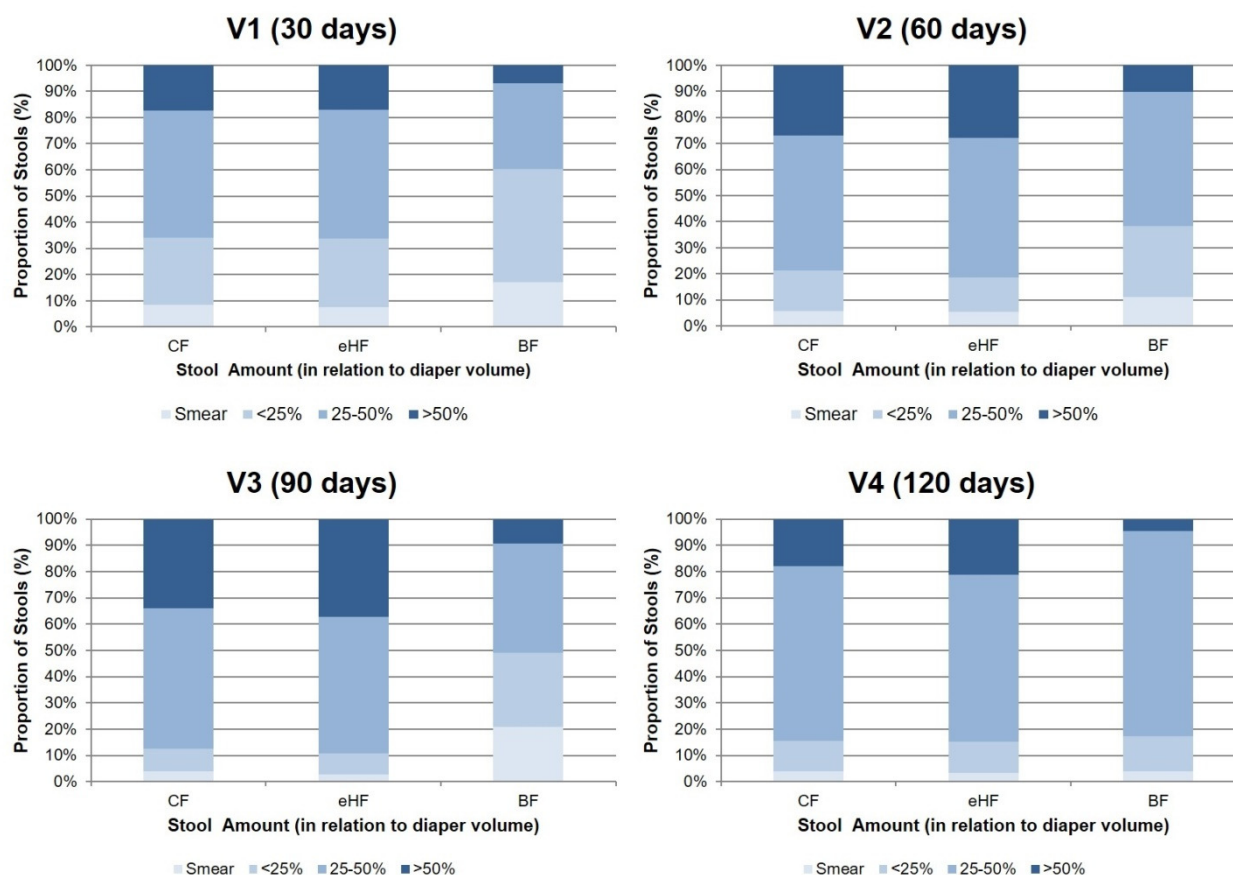


Figure S1. Proportion of stool amount (in relation to diaper volume) per diaper from 3-day diary (PPS).

Missing values in eHF: V1: $n = 2$; V4: $n = 1$.

Missing values in CF: V3: $n = 1$.

BF: breastfed reference group; CF: control formula; eHF: infant formula manufactured from extensively hydrolysed whey protein; PPS: per protocol set; V: visit.

Table S1. Selected individual items from the IGSQ (PPS)

Visit	Age at Visit (Days)		eHF (n = 149)	CF (n = 148)	BF (n = 41)
No. 3: Frequency of spitting up: “Thinking about a usual day in the past week, how many times did milk come out of your baby's mouth?”					
1	30	0 times in a usual day	77 (51.7)	79 (53.4)	21 (51.2)
		1 time in a usual day	35 (23.5)	36 (24.3)	11 (26.8)
		2 to 3 times in a usual day	32 (21.5)	31 (20.9)	7 (17.1)
		4 to 6 times in a usual day	4 (2.7)	2 (1.4)	2 (4.9)
		7 or more times in a usual day	0 (0.0)	0 (0.0)	0 (0.0)
		Do not know or no response	1 (0.7)	0 (0.0)	0 (0.0)
2	60	0 times in a usual day	83 (55.7)	85 (57.4)	22 (53.7)
		1 time in a usual day	44 (29.5)	44 (29.7)	14 (34.1)
		2 to 3 times in a usual day	19 (12.8)	19 (12.8)	5 (12.2)
		4 to 6 times in a usual day	3 (2.0)	0 (0.0)	0 (0.0)
		7 or more times in a usual day	0 (0.0)	0 (0.0)	0 (0.0)
		Do not know or no response	0 (0.0)	0 (0.0)	0 (0.0)
3	90	0 times in a usual day	91 (61.1)	82 (55.4)	17 (41.5)
		1 time in a usual day	32 (21.5)	41 (27.7)	19 (46.3)
		2 to 3 times in a usual day	23 (15.4)	24 (16.2)	4 (9.8)
		4 to 6 times in a usual day	3 (2.0)	1 (0.7)	0 (0.0)
		7 or more times in a usual day	0 (0.0)	0 (0.0)	0 (0.0)
		Do not know or no response	0 (0.0)	0 (0.0)	1 (2.4)
4	120	0 times in a usual day	113 (75.8)	117 (79.1)	27 (65.9)
		1 time in a usual day	30 (20.1)	25 (16.9)	12 (29.3)
		2 to 3 times in a usual day	4 (2.7)	6 (4.1)	2 (4.9)
		4 to 6 times in a usual day	1 (0.7)	0 (0.0)	0 (0.0)
		7 or more times in a usual day	0 (0.0)	0 (0.0)	0 (0.0)
		Do not know or no response	1 (0.7)	0 (0.0)	0 (0.0)
No. 7: Frequency of crying: „Thinking about the past week, how much total time did your baby usually cry in a day?“					
1	30	Less than 10 minutes in a day	29 (19.5)	27 (18.2)	10 (24.4)
		10 to 30 minutes in a day	52 (34.9)	60 (40.5)	11 (26.8)
		30 minutes to 1 hour in a day	39 (26.2)	33 (22.3)	8 (19.5)
		1 to 2 hours in a day	22 (14.8)	19 (12.8)	7 (17.1)
		2 or more hours in a day	3 (2.0)	6 (4.1)	3 (7.3)
		Do not know or no response	4 (2.7)	3 (2.0)	2 (4.9)
2	60	Less than 10 minutes in a day	37 (24.8)	45 (30.4)	14 (34.1)
		10 to 30 minutes in a day	42 (28.2)	47 (31.8)	11 (26.8)
		30 minutes to 1 hour in a day	50 (33.6)	37 (25.0)	13 (31.7)
		1 to 2 hours in a day	17 (11.4)	17 (11.5)	2 (4.9)
		2 or more hours in a day	2 (1.3)	1 (0.7)	0 (0.0)
		Do not know or no response	1 (0.7)	1 (0.7)	1 (2.4)
3	90	Less than 10 minutes in a day	49 (32.9)	48 (32.4)	14 (34.1)
		10 to 30 minutes in a day	43 (28.9)	46 (31.1)	16 (39.0)
		30 minutes to 1 hour in a day	38 (25.5)	38 (25.7)	11 (26.8)
		1 to 2 hours in a day	19 (12.8)	15 (10.1)	0 (0.0)
		2 or more hours in a day	0 (0.0)	0 (0.0)	0 (0.0)
		Do not know or no response	0 (0.0)	1 (0.7)	0 (0.0)

Visit	Age at Visit (Days)		eHF (n = 149)	CF (n = 148)	BF (n = 41)
4	120	Less than 10 minutes in a day	68 (45.6)	72 (48.6)	21 (51.2)
		10 to 30 minutes in a day	38 (25.5)	41 (27.7)	5 (12.2)
		30 minutes to 1 hour in a day	31 (20.8)	22 (14.9)	9 (22.0)
		1 to 2 hours in a day	11 (7.4)	12 (8.1)	5 (12.2)
		2 or more hours in a day	0 (0.0)	0 (0.0)	0 (0.0)
		Do not know or no response	1 (0.7)	1 (0.7)	1 (2.4)

No. 9: Frequency of crying during or right after feeding: "Thinking about the past week, how many times did your baby cry during or right after a feeding because the milk bothered your baby?"

1	30	0 times in the week	88 (59.1)	89 (60.1)	21 (51.2)
		1 time in the week	39 (26.2)	40 (27.0)	13 (31.7)
		2 times in the week	14 (9.4)	10 (6.8)	3 (7.3)
		3 times in the week	2 (1.3)	4 (2.7)	1 (2.4)
		4 or more times in the week	0 (0.0)	1 (0.7)	0 (0.0)
		Do not know or no response	6 (4.0)	4 (2.7)	3 (7.3)
2	60	0 times in the week	83 (55.7)	89 (60.1)	22 (53.7)
		1 time in the week	40 (26.8)	34 (23.0)	11 (26.8)
		2 times in the week	21 (14.1)	20 (13.5)	7 (17.1)
		3 times in the week	3 (2.0)	4 (2.7)	1 (2.4)
		4 or more times in the week	1 (0.7)	0 (0.0)	0 (0.0)
		Do not know or no response	1 (0.7)	1 (0.7)	0 (0.0)
3	90	0 times in the week	93 (62.4)	93 (62.8)	19 (46.3)
		1 time in the week	43 (28.9)	42 (28.4)	11 (26.8)
		2 times in the week	10 (6.7)	11 (7.4)	11 (26.8)
		3 times in the week	2 (1.3)	2 (1.4)	0 (0.0)
		4 or more times in the week	0 (0.0)	0 (0.0)	0 (0.0)
		Do not know or no response	1 (0.7)	0 (0.0)	0 (0.0)
4	120	0 times in the week	104 (69.8)	105 (70.9)	18 (43.9)
		1 time in the week	40 (26.8)	32 (21.6)	17 (41.5)
		2 times in the week	2 (1.3)	9 (6.1)	3 (7.3)
		3 times in the week	1 (0.7)	0 (0.0)	1 (2.4)
		4 or more times in the week	0 (0.0)	1 (0.7)	0 (0.0)
		Do not know or no response	2 (1.3)	1 (0.7)	2 (4.9)

No. 10: Frequency of feeling fussy: "Thinking about the past week, on how many days was your baby fussy?"

1	30	0 day	82 (55.0)	85 (57.4)	27 (65.9)
		1 day	26 (17.4)	22 (14.9)	7 (17.1)
		2 or 3 days	39 (26.2)	38 (25.7)	7 (17.1)
		4 or 5 days	2 (1.3)	3 (2.0)	0 (0.0)
		6 or more days	0 (0.0)	0 (0.0)	0 (0.0)
2	60	0 day	92 (61.7)	99 (66.9)	26 (63.4)
		1 day	20 (13.4)	16 (10.8)	7 (17.1)
		2 or 3 days	37 (24.8)	33 (22.3)	8 (19.5)
		4 or 5 days	0 (0.0)	0 (0.0)	0 (0.0)
		6 or more days	0 (0.0)	0 (0.0)	0 (0.0)
3	90	0 day	101 (67.8)	105 (70.9)	24 (58.5)
		1 day	30 (20.1)	27 (18.2)	8 (19.5)
		2 or 3 days	18 (12.1)	16 (10.8)	9 (22.0)
		4 or 5 days	0 (0.0)	0 (0.0)	0 (0.0)
		6 or more days	0 (0.0)	0 (0.0)	0 (0.0)

Visit	Age at Visit (Days)		eHF (n = 149)	CF (n = 148)	BF (n = 41)
4	120	0 day	114 (76.5)	115 (77.7)	24 (58.5)
		1 day	21 (14.1)	14 (9.5)	13 (31.7)
		2 or 3 days	14 (9.4)	19 (12.8)	4 (9.8)
		4 or 5 days	0 (0.0)	0 (0.0)	0 (0.0)
		6 or more days	0 (0.0)	0 (0.0)	0 (0.0)
No. 12: Frequency of flatulence: "Thinking about the past week, how many times in a usual day was your baby gassy?"					
1	30	0 times in a usual day	14 (9.4)	22 (14.9)	3 (7.3)
		1 time in a usual day	40 (26.8)	47 (31.8)	20 (48.8)
		2 to 3 times in a usual day	63 (42.3)	52 (35.1)	16 (39.0)
		4 to 6 times in a usual day	25 (16.8)	20 (13.5)	1 (2.4)
		7 or more times in a usual day	4 (2.7)	5 (3.4)	0 (0.0)
		Do not know or no response	3 (2.0)	2 (1.4)	1 (2.4)
2	60	0 times in a usual day	33 (22.1)	35 (23.6)	13 (31.7)
		1 time in a usual day	50 (33.6)	64 (43.2)	17 (41.5)
		2 to 3 times in a usual day	48 (32.2)	36 (24.3)	11 (26.8)
		4 to 6 times in a usual day	14 (9.4)	8 (5.4)	0 (0.0)
		7 or more times in a usual day	4 (2.7)	4 (2.7)	0 (0.0)
		Do not know or no response	0 (0.0)	1 (0.7)	0 (0.0)
3	90	0 times in a usual day	56 (37.6)	58 (39.2)	21 (51.2)
		1 time in a usual day	55 (36.9)	60 (40.5)	19 (46.3)
		2 to 3 times in a usual day	27 (18.1)	23 (15.5)	1 (2.4)
		4 to 6 times in a usual day	9 (6.0)	7 (4.7)	0 (0.0)
		7 or more times in a usual day	2 (1.3)	0 (0.0)	0 (0.0)
		Do not know or no response	0 (0.0)	0 (0.0)	0 (0.0)
4	120	0 times in a usual day	89 (59.7)	90 (60.8)	24 (58.5)
		1 time in a usual day	31 (20.8)	33 (22.3)	16 (39.0)
		2 to 3 times in a usual day	19 (12.8)	15 (10.1)	1 (2.4)
		4 to 6 times in a usual day	8 (5.4)	7 (4.7)	0 (0.0)
		7 or more times in a usual day	1 (0.7)	1 (0.7)	0 (0.0)
		Do not know or no response	1 (0.7)	2 (1.4)	0 (0.0)

Values presented as *n* (%). No missing values.

The statistical analysis with a logistic ordinal mixed model for repeated measurements showed a significant effect of visit on all individual questions ($p < 0.001$).

BF: breastfed group; CF: control formula; eHF: infant formula manufactured from extensively hydrolysed whey protein; *n*: number of observations; No.: number; PPS: per protocol set

Table S2. Comparison of IGSQ 13-item total score (a.u., range 13-65) by visit in the subgroup of infants who did not take GI tolerance medications (linear mixed model for repeated measurements) (PPS)

Visit	Group	N	LSM	SEM	95% confidence interval (2-sided)	Two-sided superiority p value
2	eHF	109	22.62	1.0169	[20.51;24.73]	0.4679
	CF	105	22.02	1.0304	[19.89;24.15]	
	eHF vs CF		0.60	0.8198	[-1.02;2.21]	
3	eHF	109	21.07	0.9315	[19.09;23.05]	0.4843
	CF	105	20.67	0.9429	[18.66;22.67]	
	eHF vs CF		0.40	0.5770	[-0.73;1.54]	
4	eHF	108	17.46	0.9465	[15.46;19.46]	0.6326
	CF	105	17.76	0.9575	[15.74;19.78]	
	eHF vs CF		-0.30	0.6241	[-1.53;0.93]	
	Product					0.5683
	Visit					<0.0001
	Sex					0.5818
	Product*Visit					0.6166

Missing values in eHF: V4: $n = 1$; V2: $n = 1$.

a.u.: arbitrary units; BF: breastfed group; CF: control formula; eHF: infant formula manufactured from extensively hydrolysed whey protein; GI: gastrointestinal; IGSQ: Infant Gastrointestinal Symptoms Questionnaire; LSM: least square means; N: number of observations; PPS: per protocol set; SEM: standard error of mean

Table S3. Comparison of IGSQ 13-item total score (a.u., range 13-65) between the two subgroups of infants who did or did not receive GI tolerance medication (three-way interaction term with infant formula group, visit, and subgroup in linear mixed model for repeated measurements) (PPS)

Visit	GI tolerance medication	Group	N	LSM	SEM	95% confidence interval (2-sided)	Two-sided superiority p value
2	Yes	eHF	149	23.56	1.2803	[20.99;26.12]	
		CF	147	23.34	1.2623	[20.81;25.87]	
	No	eHF	149	22.71	0.9958	[20.64;24.77]	
		CF	147	22.10	1.0091	[20.01;24.19]	
3	Yes	eHF	149	20.79	1.1221	[18.51;23.07]	
		CF	148	21.24	1.1042	[18.99;23.49]	
	No	eHF	149	21.16	0.9230	[19.21;23.12]	
		CF	148	20.75	0.9346	[18.77;22.72]	
4	Yes	eHF	148	17.14	1.1037	[14.89;19.39]	
		CF	148	16.68	1.0868	[14.46;18.90]	
	No	eHF	148	17.56	0.9155	[15.61;19.50]	
		CF	148	17.84	0.9263	[15.88;19.80]	
Product							0.6725
Visit							<0.0001
Sex							0.7713
GI tolerance medication							0.8097
Product*Visit							0.8965
Visit*GI tolerance medication							0.1726
Product*GI tolerance medication							0.8222
Product*Visit*GI tolerance medication							0.5689

Missing values in subgroup of infants who did not take GI tolerance medications: in eHF: V4: $n = 1$:

V2: $n = 1$. Missing values in subgroup infants who did take GI tolerance medications: in CF: V2, $n=1$.

a.u.: arbitrary units; BF: breastfed group; CF: control formula; eHF: infant formula manufactured from extensively hydrolysed whey protein; GI: gastrointestinal; IGSQ: Infant Gastrointestinal Symptoms Questionnaire; LSM: least square means; N: number of observations; PPS: per protocol set; SEM: standard error of mean

Table S4. Mean duration of uninterrupted nocturnal sleep (hours/night) and mean daily time to fall asleep (hours/day) from 3-day diary (PPS)

Visit	Age at visit (days)	Uninterrupted nocturnal sleep			Time to fall asleep		
		eHF (<i>n</i> = 149)	CF (<i>n</i> = 148)	BF (<i>n</i> = 41)	eHF (<i>n</i> = 149)	CF (<i>n</i> = 148)	BF (<i>n</i> = 41)
1	30	4.5 (1.5) (1.3 ; 9.0)	4.6 (1.5) (1.3 ; 8.3)	4.0 (1.8) (1.6 ; 6.4)	0.8 (0.4) (0.0 ; 1.8)	0.8 (0.4) (0.1 ; 3.0)	0.9 (0.4) (0.3 ; 2.2)
2	60	5.0 (1.6) (1.5 ; 9.0)	5.0 (1.6) (1.8 ; 8.5)	4.7 (1.6) (1.7 ; 6.9)	0.7 (0.3) (0.1 ; 1.8)	0.7 (0.3) (0.1 ; 1.7)	0.8 (0.3) (0.2 ; 1.4)
3	90	5.6 (1.8) (1.5 ; 12.3)	5.6 (1.7) (1.8 ; 9.4)	5.8 (1.8) (1.8 ; 8.2)	0.7 (0.3) (0.0 ; 1.5)	0.7 (0.3) (0.2 ; 1.8)	0.8 (0.5) (0.2 ; 3.3)
4	120	6.1 (1.4) (1.5 ; 10.0)	6.1 (1.6) (1.8 ; 11.1)	6.2 (1.1) (3.2 ; 8.3)	0.5 (0.2) (0.2 ; 1.5)	0.5 (0.2) (0.1 ; 1.1)	0.5 (0.2) (0.1 ; 0.9)

Values presented as mean (SD), (min ; max)

Missing values in CF for mean daily time to fall asleep: V1: *n* = 1; V2: *n* = 1

BF: breastfed group; CF: control formula; eHF: infant formula manufactured from extensively hydrolysed whey protein; *n*: number of observations; max: maximum; min: minimum; PPS: per protocol set; SD: standard deviation