



# **The Association of Formula Protein Content and Growth in Early Infancy: A Systematic Review and Meta-Analysis**

Qiqi Ren <sup>1,2</sup>, Kaifeng Li <sup>1,2</sup>, Han Sun <sup>1,2</sup>, Chengdong Zheng <sup>1,2</sup>, Yalin Zhou <sup>2,3</sup>, Ying Lyu <sup>2,3</sup>, Wanyun Ye <sup>2,3</sup>, Hanxu Shi <sup>2,3</sup>, Wei Zhang <sup>1,2</sup>, Yajun Xu <sup>2,3,4,\*</sup> and Shilong Jiang <sup>1,2,\*</sup>

- <sup>1</sup> Innovation Center, Nutrition and Metabolism Research Division, Heilongjiang Feihe Dairy Co., Ltd., C-16, 10A Jiuxianqiao Rd., Chaoyang, Beijing 100015, China; rqqrenqiqi@163.com (Q.R.); likaifeng@feihe.com (K.L.); sunhan@feihe.com (H.S.); zhengchengdong@feihe.com (C.Z.); zhangwei1@feihe.com (W.Z.)
- <sup>2</sup> PKUHSC-China Feihe Joint Research Institute of Nutrition and Healthy Lifespan Development, Xueyuan Road 38, Haidian, Beijing 100083, China; 1911110168@bjmu.edu.cn (Y.Z.); lybjmu@126.com (Y.L.); yewanyun\_vera@bjmu.edu.cn (W.Y.); 1610306136@bjmu.edu.cn (H.S.)
- <sup>3</sup> Department of Nutrition and Food Hygiene, School of Public Health, Peking University, Xueyuan Road 38, Haidian, Beijing 100083, China
- <sup>4</sup> Beijing Key Laboratory of Toxicological Research and Risk Assessment for Food Safety, Peking University, Xueyuan Road 38, Haidian, Beijing 100083, China
- \* Correspondence: xuyajun@bjmu.edu.cn (Y.X.); jiangshilong@feihe.com (S.J.); Tel.: +86-130-1111-6041 (Y.X.); +86-138-1147-1909 (S.J.)

**Abstract:** This systematic review aimed to examine differences in growth outcomes between breastfed infants and infants fed with formula with different protein/energy ratios during the first six months of life. We conducted a systematic review in the PubMed, Web of Science, and Springer databases. Twenty clinical trials qualified for inclusion. We extracted data about the growth outcomes of infants who were exclusive breastfed or exclusively infant formula fed in the first six months and used a meta-analysis to pool the finding data. We categorized study formulas into four groups according to their protein content: <1.8, 1.8–2.0, 2.1–2.2, and >2.2 g/100 kcal. In the first month of life, growth was not different between formula- and breastfed infants. During 2–3 months of life, growth was faster in infants who consumed formulas with protein contents higher than 2.0 g/100 kcal. After 3 months, formula-fed infants grew faster than breastfed infants. Our meta-analysis indicated that the growth outcomes of infants fed with infant formula with a relatively low protein/energy ratios, compared with that a relatively high protein/energy ratio, were close to those of breastfed infants.

Keywords: infant formula; protein/energy ratio; breastfed; weight gain; height gain

# 1. Introduction

Human milk is presumably the ideal source of nutrition for infants. Briefly, human milk provides infants with appropriate amounts of (1) water; (2) building blocks of the body, such as amino acids and minerals; (3) metabolic fuels, such as lactose and triglycerides, (4) coenzymes and protein cofactors, such as vitamins and minerals required for enzymatic activities and protein functions; (5) bioactive molecules, such as miRNA and metabolites that regulate biochemical pathways; (6) immunoproteins, such as immunoglobulins and lactoferrin, that grant infants protection against infections; (7) oligosaccharides that nourish infant gut microbiota; etc. [1].

Because human milk contains a comprehensive profile of nutrients, the World Health Organization (WHO) defines exclusive breastfeeding as providing human milk as the sole source of nutrition—with no additional fluid or other food provided—within the first 6 months of life. Continued breastfeeding beyond 6 months with the introduction of complementary foods is also encouraged [2]. Nevertheless, the global rate of exclusive breastfeeding was only 38% in 1995 [3]. High-income countries generally have higher



Citation: Ren, Q.; Li, K.; Sun, H.; Zheng, C.; Zhou, Y.; Lyu, Y.; Ye, W.; Shi, H.; Zhang, W.; Xu, Y.; et al. The Association of Formula Protein Content and Growth in Early Infancy: A Systematic Review and Meta-Analysis. *Nutrients* **2022**, *14*, 2255. https://doi.org/10.3390/ nu14112255

Received: 20 April 2022 Accepted: 26 May 2022 Published: 28 May 2022

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). rates of exclusive breastfeeding than low-income countries [4]. Factors such as insufficient maternal leave, lack of training from hospitals, maternal diseases and psychological problems, etc. discourage the practice of exclusive breastfeeding [5].

Not exclusively breastfeeding is associated with short- and long-term health issues. Overall, inadequate breastfeeding leads to substantial morbidity and approximately 600,000 child deaths and an additional 100,000 maternal deaths annually [6]. During lactation, because infant formula lacks protective compounds in natural human milk, the rates of otitis media and diarrhea in nonbreastfed infants are 8% and 17% higher, respectively, than those in exclusively breastfed infants [7]. In the long run, breastfed infants have higher scores on intelligence tests and lower rates of chronic diseases than formula-fed infants [8]. In fact, the concept of developmental origins of health and diseases (DOHaD) suggests that early infancy is a window of susception when inappropriate nutrition is related to increased risks of chronic diseases later in life [9]. Particularly, accelerated postnatal weight gain has been associated with overweightness and disorders in glucose homeostasis and appetite control in adulthood [10,11]. Presumably, healthy, exclusively breastfed infants exhibit the ideal growth trajectory of early postnatal growth [12]. In feeding studies, formula-fed infants usually gained weight faster than breastfed infants [13].

Inappropriate macronutrient composition is one of the possible reasons for the higher growth velocity in formula-fed infants. The protein content in infant formula displays marked differences from that in human milk. First, to compensate the different amino acid profiles and lower protein quality, infant formulas provide higher protein content than human milk [14]. Additionally, the protein concentration decreases gradually throughout lactation, whereas the protein content in infant formulas remains the same [15]. Accordingly, infant formulas are designed to meet the protein requirements during the earliest postnatal phase, when the human milk protein content is the highest [15,16]. Consequently, infant formulas provide excessive protein for infants during most postnatal periods.

The relationship between formula protein content and faster growth in formula-fed infants has been investigated in both clinical trials and meta-analyses. Several clinical trials have demonstrated that infants fed with formula with lower protein content grew slower and more closely to breastfed infants than infants fed with formula with higher protein content. These clinical trials were identified and listed in the systematic reviews by Abrams et al. and Patro-Gołąb et al., which, to the best of our knowledge, are the only two systematic reviews currently available that summarized the works on infant formula protein contents and postnatal growth [16,17]. Unfortunately, neither of these two studies compiled data from different studies together, possibly because of the inhomogeneity in protein content, duration of feeding, infant age, etc. among different studies. In our initial exploration, we found that, by compiling data from different clinical trials together, it was possible to establish the dose-dependent effects of formula protein content on infant growth and to demonstrate the effects of formula feeding on infant body growth during different postnatal stages when human milk protein content gradually decreases.

The aim of the current study was to explore the dose-dependent effects of formula protein contents on infant body growth during different stages in the first 6 months of life by performing a systematic review and meta-analysis. To achieve our goal, we separated infants into six age groups: 0–1, 1–2, 2–3, 3–4, 4–5, and 5–6 months. We also categorized infant formulas into four groups according to their protein concentrations. Our study highlighted the possible metabolic consequences of excess protein intake during early infancy and provides valuable information to academia and policy-makers.

#### 2. Materials and Methods

# 2.1. Literature Screening

The guidelines in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-p) were followed [18]. We conducted a search of the PubMed, Web of Science, and Springer databases. The searching strategy of "((infant formula) NOT (low birth weight) NOT (preterm) NOT (hydrolyzed)) AND ((trial) OR (feeding) OR (composition) OR (content) OR (growth) OR (development) OR (weight) OR (length) OR (height) OR (head circumference) OR (weight gain) OR (length gain) OR (height gain) OR (tolerance) OR (adequacy) OR (safety))" was used. The literature search was completed in August 2021. A total of 2518 duplicates and obviously irrelevant articles were removed after reading the titles and abstracts. The clinical trial articles were screened using the inclusion and exclusion criteria listed in PICOS (Supplementary Table S1). The Cochrane Collaboration's tool for assessing risk of bias was used while including the following criteria: adequacy of sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective reporting; and other biases [19]. Notably, studies were not excluded based on these results. Items were scored as having low, high, or unknown risk of bias. The literature screening process was performed independently by two investigators (Q.R. and K.L.). Discrepancies were discussed in the presence of W.Z. until consensuses were reached.

#### 2.2. Data Extraction and Analysis

The means, standard deviations (SDs), and a number of samples about growth outcomes of infants during the first six months of life were extracted, which were weight gain, height gain, and BMI. Data were pooled according to age and protein content. We categorized the studied formulas into four groups according to their protein content: <1.8, 1.8–2.0, 2.1–2.2, and >2.2 g/100 kcal. The data were pooled using the meta-analysis approach. Forest plots were generated to compare the growth outcomes of infants fed exclusively with infant formula with different protein/energy ratios with those of infants fed exclusively with breast milk. In the studies that reported continuous variables as means, the mean difference (MD) between the experimental and control groups with 95% confidence intervals (CIs) was calculated. Heterogeneity was assessed using the  $I^2$  statistic defined by the Cochrane Handbook for Systematic Reviews. A fixed-effects model was used when there was no significant heterogeneity among studies; otherwise, a random-effects model was used. p values less than 0.05 were considered statistically significant. Microsoft Excel (Microsoft Corporation, Redmond, WA, USA), Review Manager v5.4 (The Cochrane Collaboration, London, UK), and R v4.1.2 were used for data extraction and analysis. Data extraction and analysis were performed independently by two investigators (Q.R. and K.L.). Discrepancies were discussed in the presence of W.Z. until consensuses were reached.

#### 3. Results

A total of 19 articles were included and assessed in our analysis (Figures 1 and S1). Eleven studies were supported by for-profit institutes. The studies were conducted in 17 countries in East Asia, Europe, and North America between 1992 and 2021 [20–38]. Ages at enrollment ranged from birth to 15 postnatal days; feeding duration ranged from enrollment to 6 months; and protein contents of formulas ranged from 1.4 to 2.7 g/100 kcal (Supplementary Table S2).

The protein/energy ratio of infant formula in included studies ranged from 1.4 to 2.7 g/100 kcal. We categorized study formulas into four groups according to their protein content: <1.8, 1.8–2.0, 2.1–2.2, and >2.2 g/100 kcal. At 1 month of age, body weight gain, height gain, and BMI in formula-fed infants were not significantly different from those in breastfed infants (Figure 2). At 2 months of age, body weight gain in infants who consumed formula with protein content 2.1–2.2 g/100 kcal (n = 623; MD: 1.01 g; 95% CI: 0.26, 1.77) or higher than 2.2 g/100 kcal (n = 341; MD: 3.03 g; 95% CI: 2.10, 3.97) was significantly higher than that in breastfed infants, and BMI in infants that consumed formula with protein content higher than 2.2 g/100 kcal (n = 241; MD: 0.38 kg/m<sup>2</sup>; 95% CI: 0.07, 0.69) was significantly higher than that in breastfed infants, whereas height gain in formula-fed infants was not different from that in breastfed infants (Figure 3). At 3 months of age, body weight gain in infants in the 2.1–2.2 g/100 kcal group was higher than that in their breastfed counterparts (n = 529; MD: 1.74 g; 95% CI: 0.95, 2.52), whereas height gain and BMI were not different between formula- and breastfed infants (Figure 4). At 4 months

of age, body weight gain (n = 2685; MD: 2.06 g; 95% CI: 1.53, 2.59), height gain (n = 2081; MD: 0.02 mm; 95% CI: 0.00, 0.04), and BMI (n = 868; MD: 0.58 kg/m<sup>2</sup>; 95% CI: 0.40, 0.77) in formula-fed infants were significantly higher than those in breastfed infants in all formulas, except that weight gain in infants who consumed formula with protein content lower than 1.8 g/100 kcal was not significantly different from that in breastfed infants (Figure 5). Beyond 4 months of age, body weight gain and height gain in formula-fed infants were significantly higher than those in breastfed infants (Figure 6). No forest plot was created of the effects of protein content of infant formula on the weight gain and height gain of infants at 5 months of age, because there was only one study on the weight gain of infants at 5 months of age. In that study, the protein level of 2.2 g/100 kcal was investigated. Body weight gain and BMI in the formula-fed infants were higher than those in breastfed infants in gain of infants. A heat map of the effects of protein content of infant formula on the growth of infants is depicted in Figure 7. It summarizes the differences between breastfeeding and formula feeding in terms of weight gain, height gain, and BMI.

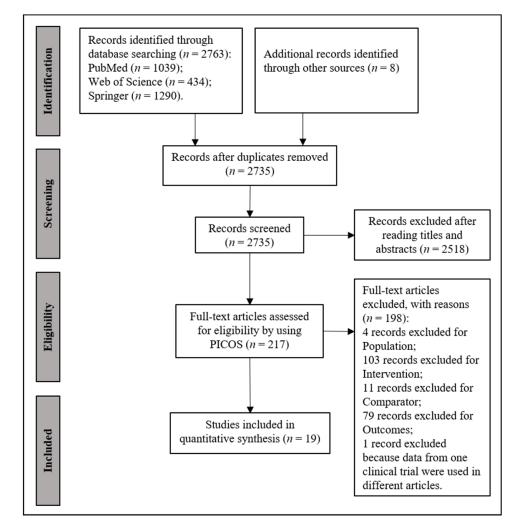


Figure 1. Flow chart of literature searching and screening.

study or Subgroup	IF-weigh Mean	ht gain SD	(g/d) Total	HM – weigh Mean				Mean Difference IV, Random, 95% Cl	Mean Difference IV, Random, 95% Cl
.1.1 1m–pro1.8~2.0									
Breij 2019	32.5	2.8	149	34.6	2.9		3.9%	-2.10 [-3.16, -1.04]	•
lanning 1992	35.2	10	45	36.7	12.4		8.7%	-1.50 [-5.83, 2.83]	
aiha 2002	26	8.3	56	27.7	9.5		9.0%	-1.70 [-5.84, 2.44]	<u> </u>
oggero 2020	41.4	5.9	26	41.5	9.7		8.6%	-0.10 [-4.46, 4.26]	T
urck 2006	36.5	7.8	51	34.2	11.4		9.5%	2.30 [-1.52, 6.12]	T.
andenplas 2020 ubtotal (95% CI)	29.5	2.2	186 513	26.8	1.9		4.2% 64.0%	2.70 [2.11, 3.29] 0.02 [-2.72, 2.76]	
eterogeneity: Tau <sup>2</sup> = 9	02: Chiž-	- 64 76		R ~ 0.00001)	17-029		04.070	0.02 [-2.72, 2.70]	Ť
est for overall effect: Z			, ui – 5 (i	- < 0.00001)	,1 = 329	0			
1.2 1m–pro2.1~2.2									
anning 1992	35.5	9.4	50	36.7	12.4	58	9.0%	-1.20 [-5.32, 2.92]	
aiha 2002	30.9	8	29	27.7	9.5		8.3%	3.20 [-1.37, 7.77]	
oggero 2020	40.8	4.8	26	41.5	9.7		9.0%	-0.70 [-4.86, 3.46]	
ıbtotal (95% CI)			105			112 2	26.3%	0.28 [-2.36, 2.91]	<b>•</b>
eterogeneity: Tau² = 0 est for overall effect: Z				= 0.32);   <sup>2</sup> = 1	12%				
1.3 1m-pro > 2.2									
urck 2006	34.9	6.8	50	34.2	11.4	50	9.8%	0.70 [-2.98, 4.38]	<u>+</u>
ubtotal (95% CI)	34.5	0.0	50	34.2	11.4	50	9.8%	0.70 [-2.98, 4.38]	
eterogeneity: Not appl	licable							,	
st for overall effect: Z		= 0.71)							
otal (95% CI)			668			414 10	00.0%	0.18 [-1.84, 2.21]	4
eterogeneity: Tau² = 7	.37; Chi² =	= 68.06		P < 0.00001)	; I² = 87%		00.070	0.10[-1.04, 2.21]	-50 -25 0 25
est for overall effect: Z	= 0.18 (P	= 0.86)							-50 -25 0 25 Favors human milk Favors infant formula
est for subaroup differ	ences. Ci	III – 0.0	19. ul – 2	(F = 0.90). I	- 0 %		(a)		
							()		
	IF – height			HM-heigt				Mean Difference	Mean Difference
tudy or Subgroup .2.1 1m–pro1.8~2.0	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
reij 2019	1.55	0.18	149	1.47	0.11	35	12.8%	0.08 [0.03, 0.13]	+
lanning 1992	1.47	0.5	45		0.41	58	9.3%		+
aiha 2002	1.49	0.47	56		0.5	28	8.0%		
oggero 2020	1.41	0.11	26		0.15	26	12.3%		-
urck 2006	1.49	0.54	51		0.55	50	8.3%		_ <b></b>
andenplas 2020	0.61	0.23	186	0.47	0.1	55	12.8%	0.14 [0.10, 0.18]	-
ubtotal (95% CI)			513			252	63.5%	0.03 [-0.08, 0.13]	<b>•</b>
leterogeneity: Tau² = 0	.01; Chi <sup>2</sup> =	= 51.40,	df = 5 (P	< 0.00001);	I² = 90%				
est for overall effect: Z	= 0.45 (P :	= 0.65)							
.2.2 1m–pro2.1~2.2									
lanning 1992	1.6	0.4	50	1.37	0.41	58	10.1%	0.23 [0.08, 0.38]	
Raiha 2002	1.57	0.57	29	1.65	0.5	28	6.6%	-0.08 [-0.36, 0.20]	
Roggero 2020	1.33	0.19	26		0.15	26	11.8%		
Subtotal (95% CI)			105			112	28.5%	-0.03 [-0.35, 0.30]	
leterogeneity: Tau² = 0 est for overall effect: Z			df = 2 (P	< 0.00001);	I <sup>2</sup> = 92%				
.2.3 1m–pro > 2.2									
urck 2006	1.46	0.59	50	1.38	0.55	50	8.0%	0.08 [-0.14, 0.30]	
Subtotal (95% CI)	1.40	0.55	50		0.55	50	8.0%		-
leterogeneity: Not appl	icahla		50			50	0.070	0.00 [-0.14, 0.50]	
est for overall effect Z		= 0.48)							
		,	660				400.0%	0.041.0.00.0.441	
otal (95% CI)	02' Chi <sup>2</sup> =	94.05	668 df = 9 (P		F = 90%	414	100.0%	0.01 [-0.09, 0.11]	
leterogeneity: Tau <sup>2</sup> = 0			ui - 0 (i	0.00001),1					-1 -0.5 0 0.5 1
		- 0.01)							
est for overall effect: Z	= 0.24 (P :		2. df = 2	(P = 0.85), I <sup>2</sup> :	= 0%		(1-)		Favors human milk Favors infant formula
est for overall effect: Z	= 0.24 (P :		2. df = 2	(P = 0.85). I <sup>z</sup> :	= 0%		(b)		
est for overall effect: Z	= 0.24 (P : ences: Ch		2. df = 2	(P = 0.85).  * = HM-BN			. ,	Difference	
est for overall effect. Z est for subaroup differ tudy or Subgroup	= 0.24 (P = ences: Ch IF- <u>Mean</u>	ni² = 0.3 <b>BMI</b>	2. df = 2   <u>Total  </u>	HM-BN	лі	Weight	Mean	Difference Fixed, 95% Cl	Favors human milk Favors infant formula
est for overall effect: Z est for subaroub differ tudy or <u>Subgroup</u> 3.1 1m—pro1.8~2.(	= 0.24 (P = ences: Ch IF- <u>Mean</u>	-BMI SD	Total	HM-BN	/II Total	<u>Weight</u> 31.4%	Mean		Favors human milk Favors infant formula Mean Difference
est for overall effect. Z est for subaroup differ tudy or <u>Subgroup</u> <b>3.1 1m – pro 1.8~2.0</b> aiha 2002	= 0.24 (P ences: Ch IF- <u>Mean</u> )	-BMI SD 0.83	<u>Total  </u> 56	HM-BN Mean SD	/II ) <u>Total</u> 28		Mean t IV, F	ixed, 95% Cl	Favors human milk Favors infant formula Mean Difference
est for overall effect. Z est for subaroup differ tudy or Subgroup 3,1 1m – pro1.8~2.0 aiha 2002 urck 2006	= 0.24 (P ences: Ch <u>IF-</u> <u>Mean</u> ) 1.3.98	-BMI SD 0.83	<u>Total  </u> 56	HM-BN Mean SD 14.26 1.01	/II ) <u>Total</u> 28	31.4%	Mean <u>IV, F</u> -0.28 0.41	Fixed, 95% Cl 3 [-0.71, 0.15]	Favors human milk Favors infant formula Mean Difference
est for overall effect. Z est for subarouu differ tudy or Subgroup 3.1 1m – pro1.8~2.( aiha 2002 urck 2006 uutotal (95% Cl) eterogeneity: Chi <sup>a</sup> =	= 0.24 (P: ences: Ch IF- Mean 1 3.98 1 4.82 4.39, df:	BMI SD 0.83 1.14 = 1 (P :	<u>Total</u> 56 51 <b>107</b> = 0.04);	HM-BN Mean SD 14.26 1.01 14.41 1.31	/II <u>Total</u> 28 50	31.4% 25.6%	Mean <u>IV, F</u> -0.28 0.41	Fixed, 95% Cl 3 [-0.71, 0.15] 1 [-0.07, 0.89]	Favors human milk Favors infant formula Mean Difference
est for overall effect. Z est for subarouu differ tudy or Subgroup 3.1 1m – pro1.8~2.( aiha 2002 urck 2006 uutotal (95% Cl) eterogeneity: Chi <sup>a</sup> =	= 0.24 (P : ences: Ch IF- Mean 1 3.98 1 4.82 4.39, df :	BMI SD 0.83 1.14 = 1 (P :	<u>Total</u> 56 51 <b>107</b> = 0.04);	HM-BN Mean SD 14.26 1.01 14.41 1.31	/II <u>Total</u> 28 50	31.4% 25.6%	Mean <u>IV, F</u> -0.28 0.41	Fixed, 95% Cl 3 [-0.71, 0.15] 1 [-0.07, 0.89]	Favors human milk Favors infant formula Mean Difference
est for overall effect. Z est for subgroup 3.1 fm—pro1.8~2.( ainha 2002 urck 2006 ubtotal (95% Cl) leterogeneity: Chi <sup>2</sup> = est for overall effect: 3.2 fm—pro2.1~2. <i>i</i> .	= 0.24 (P : ences: Ch IF- Mean 13.98 14.82 4.39, df: Z = 0.18 2	-BMI 50 0.83 1.14 = 1 (P = (P = 0	<u>Total  </u> 56 51 <b>107</b> = 0.04); 86)	HM-BN Mean SD 14.26 1.01 14.41 1.31 I <sup>2</sup> = 77%	/II <u>7 Total</u> 28 50 78	31.4% 25.6% <b>57.0</b> %	Mean <b>IV, F</b> -0.28 0.41 0.03	Fixed, 95% Cl 3 [-0.71, 0.15] 1 [-0.07, 0.89] 5 [-0.29, 0.35]	Favors human milk Favors infant formula Mean Difference
est for overall effect. Z est for subaroup differ 3.1 1m–pro1.8~2.0 (aiha 2002 urck 2006 ubtotal (95% CI) leterogeneity: Chi <sup>2</sup> = est for overall effect: 3.2 1m–pro2.1~2.7 (aiha 2002	= 0.24 (P : ences: Ch IF- Mean 13.98 14.82 4.39, df : Z = 0.18	-BMI 50 0.83 1.14 = 1 (P = (P = 0	<u>Total  </u> 56 51 <b>107</b> = 0.04); 86) 29	HM-BN Mean SD 14.26 1.01 14.41 1.31	/II 28 50 78 28	31.4% 25.6% <b>57.0</b> % 18.8%	Mean <b>IV. F</b> -0.28 0.41 0.03 0.20	Fixed, 95% Cl 3 [-0.71, 0.15] [-0.07, 0.89] [-0.29, 0.35]	Favors human milk Favors infant formula Mean Difference
est for overall effect. Z est for subaroup differ 3.1 1m-pro1.8~2.( aiha 2002 urck 2006 ubtotal (95% Cl) eterogeneity: Chi <sup>2</sup> = est for overall effect: 3.2 1m-pro2.1~2.2 aiha 2002 ubtotal (95% Cl)	= 0.24 (P : ences: Ch <u>IF-</u> <u>Mean</u> 13.98 14.82 4.39, df: Z = 0.18 2 14.46	-BMI SD 0.83 1.14 (P = 0 1.14	<u>Total  </u> 56 51 <b>107</b> = 0.04); 86)	HM-BN Mean SD 14.26 1.01 14.41 1.31 I <sup>2</sup> = 77%	/II <u>7 Total</u> 28 50 78	31.4% 25.6% <b>57.0</b> %	Mean <b>IV. F</b> -0.28 0.41 0.03 0.20	Fixed, 95% Cl 3 [-0.71, 0.15] 1 [-0.07, 0.89] 5 [-0.29, 0.35]	Favors human milk Favors infant formula Mean Difference
est for overall effect. Z est for subaroup differ 3.1 1m-pro1.8-2.( aiha 2002 urck 2006 ubtotal (95% CI) eterogeneity: Chi <sup>2</sup> = est for overall effect: 3.2 1m-pro2.1-2.2 aiha 2002 ubtotal (95% CI) eterogeneity: Not ap	= 0.24 (P : ences: Ch IF- Mean 13.98 14.82 4.39, df : Z = 0.18 2 14.46 pplicable	<b>BMI</b> 5D 0.83 1.14 = 1 (P = 0 1.14	Total   56 51 107 = 0.04); 86) 29 29 29	HM-BN Mean SD 14.26 1.01 14.41 1.31 I <sup>2</sup> = 77%	/II 28 50 78 28	31.4% 25.6% <b>57.0</b> % 18.8%	Mean <b>IV. F</b> -0.28 0.41 0.03 0.20	Fixed, 95% Cl 3 [-0.71, 0.15] [-0.07, 0.89] [-0.29, 0.35]	Favors human milk Favors infant formula Mean Difference
Test for overall effect. Z est for subaroup differ subaroup differ 3.1 1m - pro1.8~2.( taiha 2002 urck 2006 ubtotal (95% CI) leterogeneity: Chi <sup>2</sup> = est for overall effect: 3.2 1m - pro2.1~2.7 taiha 2002 ubtotal (95% CI) leterogeneity: Not ap	= 0.24 (P : ences: Ch IF- Mean 13.98 14.82 4.39, df : Z = 0.18 2 14.46 pplicable	<b>BMI</b> 5D 0.83 1.14 = 1 (P = 0 1.14	Total   56 51 107 = 0.04); 86) 29 29 29	HM-BN Mean SD 14.26 1.01 14.41 1.31 I <sup>2</sup> = 77%	/II 28 50 78 28	31.4% 25.6% <b>57.0</b> % 18.8%	Mean <b>IV. F</b> -0.28 0.41 0.03 0.20	Fixed, 95% Cl 3 [-0.71, 0.15] [-0.07, 0.89] [-0.29, 0.35]	Favors human milk Favors infant formula Mean Difference
tudy or Subgroup isst for subgroup 	= 0.24 (P : ences: Ch IF- Mean 13.98 14.82 4.39, df : Z = 0.18 2 14.46 pplicable	<b>BMI</b> 5D 0.83 1.14 = 1 (P = 0 1.14	Total   56 51 107 = 0.04); 86) 29 29 29	HM-BN Mean SD 14.26 1.01 14.41 1.31 I <sup>2</sup> = 77%	/II 28 50 78 28	31.4% 25.6% <b>57.0</b> % 18.8%	Mean <b>IV. F</b> -0.28 0.41 0.03 0.20	Fixed, 95% Cl 3 [-0.71, 0.15] [-0.07, 0.89] [-0.29, 0.35]	Favors human milk Favors infant formula Mean Difference
tudy or Subgroup tudy or Subgroup .3.1 1m-pro1.8~2.( taiha 2002 urck 2006 ubtotal (95% CI) leterogeneity: Chi <sup>2</sup> = est for overall effect: .3.2 1m-pro2.1~2.7 taiha 2002 ubtotal (95% CI) leterogeneity: Not ag est for overall effect: .3.3 1m-pro > 2.2	= 0.24 (P : ences: Ch IF- Mean 13.98 14.82 4.39, df : Z = 0.18 2 14.46 pplicable	<b>BMI</b> 5D 0.83 1.14 = 1 (P = 0 1.14	Total   56 107 = 0.04); 86) 29 29 48)	HM-BN Mean SD 14.26 1.01 14.41 1.31 I <sup>2</sup> = 77%	/II 28 50 78 28 28 28	31.4% 25.6% <b>57.0</b> % 18.8% <b>18.8</b> %	Mean -0.28 0.41 0.03 0.20 0.20	Fixed, 95% Cl 3 [-0.71, 0.15] [-0.07, 0.89] [-0.29, 0.35]	Favors human milk Favors infant formula Mean Difference
iest for overall effect. Z iest for subaroup differ 3.1 1m-pro 1.8~2.0 (aiha 2002 urck 2006 ubtotal (95% Cl) leterogeneity: Chi <sup>2</sup> = est for overall effect: aiha 2002 uubtotal (95% Cl) leterogeneity: Not ag est for overall effect:	= 0.24 (P : ences: Ch IF- Mean 13.98 14.82 4.39, df : Z = 0.18 2 14.46 pplicable Z = 0.70	-BMI SD 0.83 1.14 = 1 (P = (P = 0 1.14 (P = 0	Total   56 107 = 0.04); 86) 29 29 48)	HM — BN Mean SD 14.26 1.01 14.41 1.31 I <sup>≠</sup> = 77% 14.26 1.01	/II 28 50 78 28 28 28	31.4% 25.6% 57.0% 18.8% 18.8% 24.2%	Mean <b>IV, F</b> 0.28 0.41 0.03 0.20 0.20 0.20	Fixed, 95% Cl 3 [-0.71, 0.15] 1 [-0.07, 0.89] [-0.29, 0.35] [-0.29, 0.35] 0 [-0.36, 0.76] [-0.36, 0.76]	Favors human milk Favors infant formula Mean Difference
tudy or Subgroup ast for subgroup 3.1 1m—pro1.8~2.( ainha 2002 urck 2006 ubtotal (95% CI) leterogeneity: Chi <sup>2</sup> = est for overall effect: 3.2 1m—pro2.1~2.7 ainha 2002 ubtotal (95% CI) leterogeneity: Not ag est for overall effect: 3.3 1m—pro > 2.2 urck 2006 ubtotal (95% CI) leterogeneity: Not ag est for Overall effect: 3.3 1m—pro > 2.2	= 0.24 (P : ences: Ch Mean 13.98 14.82 4.39, df: Z = 0.18 2 14.46 oplicable Z = 0.70 14.39 oplicable		Total   56 51 107 = 0.04); 86) 29 29 29 48) 50 50	HM — BN Mean SD 14.26 1.01 14.41 1.31 I <sup>≠</sup> = 77% 14.26 1.01	/II 28 50 78 28 28 28 50	31.4% 25.6% 57.0% 18.8% 18.8% 24.2%	Mean <b>IV, F</b> 0.28 0.41 0.03 0.20 0.20 0.20	Fixed, 95% Cl 3 [-0.71, 0.15] 1 [-0.07, 0.89] [-0.29, 0.35] 0 [-0.36, 0.76] [-0.36, 0.76] 2 [-0.51, 0.47]	Favors human milk Favors infant formula Mean Difference
tudy or Subgroup ast for subgroup 3.1 1m-pro1.8~2.( aiha 2002 urck 2006 ubtotal (95% Cl) leterogeneity: Chi <sup>2</sup> = est for overall effect 3.2 1m-pro2.1~2.2 ubtotal (95% Cl) leterogeneity: Not ag est for overall effect .3.3 1m-pro 2.2 urck 2006 ubtotal (95% Cl)	= 0.24 (P : ences: Ch Mean 13.98 14.82 4.39, df: Z = 0.18 2 14.46 oplicable Z = 0.70 14.39 oplicable		Total   56 51 107 = 0.04); 86) 29 29 29 48) 50 50	HM — BN Mean SD 14.26 1.01 14.41 1.31 I <sup>≠</sup> = 77% 14.26 1.01	/II 28 50 78 28 28 28 50	31.4% 25.6% 57.0% 18.8% 18.8% 24.2%	Mean <b>IV, F</b> 0.28 0.41 0.03 0.20 0.20 0.20	Fixed, 95% Cl 3 [-0.71, 0.15] 1 [-0.07, 0.89] [-0.29, 0.35] 0 [-0.36, 0.76] [-0.36, 0.76] 2 [-0.51, 0.47]	Favors human milk Favors infant formula Mean Difference
tudy or Subgroup ast for subgroup 3.1 1m—pro1.8~2.( aiha 2002 urck 2006 ubtotal (95% CI) eterogeneity: Chi <sup>2</sup> = est for overall effect: 3.2 1m—pro2.1~2.7 aiha 2002 ubtotal (95% CI) eterogeneity: Not ag est for overall effect: 3.3 1m—pro > 2.2 urck 2006 ubtotal (95% CI) eterogeneity: Not ag	= 0.24 (P : ences: Ch Mean 13.98 14.82 4.39, df: Z = 0.18 2 14.46 oplicable Z = 0.70 14.39 oplicable		Total   56 51 107 = 0.04); 86) 29 29 29 48) 50 50	HM — BN Mean SD 14.26 1.01 14.41 1.31 I <sup>≠</sup> = 77% 14.26 1.01	//I 28 50 78 28 28 28 50 50 50	31.4% 25.6% 57.0% 18.8% 18.8% 24.2%	Mean Mean 0.22 0.41 0.03 0.20 0.20 0.20 0.20 0.20	Fixed, 95% Cl 3 [-0.71, 0.15] 1 [-0.07, 0.89] [-0.29, 0.35] 0 [-0.36, 0.76] [-0.36, 0.76] 2 [-0.51, 0.47]	Favors human milk Favors infant formula Mean Difference
tudy or Subgroup ast for subgroup 3.1 1m-pro1.8-2.0 aiha 2002 urck 2006 ubtotal (95% CI) eterogeneity: Chi <sup>2</sup> = ast for overall effect: 3.2 1m-pro2.1-2.2 aiha 2002 ubtotal (95% CI) eterogeneity: Not ag ast for overall effect: 3.3 1m-pro > 2.2 urck 2006 ubtotal (95% CI) eterogeneity: Not ag ast for overall effect: 3.3 tor overall effect: bit for overa	= 0.24 (P: mean 13.98 14.82 4.39, dfr 14.46 pplicable Z = 0.70 14.39 pplicable Z = 0.08	-BMI SD 0.83 1.14 =1 (P = 0 1.14 (P = 0 1.2 (P = 0	Total 1 56 107 = 0.04); 886) 29 29 448) 50 50 94) 186	HM — BN Mean SD 14.26 1.01 14.41 1.31 I <sup>≠</sup> = 77% 14.26 1.01 14.41 1.31	//I 28 50 78 28 28 28 50 50 50	31.4% 25.6% 57.0% 18.8% 18.8% 24.2% 24.2%	Mean Mean 0.22 0.41 0.03 0.20 0.20 0.20 0.20 0.20	Eixed, 95% Cl 3 [-0.71, 0.15] 1 [-0.07, 0.89] [-0.29, 0.35] 0 [-0.36, 0.76] [-0.36, 0.76] 2 [-0.51, 0.47] [-0.51, 0.47] 	Favors human milk Favors infant formula
udy or Subgroup 3.1 Im-pro1.8-2.( aiha 2002 urck 2006 ubtotal (95% CI) eterogeneity: Chi <sup>2</sup> = ast for overall effect: 3.2 Im-pro2.1-2.( aiha 2002 ubtotal (95% CI) eterogeneity: Not a; ast for overall effect: 3.3 Im-pro > 2.2 urck 2006 ubtotal (95% CI) eterogeneity: Not a; ast for overall effect:	= 0.24 (P- ences: Ch 13.98 13.98 14.82 2 14.42 2 14.46 0pplicable 2 = 0.70 14.39 pplicable 2 = 0.70 14.39	-BMI = 0.3 0.83 1.14 $= 1 (P = 0$ 1.14 $(P = 0$ 1.2 $(P = 0 = 3) (P = 0$	Total 1 56 51 107 29 29 29 48) 50 50 94) 186 = 0.19);	HM — BN Mean SD 14.26 1.01 14.41 1.31 I <sup>≠</sup> = 77% 14.26 1.01 14.41 1.31	//I 28 50 78 28 28 28 50 50 50	31.4% 25.6% 57.0% 18.8% 18.8% 24.2% 24.2%	Mean Mean 0.22 0.41 0.03 0.20 0.20 0.20 0.20 0.20	Fixed, 95% Cl 3 [-0.71, 0.15] 1 [-0.07, 0.89] [-0.29, 0.35] 0 [-0.36, 0.76] [-0.36, 0.76] 2 [-0.51, 0.47] [-0.51, 0.47]	Favors human milk Favors infant formula

**Figure 2.** Forest plot of the effects of protein content of infant formula on the weight gain, height gain, and BMI of infants at 1 month of age. (a) The effects on weight gain. (b) The effects on height gain. (c) The effects on BMI.

(c)

itudy or Subgroup	IF—weigh Mean	t gain () SD	g/d) Total	HM—weigh Mean				Mean Difference IV, Random, 95% Cl	Mean Difference IV, Random, 95% Cl
<b>.1.1 2m–pro1.8~2.0</b> reij 2019	27.3	2.2	162	30.9	3.1	74	8.6%	-3.60 [-4.38, -2.82]	+
anning 1992	34.2	9.4	45		11.2	58 :	5.4%	0.30 [-3.68, 4.28]	
iotto 2018 utet 2016	34.5 30.3	4 2.5	50 72	30.3 29.7	4.2 4.5		8.0% 8.3%	4.20 [2.59, 5.81] 0.60 [-0.60, 1.80]	+- <sup>-</sup>
aiha 2002	28.8	7.3	56	30.1	6.7 10 4	28	6.4%	-1.30 [-4.43, 1.83]	<u>+</u>
Turck 2006 Yandenplas 2020	34.1 30.8	7.9 2.8	51 173	31.4 28.8	10.4 2.6		5.6% 8.5%	2.70 [-1.09, 6.49] 2.00 [1.19, 2.81]	
ubtotal (95% CI)			609			377 5	0.8%	0.67 [-1.88, 3.22]	*
leterogeneity: Tau <sup>2</sup> = 'est for overall effect: .			2, df = 8	6 (P < 0.0000	1); I² = 9	6%			
.1.2 2m–pro2.1~2.2									
Davis 2008 Januiro 4992	35.5 33.3	8.8 8.5	87 50	34.5	8.7 11.2		6.8% 6.7%	1.00 [-1.75, 3.75]	<del></del>
Hanning 1992 Raiha 2002	33.3 32.8	8.5 6.7	50 29	33.9 30.1	11.2 6.7		5.7% 6.0%	-0.60 [-4.32, 3.12] 2.70 [-0.78, 6.18]	
Singhal 2010	28.2	3.6	200	27.2	3.4	101	8.5%	1.00 [0.17, 1.83]	<b>★</b>
iubtotal (95% CI) leterogeneity: Tau² =	0.00; Chi <b>ř</b> =	: 1.63, d	366 f = 3 (P	= 0.65); I <sup>2</sup> = 0	)%	257 2	7.0%	1.01 [0.26, 1.77]	•
est for overall effect: .	Z = 2.62 (P	= 0.009)	I.						
.1.3 2m—pro > 2.2	22.0	24	60	20.2	10	<i>c</i> o ,	0.4.04	2 00 12 4 5 5 0 5	
Liotto 2018 Putet 2016	33.9 32.3	3.1 3.5	50 77	30.3 29.7	4.2 4.5		8.1% 8.2%	3.60 [2.15, 5.05] 2.60 [1.29, 3.91]	
Turck 2006	34.2	6.4	50		10.4	43 :	5.9%	2.80 [-0.78, 6.38]	+
iubtotal (95% CI) leterogeneity: Tau² =	0 00° Chiř =	:103 d	177 f= 2 (P	= 0.60); 12 = 0	196	164 2	2.2%	3.03 [2.10, 3.97]	•
est for overall effect: .				0.007,1					
otal (95% CI)			1152			798 10	0.0%	1.28 [-0.22, 2.79]	
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: .			, df = 13	8 (P ≤ 0.0000	1); I² = 9	3%			
est for subaroup diffe			51. df=	2 (P = 0.003)	. I² = 82.	6%	(a)		Favors human milk Favors infant formula
							(a)		
	IF-height			HM-heigh				Mean Difference	Mean Difference
itudy or Subgroup .2.1 2m–pro1.8~2.0	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% Cl	IV, Random, 95% Cl
Breij 2019 Hanning 1992	1.22 1.36	0.07 0.38	162 45	1.2 1.29	0.05 0.36	74 58	17.2%		
Hanning 1992 Liotto 2018	1.36	0.38	45 50	1.29	0.36	58 50	1.8%		
Putet 2016	1.38	0.07	72	1.35	0.04	71	16.5%	0.03 [0.01, 0.05]	
Raiha 2002 Furck 2006	1.32 1.28	0.26 0.49	56 51	1.35 1.23	0.24 0.45	28 43	2.8% 1.1%		
/andenplas 2020	0.79	0.12	173	0.73	0.05	53 377	15.6%	0.06 [0.04, 0.08]	<b>_</b>
Subtotal (95% CI) Heterogeneity: Tau² = I	0.00; Chi² =	22.24, d		= 0.001); I <sup>2</sup> =	73%	511	62.1%	0.02 [-0.01, 0.05]	$\mathbf{T}$
Fest for overall effect 2									
I.2.2 2m-pro2.1~2.2	4.0	0.00		1.00		70	0.00	0.0410.05.0.10	
Davis 2008 Hanning 1992	1.3 1.36	0.29 0.37	87 50	1.26 1.29	0.3 0.36	70 58	3.8% 2.0%		
Raiha 2002	1.41	0.25	29	1.35	0.24	28	2.3%	0.06 [-0.07, 0.19]	
Subtotal (95% CI) Heterogeneity: Tau² = I	0.00; Chi² =	0.14, df	166 = 2 (P =	0.93); I² = 09	6	156	8.1%	0.05 [-0.01, 0.12]	
Fest for overall effect: 2									
l.2.3 2m–pro > 2.2									
Liotto 2018 Putet 2016	1.3 1.37	0.12 0.08	50 77	1.33 1.35	0.02 0.04	50 71	12.6%		
Furck 2006	1.37	0.08	50	1.35	0.04	43	1.1%	0.07 [-0.12, 0.26]	
Subtotal (95% Cl) Heterogeneity: Tau² = I	100.058-	6 6 F ~*	177 - 2 (P -	0.04):12 - 20	96	164	29.9%	0.00 [-0.04, 0.05]	<b></b>
Heterogeneity: Taur = 1 Fest for overall effect: 2			- 2 (P =	0.04), F = 70	- 10				
fotal (95% CI)			952			697	100.0%	0.02 [-0.00, 0.04]	•
Heterogeneity: Tau <sup>2</sup> = 1 Fest for overall effect: 2			lf = 12 (F	P = 0.0007); P	°= 65%				-0.2 -0.1 0 0.1 0.2
Fest for subaroup diffe			df = 2 (	P = 0.45). I <sup>2</sup> =	0%		<b>.</b>		Favors human milk Favors infant formula
							(b)		
	1	-BMI		HM-BN	ЛІ		Mean	Difference	Mean Difference
Study or Subgrou 1.3.1 2m-pro1.8-	p Mean		Total	Mean SD	Total	Weight		ixed, 95% Cl	IV, Fixed, 95% Cl
Putet 2016	15.3	1.1	72	15.2 1.3	8 71	19.1%	0.10	I [-0.29, 0.49]	
Raiha 2002	15.27	1.21	56	15.71 1.17	28	10.3%	-0.44	[-0.98, 0.10]	
Turck 2006 Subtotal (95% CI)	16.02	1.1	51 179	15.35 1.42	2 43 142	11.0% 40.3%		7 [0.15, 1.19] [-0.15, 0.39]	•
Heterogeneity: Ch			= 0.01);	I² = 76%					ſ
Test for overall effe	ect: Z = 0.8	4 (P = 0	.40)						
1.3.2 2m-pro2.1~		1.00		15 74 4	,	0.00	0.00	1055.0041	
Deibe 2022	15.74 16.05		29 200	15.71 1.17		8.8% 19.6%		i [-0.55, 0.61] i [-0.04, 0.74]	
Raiha 2002 Singhal 2010			229		129	28.4%		[-0.07, 0.57]	◆
Singhal 2010 Subtotal (95% CI)				; I² = 0%					
Singhal 2010 Subtotal (95% Cl) Heterogeneity: Ch		- () - 0							
Singhal 2010 <b>Subtotal (95% Cl)</b> Heterogeneity: Ch Test for overall effe	ect: Z = 1.5					10.00	e 4	0 10 04 0 701	
Singhal 2010 Subtotal (95% Cl) Heterogeneity: Ch Test for overall effe 1.3.3 2m-pro > 2.	ect: Z = 1.5: 2			45.0		19.6%	U.4	0 [0.01, 0.79]	<b>—</b>
Singhal 2010 Subtotal (95% Cl) Heterogeneity: Ch Test for overall effe 1.3.3 2m – pro > 2. Putet 2016	ect: Z = 1.5: 2 15.6			15.2 1.3 15.35 1.42			0.34	6.6.17 0.851	+
Singhal 2010 Subtotal (95% Cl) Heterogeneity: Ch Test for overall effe 1.3.3 2m-pro > 2: Putet 2016 Turck 2006 Subtotal (95% Cl)	ect: Z = 1.5: 2 15.6 15.69	0.99	50 127	15.35 1.42		11.6% <b>31.2</b> %		[-0.17, 0.85] 3 [0.07, 0.69]	•
Singhal 2010 Subtotal (95% CI) Heterogeneity: Ch Test for overall effe 1.3.3 2m-pro > 2. Putet 2016 Turck 2006 Subtotal (95% CI) Heterogeneity: Ch	ect: Z = 1.5: 2 15.6 15.69 F = 0.03, dt	0.99 f= 1 (P :	50 <b>127</b> = 0.85);	15.35 1.42	2 43	11.6%			•
Singhal 2010 Subtotal (95% Cl) Heterogeneity: Ch Test for overall effe 1.3.3 2m-pro > 2: Putet 2016 Turck 2006 Subtotal (95% Cl)	ect: Z = 1.5: 2 15.6 15.69 F = 0.03, dt	0.99 f= 1 (P :	50 <b>127</b> = 0.85);	15.35 1.42	2 43	11.6%			•
Singhal 2010 Subtotal (95% CI) Heterogeneity: Ch Test for overall effe 1.3.3 2m-pro > 2. Putet 2016 Turck 2006 Subtotal (95% CI) Heterogeneity: Ch Test for overall effe Total (95% CI)	ect: Z = 1.5: 2 15.6 15.69 ₹ = 0.03, dt ect: Z = 2.40	0.99 f = 1 (P : 0 (P = 0	50 <b>127</b> = 0.85); .02) <b>535</b>	15.35 1.42 ; I <sup>z</sup> = 0%	2 43 114	11.6%	0.38		• · · ·
Singhal 2010 Subtotal (95% CI) Heterogeneity: Ch Test for overall effe 1.3.3 2m – pro > 2. Putet 2016 Turck 2006 Subtotal (95% CI) Heterogeneity: Ch Test for overall effe	ect: Z = 1.5: 2 15.6 15.69 ₹ = 0.03, di ect: Z = 2.4 ₹ = 10.87, 1	0.99 f = 1 (P : 0 (P = 0 df = 6 (F	50 <b>127</b> = 0.85); .02) <b>535</b> ? = 0.09	15.35 1.42 ; I <sup>z</sup> = 0%	2 43 114	11.6% <b>31.2</b> %	0.38	3 [0.07, 0.69]	-2 0 2 4 Favors infant formula

**Figure 3.** Forest plot of the effects of protein content of infant formula on the weight gain, height gain, and BMI of infants at 2 months of age. (a) The effects on weight gain. (b) The effects on height gain. (c) The effects on BMI.

Study of Subgroup	IF-weigl			HM-weig				Mean Difference	Mean Difference
Study or Subgroup 1.1.1 3m-pro1.8~2.0	Mean	SD	Total	Mean	SD	rotal V	rengtitt	IV, Random, 95% Cl	IV, Random, 95% Cl
Breij 2019	28.4	2.6	148	29.9	3.5	70	8.4%	-1.50 [-2.42, -0.58]	<u>+</u>
Hanning 1992 Raiha 2002	31.7 27.9	8.6 6.1	45 56	30.5 27.8	10.7 5.3	58 28	5.6% 6.9%	1.20 [-2.53, 4.93] 0.10 [-2.43, 2.63]	
Roggero 2020	32.7	3.4	26	34.2	5.8	26	6.9%	-1.50 [-4.08, 1.08]	
Turck 2006 Vandenplas 2020	31.3 30	7.4 2.8	51 168	28 27.6	10.1 2.7	31 51	5.2% 8.5%	3.30 [-0.79, 7.39] 2.40 [1.55, 3.25]	
Subtotal (95% CI)	30	2.8	494	27.6	2.1		8.5% 41.5%	0.51 [-1.56, 2.58]	•
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:			df = 5 (F	P < 0.00001	); I² = 889	6			
<b>1.1.2 3m – pro2.1~2.2</b> Hanning 1992	30.6	8.4	50	30.5	10.7	58	5.7%	0 10 1 2 61 2 71	
Kennedy 1992	30.6	2.7	75	27.8	2.7	58 109	5.7% 8.5%	0.10 [-3.51, 3.71] 2.30 [1.51, 3.09]	+
Raiha 2002	30.8	5.6	29	27.8	5.3	28	6.6%	3.00 [0.17, 5.83]	
Roggero 2020 Wu 2017	33.6 35.7	4.2 2.4	26 65	34.2 34.1	5.8 1.2	26 63	6.7% 8.6%	-0.60 [-3.35, 2.15] 1.60 [0.95, 2.25]	
Subtotal (95% CI)	33.7	2.4	245	34.1	1.2		36.1%	1.74 [0.95, 2.52]	◆
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:				= 0.17); I <sup>z</sup> =	37%				
1.1.3 3m – pro > 2.2	22.2	24	70	27.0	0.7	400	0.40	1.50 10 61 5 001	-
Kennedy 1999 Litmanovitz 2013	32.3 32.2	3.1 1.1	76 51	27.8 34.5	2.7 1.1	109 25	8.4% 8.6%	4.50 [3.64, 5.36] -2.30 [-2.83, -1.77]	+
Turck 2006	31.1	6.3	50	28	10.1	31	5.4%	3.10 [-0.86, 7.06]	
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> =	22.12· Chi	8 - 177 -	177	/P ~ 0.000	013-18-0		22.4%	1.69 [-3.79, 7.17]	
Test for overall effect:			24, at = 2	2 (P < 0.000	01); F = 9	9%			
Total (95% Cl) Heterogeneity: Tau <sup>2</sup> =	6 67' Chi <b>F</b> :	= 268.48	916 df = 13	? (P ≤ 0 000	01): P = 9	713 1	00.0%	1.06 [-0.42, 2.55]	<b>         </b>
Test for overall effect . Test for subgroup diffe	Z = 1.41 (P	= 0.16)							-10 -5 0 5 10 Favors human milk Favors infant formula
, sorior oupuroup ulli		1.1	o. ur = 2	= 0.000.	0.00		(a)		
	10 L							Marca Diff	
Study or Subgroup 1.2.1 3m-pro1.8~2.0	IF-height Mean	gain (m SD	m/d) Total	HM—heig Mean	ht gain (n SD		Weight	Mean Difference t IV, Random, 95% Cl	Mean Difference IV. Random, 95% Cl
Breij 2019	1.22	0.04	148	1.2	0.06	70	19.1%	0.02 [0.00, 0.04]	-
Hanning 1992	1.22	0.37	45	1.17	0.36	58	2.0%	0.05 [-0.09, 0.19]	
Raiha 2002 Roggero 2020	1.18 1.25	0.22 0.02	56 26	1.25 1.3	0.17 0.1	28 26	4.8%		
Turck 2006	1.19	0.46	51	1.15	0.46	31	1.0%	0.04 [-0.17, 0.25]	
Vandenplas 2020 Subtotal (95% CI)	0.84	0.07	168 494	0.81	0.01	51 264	20.1%		<b>_</b>
Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: Z				= 0.001); I² =	= 75%	204	39.47	0.00 [-0.02, 0.03]	
1.2.2 3m-pro2.1~2.2									
Hanning 1992	1.27	0.36	50	1.17	0.36	58	2.2%		
Raiha 2002 Roggero 2020	1.26 1.22	0.15 0.05	29 26	1.25 1.3	0.17	28 26	5.0% 11.4%		
Wu 2017	1.24	0.01	65	1.2	0.01	63	21.1%	0.04 [0.04, 0.04]	
Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0	1.00: ChiZ=	21.00 4	170 f = 3 /D	~ 0.000043-	R = 0.000	175	39.7%	6 0.01 [-0.07, 0.09]	-
Test for overall effect: Z			a = 3 (P	< 0.00001),	1-= 90%				
1.2.3 3m–pro > 2.2 Turck 2006	1.24	0.49	50	1.15	0.46	31	1.0%	6 0.09 [-0.12, 0.30]	
Subtotal (95% CI) Heterogeneity: Not app	licable		50			31	1.0%	6 0.09 [-0.12, 0.30]	
Test for overall effect: Z		= 0.40)							
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = (			714 f= 10 (F	P < 0.00001)	; I² = 84%		100.0%	6 0.00 [-0.02, 0.03]	-0.5 -0.25 0 0.25 0.5
Test for overall effect: Z Test for subaroup diffe			. df = 2 (	P = 0.72). I <sup>2</sup>	= 0%				Favors human milk Favors infant formula
							( <b>b</b> )		
		F-BMI		HM-B			Mean	Difference	Mean Difference
Study or Subgroup 1.3.1 3m-pro1.8~		SD	fotal	Mean S	u Total	Weight	t IV, I	Hixed, 95% Cl	IV, Fixed, 95% Cl
Raiha 2002		1.43	56	16.03 1.3	5 28	26.4%	0.14	4 [-0.48, 0.76]	<b></b>
Turck 2006		1.06	51	16.34 3.8	6 31	5.3%	6 0.23	3 [-1.16, 1.62]	<u> </u>
Subtotal (95% CI) Heterogeneity: Chi	² = 0.01, df	f=1 (P:	<b>107</b> = 0.91);	I² = 0%	59	31.8%	0.16	6 [-0.41, 0.72]	•
Test for overall effe		3 (P = 0	.59)						
1.3.2 3m–pro2.1~ Raiha 2002		1.28	29	16.03 1.3	5 28	22.1%	5 0.44	6 [-0.22, 1,14]	<b></b>
Wu 2017		1.4	29 65	17.1 1.				0 [-0.22, 1.14] D [-0.50, 0.50]	
Subtotal (95% CI)			94		91			6 [-0.24, 0.57]	+
Heterogeneity: Chi Test for overall effe				I <sup>z</sup> = 11%					
1.3.3 3m-pro > 2.		4.00	60	10.04 .0.0	e	<i>c</i> ~~		514 74 4 6 4	
Turck 2006 Subtotal (95% CI)	15.99	1.09	50 50	16.34 3.8	6 31 31			5 [-1.74, 1.04] 5 [- <b>1.74, 1.04]</b>	-
Heterogeneity: Not Test for overall effe									
Total (95% CI)		= 0	251		404	100.0%	0.43	8 [-0.19, 0.45]	▲
Heterogeneity: Chi	<sup>2</sup> = 1.63, dt	f= 4 (P :		I² = 0%	181	100.0%	0.13		<u> </u>
Test for overall effe	ct: Z = 0.8	1 (P = 0	.42)						-4 -2 0 2 4 Favors human milk Favors infant formula
Test for subaroup	difference:	s: Chi²=	= 0.49. c	lf = 2 (P = 0	1.78). I² =	0%	$(\mathbf{c})$		

Figure 4. Forest plot of the effects of protein content of infant formula on the weight gain, height gain, and BMI of infants at 3 months of age. (a) The effects on weight gain. (b) The effects on height gain. (c) The effects on BMI.

(c)

Study or Subgroup	Mean	SD	g/d) Total	Mean	ght gain (g SD			Mean Difference IV, Random, 95% Cl	Mean Difference IV, Random, 95% Cl
.1.1 4m-pro < 1.8	26.0	2.2	00	247	26	65	6 1 04	2 20 14 24 2 401	
Kouwenhoven 2019 Dropeza-Ceja 2018	26.9 26.8	2.2 1.9	88 17	24.7 27.8	3.6 1.4	65 82	6.1% 6.2%	2.20 [1.21, 3.19] -1.00 [-1.95, -0.05]	
Subtotal (95% CI)	20.0	1.9	105	27.0	1.4	147	12.2%	0.60 [-2.54, 3.73]	-
Heterogeneity: Tau <sup>2</sup> =	4.87: Chi <sup>2</sup> =	= 20.87.		< 0.00001	): I <sup>2</sup> = 95%		12.2 /0	0.00 [-2.04, 0.1 0]	T
Fest for overall effect: .					//				
l.1.2 4m-pro1.8~2.0	1								
Breij 2019	27.1	2.5	128	27.3	3.6	65	6.1%	-0.20 [-1.18, 0.78]	+
Daniels 2008	28.8	3.3	113	26.8	3	56	6.1%	2.00 [1.01, 2.99]	-
Liotto 2018	29.9	3.8	50	27.5	3.5	50	4.9%	2.40 [0.97, 3.83]	
Oropeza-Ceja 2018	30.8	0.5	18	27.8	1.4	82	7.4%	3.00 [2.62, 3.38]	-
Putet 2016	26.1	2.4	71	24	3.1	65	6.2%	2.10 [1.16, 3.04]	-
Raiha 2002	26.5	5.4	56	25.4	4.6	28	3.3%	1.10 [-1.11, 3.31]	
Trabulsi 2010	27.8	5.3	103	26.6	5.4	110	4.9%	1.20 [-0.24, 2.64]	
Furck 2006	29.7	5.4	51	25.3	9.6	25	1.4%	4.40 [0.36, 8.44]	
/andenplas 2020	29.4	3	166	26.7	2.6	50	6.4%	2.70 [1.85, 3.55]	<b>⊥</b>
Subtotal (95% CI) Heterogeneity: Tau² =	1.08: Chi <sup>2</sup> =	= 43.16.	756 1f=8 (P	< 0.00001	): I <sup>2</sup> = 81%	531	46.7%	1.95 [1.13, 2.76]	•
Fest for overall effect: .					,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,				
1.1.3 4m–pro2.1~2.2									
Kouwenhoven 2019	27.3	2	85	24.7	3.6	65	6.1%	2.60 [1.63, 3.57]	
Oropeza-Ceja 2018	30.6	0.1	24	27.8	1.4	82	7.5%	2.80 [2.49, 3.11]	-
Raiha 2002	28.6	4.4	29	25.4	4.6	28	3.1%	3.20 [0.86, 5.54]	
Singhal 2010	26.6	2.7	200	24.5	3.4	101	6.6%	2.10 [1.34, 2.86]	+
Trabulsi 2010	28.1	5.4	108	26.6	5.4	110	4.9%	1.50 [0.07, 2.93]	<u>⊢-</u>
Subtotal (95% CI)			446			386	28.3%	2.52 [2.08, 2.96]	•
Heterogeneity: Tau² = Test for overall effect: 3				: 0.23); I <sup>z</sup> =	29%				
1.1.4 4m-pro > 2.2	· v								
Liotto 2018	29.6	3.1	50	27.5	3.5	50	5.3%	2.10 [0.80, 3.40]	
Putet 2016	29.6	2.9	74	27.5	3.5	50 65	5.3% 6.0%	3.70 [2.70, 4.70]	<b>→</b>
Turck 2006	27.7	3.7	50	24	3.1 9.6	25	1.5%	4.00 [0.10, 7.90]	<u> </u>
Subtotal (95% CI)	23.3	3.7	174	ت.ل ع	0.0	140	12.8%	3.07 [1.81, 4.33]	•
Heterogeneity: Tau <sup>2</sup> =	0.58; Chi <sup>2</sup> =	= 3.86, di		0.15); I <sup>2</sup> =	48%	. 10		2001 [ 10 1, 400]	•
Test for overall effect: 2									
			1481			1204	100.0%	2.06 [1.53, 2.59]	.
							100.0%	2.00 [1.55, 2.59]	
	0.05.052	400.00		(n	040.12 0				
Heterogeneity: Tau² =			df= 18	(P < 0.000	101); I² = 8	3%			-10 -5 0 5 10
Heterogeneity: Tau² = Test for overall effect: 3	Z=7.61 (P	< 0.0000	, df = 18 )1)					_	
Heterogeneity: Tau² = Test for overall effect: 3	Z=7.61 (P	< 0.0000	, df = 18 )1)					_	-10 -5 0 5 10 Favors human milk Favors infant formula
Heterogeneity: Tau² = Test for overall effect: 3	Z=7.61 (P	< 0.0000	, df = 18 )1)				(a)	_	
Heterogeneity: Tau² = Test for overall effect: 3	Z=7.61 (P	< 0.0000	, df = 18 )1)				(a)	_	
Heterogeneity: Tau² = Test for overall effect: 3	Z=7.61 (P	< 0.0000	, df = 18 )1)				(a)	_	
Heterogeneity: Tau² = Test for overall effect: . Test for subαroup diffe	Z = 7.61 (P erences: Ch IF—height	< 0.0000 ni² = 3.82 gain (m	, df = 18 )1) df = 3 ( m/d)	P = 0.28). HM-heig	l² = 21.6% jht gain (n	nm/d)		Mean Difference IV, Random, 95% Cl	Favors human milk Favors infant formula Mean Difference
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect : Test for suboroup diffe Study or Subgroup 1.2.1 4m—pro < 1.8	Z = 7.61 (P erences: Ch IF—height <u>Mean</u>	< 0.0000 ni² = 3.82 gain (m SD	,df=18 )1) ∴df=3( m/d) <u>Total</u>	P = 0.28). HM – heig Mean	² = 21.6%  ht gain (n  SD	nm/d) Total	Weight	IV, Random, 95% Cl	Favors human milk Favors infant formula
Heterogeneity: Tau <sup>2</sup> = Test for overall effect Test for subaroup diffe Study or Subaroup I.2.1 4m – pro < 1.8 Oropeza-Ceja 2018	Z = 7.61 (P erences: Ch IF—height	< 0.0000 ni² = 3.82 gain (m	, df= 18 11) 1. df= 3 ( m/d) <u>Total</u> 17	P = 0.28). HM-heig	l² = 21.6% jht gain (n	nm/d) Total 82	Weight 7.0%	IV, Random, 95% Cl	Favors human milk Favors infant formula Mean Difference
Heterogeneity: Tau <sup>2</sup> = Test for overall effect : Test for subaroup diffe Study or Subaroup 1.2.1 4m-pro <1.8 Corpeza-Ceja 2018 Subtotal (9% CI)	Z = 7.61 (P erences: Ch IF—height <u>Mean</u> 0.83	< 0.0000 ni² = 3.82 gain (m SD	,df=18 )1) ∴df=3( m/d) <u>Total</u>	P = 0.28). HM – heig Mean	² = 21.6%  ht gain (n  SD	nm/d) Total	Weight 7.0%	IV, Random, 95% Cl	Favors human milk Favors infant formula Mean Difference
Heterogeneity: Tau <sup>2</sup> = Test for overall effect . Fest for subaroup diffe study or <u>Subaroup</u> .2.14m-pro < 1.8 propeza-Ceja 2018 Subtotal (95% CI) Heterogeneity. Not app	Z = 7.61 (P erences: Cr IF—height Mean 0.83 olicable	< 0.000( ni <sup>z</sup> = 3.82 gain (m <u>SD</u> 0.03	, df= 18 11) 1. df= 3 ( m/d) <u>Total</u> 17	P = 0.28). HM – heig Mean	² = 21.6%  ht gain (n  SD	nm/d) Total 82	Weight 7.0%	IV, Random, 95% Cl	Favors human milk Favors infant formula Mean Difference
Heterogeneity: Tau <sup>2</sup> = Test for overall effect . Fest for subaroup diffe study or <u>Subaroup</u> .2.14m-pro < 1.8 propeza-Ceja 2018 Subtotal (95% CI) Heterogeneity. Not app	Z = 7.61 (P erences: Cr IF—height Mean 0.83 olicable	< 0.000( ni <sup>z</sup> = 3.82 gain (m <u>SD</u> 0.03	, df= 18 11) 1. df= 3 ( m/d) <u>Total</u> 17	P = 0.28). HM – heig Mean	² = 21.6%  ht gain (n  SD	nm/d) Total 82	Weight 7.0%	IV, Random, 95% Cl	Favors human milk Favors infant formula Mean Difference
Heterogeneity: Tau <sup>2</sup> = Test for overall effect : Test for subaroup diffe study or Subgroup 1.2.1 4m—pro < 1.8 Dropeza-Ceja 2018 Subtotal (9% CI) Heterogeneity: Not app Fest for overall effect Z	Z = 7.61 (P erences: Cr IF—height Mean 0.83 olicable	< 0.000( ni <sup>z</sup> = 3.82 gain (m <u>SD</u> 0.03	, df= 18 11) 1. df= 3 ( m/d) <u>Total</u> 17	P = 0.28). HM – heig Mean	² = 21.6%  ht gain (n  SD	nm/d) Total 82	Weight 7.0%	IV, Random, 95% Cl	Favors human milk Favors infant formula Mean Difference
Heterogeneity: Tau <sup>2</sup> = Test for overall effect : Test for subaroup L2.1 4m – pro < 1.8 Dropeza-Ceja 2018 Subtotal (95% C) Heterogeneity: Not app Test for overall effect :Z L.2.2 4m – pro1.8–2.0	Z = 7.61 (P erences: Ch IF — height Mean 0.83 blicable Z = 3.11 (P =	< 0.000( ni <sup>2</sup> = 3.82 gain (m <u>SD</u> 0.03 : 0.002)	, df = 18 )1) :. df = 3 ( <u>Total</u> 17 <b>17</b>	P = 0.28). HM – heig Mean 0.88	* = 21.6%  ht gain (n <u>SD</u> 0.13	nm/d) <u>Total</u> 82 <b>82</b>	Weight 7.0% 7.0%	IV, Random, 95% Cl -0.05 [-0.08, -0.02] -0.05 [-0.08, -0.02]	Favors human milk Favors infant formula Mean Difference
Heterogeneity: Tau <sup>2</sup> = Test for overall effect : Test for subgroup 1.2.1 4m-pro < 1.8 Subtotal (95% Cl) Heterogeneity: Not app Fest for overall effect Z 1.2.2 4m-pro 1.8-2.0 3reij 2019	Z = 7.61 (P erences: Cr IF—height Mean 0.83 olicable	< 0.000( ni <sup>z</sup> = 3.82 gain (m <u>SD</u> 0.03	, df= 18 11) 1. df= 3 ( m/d) <u>Total</u> 17	P = 0.28). HM – heig Mean	² = 21.6%  ht gain (n  SD	nm/d) Total 82	Weight 7.0% 7.0%	IV. Random, 95% Cl -0.05 [-0.08, -0.02] -0.05 [-0.08, -0.02] 0.01 [-0.00, 0.02]	Favors human milk Favors infant formula Mean Difference
Heterogeneity. Tau" = Test for overall effect : Test for suboroup I.2.1 4m – pro < 1.8 Dropeza-Ceja 2018 Subtotal (95% CI) Heterogeneity. Not app Test for overall effect Z I.2.2 4m – pro 1.8–2.0 Breij 2019 Janiels 2008	Z = 7.61 (P erences: CP IF-height Mean 0.83 0.83 0.83 0.83 0.83 0.83 0.83 0.83	< 0.000( ni <sup>z</sup> = 3.82 gain (m <u>SD</u> 0.03 : 0.002) 0.04	, df = 18 )1) :. df = 3 ( df = 18) df = 3 ( df = 18) df = 3 ( df = 3 ( d	P = 0.28). HM-heig Mean 0.88 1.1	1 <sup>#</sup> = 21.6% pht gain (n <u>SD</u> 0.13 0.05	nm/d) <u>Total</u> 82 82 65	Weight 7.0% 7.0% 9.0%	IV, Random, 95% Cl -0.05 [-0.08, -0.02] -0.05 [-0.08, -0.02]	Favors human milk Favors infant formula Mean Difference
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: : Test for subaroup diffe subtoral subaroup diffe uppeza-Ceja 2018 subtoral (95% CI) Heterogeneity: Not app rest for overall effect Z 1.2.2 4m – pro1.8~2.0 3reij 2019 Daniels 2008 Jotto 2018	Z = 7.61 (P erences: CP IF - height Mean 0.83 blicable Z = 3.11 (P = 1.11 1.06	< 0.000( ni <sup>2</sup> = 3.82 gain (m SD 0.03 0.002) 0.04 0.04	, df = 18 11) 1. df = 3 ( <b>m/d)</b> <b>Total</b> 17 <b>17</b> 128 113	P = 0.28). HM-heig Mean 0.88 1.1 1.02	I <sup>#</sup> = 21.6% I <sup>ht</sup> gain (n <u>SD</u> 0.13 0.05 0.03	nm/d) <u>Total</u> 82 82 65 56	Weight 7.0% 7.0% 9.0% 9.3% 8.1%	IV, Random, 95% Cl -0.05 [-0.08, -0.02] -0.05 [-0.08, -0.02] 0.01 [-0.00, 0.02] 0.04 [0.03, 0.05]	Favors human milk Favors infant formula Mean Difference
Heterogeneity: Tau <sup>2</sup> = Test for overall effect : Test for subgroup L.2.1 4m – pro <1.8 Subtotal (95% Cl) Heterogeneity: Not app Test for overall effect Z L.2.2 4m – pro 1.8–2.0 reij 2019 Daniels 2008 Jotto 2018 Jongeza-Ceja 2018	Z = 7.61 (P erences: Cf IF-height Mean 0.83 01/cable Z = 3.11 (P = 1.11 1.06 1.13	< 0.000( ni <sup>2</sup> = 3.82 gain (m SD 0.03 0.002) 0.04 0.04 0.08	, df = 18 11) :. df = 3 ( <b>m/d)</b> 17 17 128 113 50	P = 0.28). HM – heig <u>Mean</u> 0.88 1.1 1.02 1.14	I <sup>≠</sup> = 21.6% I <sup>ht</sup> gain (n <u>SD</u> 0.13 0.05 0.03 0.01	nm/d) <u>Total</u> 82 82 65 56 50	Weight 7.0% 7.0% 9.0% 9.3% 8.1% 3.9%	IV, Random, 95% Cl -0.05 [-0.08, -0.02] -0.05 [-0.08, -0.02] 0.01 [-0.00, 0.02] 0.04 [0.03, 0.05] -0.01 [-0.03, 0.01]	Favors human milk Favors infant formula Mean Difference
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: : Test for subaroup L2.1 4m – pro < 1.8 Propeza-Ceja 2018 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: Z L.2.2 4m – pro1.8–2.0 Breij 2019 Janiels 2008 Joito 2018 Dropeza-Ceja 2018 Viet 2016	Z = 7.61 (P erences: Cf IF-height Mean 0.83 olicable Z = 3.11 (P = 1.11 1.06 1.13 0.8	< 0.000( ni <sup>2</sup> = 3.82 gain (m SD 0.03 0.002) 0.04 0.04 0.04 0.08 0.12	, df = 18 11) .: df = 3 ( <b>m/d)</b> 17 17 17 128 113 50 18	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88	I <sup>p</sup> = 21.6% I <sup>p</sup> t gain (n SD 0.13 0.13 0.05 0.03 0.01 0.13	nm/d) Total 82 82 85 56 50 82 65 28	Weight 7.0% 7.0% 9.0% 9.3% 8.1% 3.8% 3.8%	W. Random, 95% Cl -0.05 [-0.08, -0.02] -0.05 [-0.08, -0.02] 0.01 [-0.00, 0.02] 0.04 [0.03, 0.05] -0.01 [-0.03, 0.01] 0.02 [-0.04, 0.08]	Favors human milk Favors infant formula Mean Difference
-leterogeneity: Tau <sup>2</sup> = Test for overall effect: : Test for subgroup .2.1 4m-pro < 1.8 .00000000000000000000000000000000000	Z = 7,61 (P erences: Cf IF-height Mean 0.83 plicable Z = 3,11 (P = 1,11 1.06 1,13 0,13	< 0.000( hi <sup>2</sup> = 3.82 gain (m SD 0.03 0.04 0.04 0.04 0.04 0.04 0.04 0.04 0.03	, df = 18 11) df = 3 ( <b>m/d)</b> <b>Total</b> 17 <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b>	P = 0.28). HM-heig Mean 0.88 1.1 1.02 1.14 0.88 1.09	I <sup>#</sup> = 21.6% I <sup>II</sup> gain (n SD 0.13 0.05 0.03 0.01 0.13 0.07	nm/d) Total 82 82 82 65 56 50 82 85	Weight 7.0% 7.0% 9.0% 9.3% 8.1% 3.8% 3.8%	W. Random, 95% Cl -0.05 [-0.08, -0.02] -0.05 [-0.08, -0.02] 0.04 [0.03, 0.05] -0.01 [-0.03, 0.01] 0.02 [-0.04, 0.08] 0.04 [0.02, 0.06]	Favors human milk Favors infant formula Mean Difference
Heterogeneity. Tau" = Test for overall effect : Test for suboroup diffe study or Subgroup 1.2.1 4m - pro < 1.8 Dropeza-Ceja 2018 Subtotal (95% CI) Heterogeneity. Not app Test for overall effect Z L2.2 4m - pro 1.8-2.0 Breij 2019 Janiels 2008 Joito 2018 Dropeza-Ceja 2018 Putel 2016 Raiha 2002 Tabulsi 2010	Z = 7.61 (P erences: Cf Mean 0.83 blicable Z = 3.11 (P = 1.11 1.06 1.13 0.9 1.13 1.09	< 0.000( hi <sup>2</sup> = 3.82 gain (m SD 0.03 0.03 0.04 0.04 0.04 0.04 0.04 0.04 0.04 0.03 0.12 0.03 0.16	, df = 18 11) df = 3 ( df = 3 (	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.09 1.13	I <sup>≠</sup> = 21.6% I <sup>t</sup> gain (n <u>SD</u> 0.13 0.13 0.05 0.03 0.01 0.13 0.07 0.13	nm/d) Total 82 82 85 56 50 82 65 28	Weight 7.0% 7.0% 9.0% 9.3% 8.1% 3.9% 8.6% 3.8% 7.1%	W. Random, 95% Cl -0.05 [-0.08, -0.02] -0.05 [-0.08, -0.02] 0.04 [-0.00, 0.02] 0.04 [0.03, 0.05] -0.01 [-0.03, 0.01] 0.02 [-0.04, 0.08] 0.04 [0.02, 0.08] -0.04 [-0.10, 0.02]	Favors human milk Favors infant formula Mean Difference
Heterogeneity. Tau" = Test for overall effect : Test for suboroup diffe http://www.action.com/ http://www.action.com/ http://www.action.com/ rest for overall effect Z http://www.action.com/ propeza-ceja 2018 Jointo 2018 Jonepeza-ceja 2018 Julet 2016 Raiha 2002 Trabulsi 2010 Turck 2006 Yandenplas 2020	Z = 7.61 (P erences: Cf IF-height Mean 0.83 blicable Z = 3.11 (P = 1.11 1.06 1.13 1.09 1.13 1.09 1.07	< 0.000( hi <sup>#</sup> = 3.82 gain (m SD 0.03 0.03 0.04 0.04 0.04 0.04 0.04 0.04 0.04 0.03 0.12 0.03	df = 18 % (df = 17 % (	P = 0.28). HM - heig Mean 0.88 1.11 1.02 1.14 0.88 1.09 1.13 1.04	I <sup>µ</sup> = 21.6% I <sup>µ</sup> gain (n SD 0.13 0.13 0.03 0.01 0.13 0.07 0.13 0.11	mm/d) Total 82 82 82 65 56 50 82 65 28 10 28 110 50	Weight 7.0% 7.0% 9.0% 9.3% 8.1% 3.9% 8.6% 3.8% 7.1% 0.3%	IV. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.05 [-0.08, -0.02]           0.04 [-0.03, 0.05]           0.04 [0.03, 0.05]           0.04 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [-0.10, 0.02]           0.03 [-0.04, 0.03]           0.03 [-0.24, 0.30]           0.03 [-0.24, 0.30]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
Heterogeneity: Tau" = Test for overall effect: : Test for subaroup L2.1 4m - pro < 1.8 Propeza-Ceja 2018 Subtotal (95% CI) L2.2 4m - pro 1.8 - 2.0 Breiz 1019 Janiels 2008 Jointo 2018 Dropeza-Ceja 2018 Viete 2016 Raiha 2002 Trabulsi 2010 Viete 2016 Raiha 2002 Frabulsi 2010 Viete 2016 Raiha 2002 Frabulsi 2010 Viete 2016 Raiha 2002 Frabulsi 2010 Viete 2016 Raiha 2002 Frabulsi 2010	Z = 7.61 (P erences: Cf <u>Mean</u> 0.83 olicable Z = 3.11 (P = 1.11 1.06 1.13 0.9 1.13 1.09 1.07 1.12 0.88	< 0.0000 ji <sup>2</sup> = 3.82 gain (m SD 0.03 0.03 0.04 0.04 0.08 0.12 0.03 0.16 0.12 0.43 0.06	df = 18 (df = 3 ( m/d) <u>Total</u> 17 <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b>	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.02 1.14 0.88 1.09 1.13 1.09 0.85	I <sup>µ</sup> = 21.6% I <sup>µ</sup> = 21.6% 0.13 0.13 0.13 0.01 0.13 0.01 0.13 0.13 0.11 0.62 0.01	nm/d) Total 82 82 82 82 85 56 82 85 28 110 25	Weight 7.0% 7.0% 9.0% 9.3% 8.1% 3.9% 8.6% 3.8% 7.1% 0.3%	W. Random, 95% Cl -0.05 [-0.08, -0.02] -0.05 [-0.08, -0.02] 0.04 [0.03, 0.05] -0.01 [-0.03, 0.01] 0.02 [-0.04, 0.08] 0.04 [0.02, 0.06] -0.04 [-0.10, 0.02] 0.03 [-0.02, 0.06] 0.03 [-0.24, 0.30]	Favors human milk Favors infant formula Mean Difference
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: : Test for subgroup .2.1 4m-pro < 1.8 .70peza-Ceja 2018 Jubtotal (95% CI) Heterogeneity: Not app rest for overall effect Z .2.2 4m-pro1.8-2.0 Breij 2019 Janiels 2008 Joito 2018 Dropeza-Ceja 2018 Videt 2016 Videt 2017 Videt 2016 Videt 2016 Videt 2018 Videt 2016 Videt 2018 Videt 2018 V	Z = 7,61 (P erences: Cf Mean 0.83 01cable Z = 3.11 (P = 1.11 1.06 1.13 1.09 1.09 1.09 1.09 1.09 1.09 1.09 1.09	< 0.000( <b>gain (m</b> <b>SD</b> 0.03 0.04 0.04 0.04 0.08 0.08 0.08 0.12 0.03 0.16 0.12 0.43 0.06 28.40, dt	df = 18 (df = 3 ( m/d) <u>Total</u> 17 <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b>	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.02 1.14 0.88 1.09 1.13 1.09 0.85	I <sup>µ</sup> = 21.6% I <sup>µ</sup> = 21.6% 0.13 0.13 0.13 0.01 0.13 0.01 0.13 0.13 0.11 0.62 0.01	mm/d) Total 82 82 82 65 56 50 82 65 28 10 28 110 50	Weight 7.0% 7.0% 9.0% 9.3% 8.1% 3.9% 8.6% 3.8% 7.1% 0.3%	IV. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.05 [-0.08, -0.02]           0.04 [-0.03, 0.05]           0.04 [0.03, 0.05]           0.04 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [-0.10, 0.02]           0.03 [-0.04, 0.03]           0.03 [-0.24, 0.30]           0.03 [-0.24, 0.30]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: : Test for subaroup diffe L2.14m-pro < 1.8 Dropeza-Ceja 2018 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect Z J.2.24m-pro1.8-2.0 Janiels 2008 Janiels 2008 Janiels 2008 Janiels 2018 Dropeza-Ceja 2018 Vuet 2016 Raiha 2002 Trabulsi 2010 Turck 2006 Yandhotal (95% CI) Heterogeneity: Tau <sup>2</sup> = C Fest for overall effect Z	Z = 7,61 (P erences: Cf Mean 0.83 01cable Z = 3.11 (P = 1.11 1.06 1.13 1.09 1.09 1.09 1.09 1.09 1.09 1.09 1.09	< 0.000( <b>gain (m</b> <b>SD</b> 0.03 0.04 0.04 0.04 0.08 0.08 0.08 0.12 0.03 0.16 0.12 0.43 0.06 28.40, dt	df = 18 (df = 3 ( m/d) <u>Total</u> 17 <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>17</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b>	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.02 1.14 0.88 1.09 1.13 1.09 0.85	I <sup>µ</sup> = 21.6% I <sup>µ</sup> = 21.6% 0.13 0.13 0.13 0.01 0.13 0.01 0.13 0.13 0.11 0.62 0.01	mm/d) Total 82 82 82 65 56 50 82 65 28 10 28 110 50	Weight 7.0% 7.0% 9.0% 9.3% 8.1% 3.9% 8.6% 3.8% 7.1% 0.3%	IV. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.05 [-0.08, -0.02]           0.04 [-0.03, 0.05]           0.04 [0.03, 0.05]           0.04 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [-0.10, 0.02]           0.03 [-0.04, 0.03]           0.03 [-0.24, 0.30]           0.03 [-0.24, 0.30]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
Heterogeneity: Tau" = Test for overall effect : Test for suboroup diffe L2.1 4m - pro < 1.8 Dropeza-Ceja 2018 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect Z Janiels 2008 Jointo 2018 Dropeza-Ceja 2018 Juito 2018 Dropeza-Ceja 2018 Videt 2016 Asiha 2002 Trabulsi 2010 Trabulsi 2010 Trabulsi 2010 Fest for overall effect Z Fest for overall effect Z L2.3 4m - pro2.1-2.2	Z = 7.61 (P erences: Cf <u>Mean</u> 0.83 olicable Z = 3.11 (P = 1.11 1.06 1.13 0.9 1.07 1.02 0.88 0.00; Ch <sup>2</sup> = Z = 3.18 (P =	< 0.000( gain (m SD 0.03 0.04 0.04 0.04 0.04 0.02 0.12 0.03 0.12 0.03 0.12 0.03 0.12 0.03 0.12 0.03 0.04 0.02 0.12 0.03 0.12 0.03 0.12 0.03 0.12 0.03 0.12 0.03 0.12 0.03 0.12 0.12 0.12 0.12 0.03 0.12 0.12 0.03 0.12 0.04 0.001 0.12 0.04 0.04 0.001 0.04 0.001 0.04 0.04 0.001 0.04 0.001 0.04 0.04 0.001 0.04 0.04 0.001 0.04 0.04 0.001 0.04 0	df = 18 (df = 3 d (df = 3 d (d	HM – heig Mean 0.88 1.1 1.02 1.14 0.88 1.09 1.13 1.04 1.09 0.85 0.0004); F	pht gain (n SD 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13	5 Total 822 822 655 506 228 2101 255 500 531	Weight 7.0% 7.0% 9.0% 9.3% 8.6% 8.6% 3.8% 7.1% 0.3% 9.3% 59.5%	N. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.04 [0.03, 0.05]           -0.04 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.04]           0.03 [-0.24, 0.30]           0.03 [-0.24, 0.30]           0.03 [-0.24, 0.30]           0.03 [0.02, 0.04]           0.03 [0.02, 0.04]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
Heterogeneity: Tau" = Test for overall effect : Test for subaroup L2.1 4m - pro < 1.8 Propeza-Ceja 2018 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect .2 L.2.2 4m - pro1.8-2.0 Breij 2019 Janiels 2008 Jointo 2018 Propeza-Ceja 2018 Videt 2016 Raiha 2002 Trabulsi 2010 Furck 2006 Aradenplas 2020 Subtotal (95% CI) Heterogeneity: Tau" = Cest for overall effect .2 L.2.3 4m - pro2.1-2.2	Z = 7.61 (P erences: Cr Mean 0.83 blicable = 3.11 (P = 1.11 1.06 1.13 0.9 1.13 1.09 1.13 1.09 1.12 0.88 0.00; Chi <sup>2</sup> = Z = 3.18 (P = 0.95	<ul> <li>&lt; 0.000(0)</li> <li>gain (m</li> <li>SD</li> <li>0.03</li> <li>0.04</li> <li>0.06</li> <li>28.40, dt</li> <li>0.001</li> <li>0.09</li> </ul>	df = 18 df = 3 d m/d) Total 17 17 17 128 113 50 103 56 103 56 756 756 756 756 24	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.09 1.03 1.04 1.09 0.85 0.0004); F	P <sup>*</sup> = 21.6% pht gain (n SD 0.13 0.13 0.13 0.07 0.13 0.07 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13	5 Total 82 82 82 82 82 82 82 82 82 82	Weight 7.0% 7.0% 9.0% 9.3% 8.1% 3.9% 8.6% 3.8% 7.1% 0.3% 9.3% 59.5%	W. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.01 [-0.00, 0.02]           0.04 [0.03, 0.05]           -0.01 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.06]           -0.03, 0.01]           0.04 [0.02, 0.06]           0.03 [-0.00, 0.06]           0.03 [-0.00, 0.06]           0.03 [-0.02, 0.04]           0.03 [0.02, 0.04]           0.02 [0.01, 0.04]           0.07 [0.02, 0.12]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: : Test for subaroup diffe 	Z = 7.61 (P erences: Ch Mean 0.83 0.83 0.83 0.83 0.83 0.83 0.83 0.83	<pre>&lt; 0.000( )P = 3.82 gain (m SD 0.03 0.04 0.04 0.04 0.03 0.04 0.03 0.04 0.03 0.04 0.03 0.04 0.03 0.04 0.03 0.04 0.02 0.03 0.04 0.03 0.02 0.03 0.03</pre>	df = 18 % (df = 3 d (df = 3 d	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.09 1.13 0.0004); F 0.888 1.13	pri gain (n           std           std           0.05           0.03           0.13           0.05           0.03           0.13           0.05           0.03           0.13           0.13           0.13           0.13           0.13           0.13           0.13           0.13           0.13           0.13           0.13           0.13	5 Total 82 82 82 82 82 82 82 82 82 82	Weight 7,0% 7,0% 9,0% 9,3% 8,6% 3,9% 8,6% 3,8% 7,1% 0,3% 9,3% 59,5%	N. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.01 [-0.00, 0.02]           0.04 [0.03, 0.05]           -0.01 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.06]           -0.04 [-0.03, 0.01]           0.03 [-0.24, 0.08]           0.03 [-0.24, 0.30]           0.03 [-0.24, 0.30]           0.03 [0.02, 0.04]           0.02 [0.01, 0.04]           0.07 [0.02, 0.12]           0.04 [-0.02, 0.12]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
Heterogeneity: Tau" = Test for overall effect : Test for suboroup diffe L2.1 4m - pro < 1.8 Dropeza-Ceja 2018 Subtotal (95% CI) deterogeneity: Not app Test for overall effect Z L2.2 4m - pro 1.8 - 2.0 Breij 2019 Janiels 2008 Janiels 2008 Janiels 2008 Putel 2016 Vandenplas 2020 Subtotal (95% CI) deterogeneity: Tau" = ( Test for overall effect Z L2.3 4m - pro 2.1 - 2.2 Dropeza-Ceja 2018 Vala 2002 Tabulsi 2010 Subtotal (95% CI) deterogeneity: Tau" = ( Test for overall effect Z L2.3 4m - pro 2.1 - 2.2 Dropeza-Ceja 2018 Vala 2002 Tabulsi 2010	Z = 7.61 (P erences: Cr Mean 0.83 blicable = 3.11 (P = 1.11 1.06 1.13 0.9 1.13 1.09 1.13 1.09 1.12 0.88 0.00; Chi <sup>2</sup> = Z = 3.18 (P = 0.95	<ul> <li>&lt; 0.000(0)</li> <li>gain (m</li> <li>SD</li> <li>0.03</li> <li>0.04</li> <li>0.06</li> <li>28.40, dt</li> <li>0.001</li> <li>0.09</li> </ul>	df = 18 df = 3 d m/d) Total 17 17 17 128 113 50 103 56 103 56 756 756 756 756 24	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.09 1.03 1.04 1.09 0.85 0.0004); F	P <sup>*</sup> = 21.6% pht gain (n SD 0.13 0.13 0.13 0.07 0.13 0.07 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13 0.13	5 Total 82 82 82 82 82 82 82 82 82 82	Weight 7.0% 7.0% 9.0% 9.3% 8.1% 3.8% 3.8% 3.8% 5.3% 59.5% 59.5%	W. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.01 [-0.00, 0.02]           0.04 [0.03, 0.05]           -0.01 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.06]           0.03 [-0.00, 0.06]           0.03 [-0.00, 0.06]           0.03 [-0.2, 0.04]           0.03 [0.02, 0.04]           0.07 [0.02, 0.12]           0.07 [0.02, 0.12]           0.03 [-0.00, 0.06]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
<pre>teterogeneity. Tau" = Crest for overall effect :</pre>	Z = 7.61 (P erences: Cf Mean 0.83 olicable Z = 3.11 (P = 1.11 1.06 1.13 1.09 1.13 1.09 1.13 1.09 1.12 0.88 0.00; Chi <sup>2</sup> = 0.95 1.17 1.07 0.00; Chi <sup>2</sup> =	<ul> <li>&lt; 0.000(0)</li> <li>a)<sup>µ</sup> = 3.82</li> <li>gain (m</li> <li>SD</li> <li>0.03</li> <li>0.03</li> <li>0.04</li> <li>0.06</li> <li>0.12</li> <li>0.03</li> <li>0.06</li> <li>28.40, dt</li> <li>0.07</li> <li>0.11</li> <li>2.09, dt<sup>2</sup></li> </ul>	df = 18 % (df = 3 % (df =	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.13 1.04 1.09 0.85 0.0004); F 0.88 1.13 1.04 1.3 1.04	0.05 0.03 0.13 0.03 0.01 0.13 0.01 0.13 0.01 0.13 0.07 0.01 0.13 0.07 0.01 0.13 0.01 0.13 0.01	5 Total 82 82 82 82 82 82 82 82 82 82	Weight 7.0% 7.0% 9.0% 9.3% 8.1% 3.8% 3.8% 3.8% 5.3.8% 59.5% 59.5% 5.4% 2.9% 7.3%	N. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.01 [-0.00, 0.02]           0.04 [0.03, 0.05]           -0.01 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.06]           -0.04 [-0.03, 0.01]           0.03 [-0.24, 0.08]           0.03 [-0.24, 0.30]           0.03 [-0.24, 0.30]           0.03 [0.02, 0.04]           0.02 [0.01, 0.04]           0.07 [0.02, 0.12]           0.04 [-0.02, 0.12]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
Heterogeneity: Tau" = C Test for overall effect : Test for suboroup diffe Study or Suboroup diffe Suboroup 2000 Suboroup	Z = 7.61 (P erences: Cf Mean 0.83 olicable Z = 3.11 (P = 1.11 1.06 1.13 1.09 1.13 1.09 1.13 1.09 1.12 0.88 0.00; Chi <sup>2</sup> = 0.95 1.17 1.07 0.00; Chi <sup>2</sup> =	<ul> <li>&lt; 0.000(0)</li> <li>a)<sup>µ</sup> = 3.82</li> <li>gain (m</li> <li>SD</li> <li>0.03</li> <li>0.03</li> <li>0.04</li> <li>0.05</li> <li>0.04</li> <li>0.06</li> <li>0.06</li> <li>0.07</li> <li>0.11</li> <li>2.09, df<sup>2</sup></li> </ul>	df = 18 % (df = 3 % (df =	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.13 1.04 1.09 0.85 0.0004); F 0.88 1.13 1.04 1.3 1.04	0.05 0.03 0.13 0.03 0.01 0.13 0.01 0.13 0.01 0.13 0.07 0.01 0.13 0.07 0.01 0.13 0.01 0.13 0.01	5 Total 82 82 82 82 82 82 82 82 82 82	Weight 7.0% 7.0% 9.0% 9.3% 8.1% 3.8% 3.8% 3.8% 5.3% 59.5% 59.5%	W. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.01 [-0.00, 0.02]           0.04 [0.03, 0.05]           -0.01 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.06]           0.03 [-0.00, 0.06]           0.03 [-0.00, 0.06]           0.03 [-0.2, 0.04]           0.03 [0.02, 0.04]           0.07 [0.02, 0.12]           0.07 [0.02, 0.12]           0.03 [-0.00, 0.06]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
Heterogeneity: Tau" = 1 Test for overall effect : Test for suboroup diffe L2.1 4m - pro < 1.8 Dropeza-Ceja 2018 Subtotal (95% CI) deterogeneity: Not app Test for overall effect Z L2.2 4m - pro 1.8 - 2.0 Breij 2019 Janiels 2008 Janiels 2008 Janiels 2008 Dropeza-Ceja 2018 Putel 2016 Tabulsi 2010 Turck 2006 Yandenplas 2020 Subtotal (95% CI) deterogeneity: Tau" = 0 Fest for overall effect Z L2.3 4m - pro 2.1 - 2.2 Dropeza-Ceja 2018 Tabulsi 2010 Subtotal (95% CI) deterogeneity: Tau" = 0 Fest for overall effect Z L3.3 4m - pro 2.1 - 2.2	Z = 7.61 (P erences: Cr Mean 0.83 blicable = 3.11 (P = 1.11 1.06 1.03 1.13 0.9 1.13 1.09 1.07 1.12 0.88 0.00; Chi <sup>p</sup> = Z = 3.18 (P = 0.95 1.17 1.07 1.07 0.00; Chi <sup>p</sup> = Z = 3.36 (P =	<ul> <li>&lt; 0.000( <sup>1</sup>)<sup>2</sup> = 3.82         <sup>1</sup></li> <li>gain (m         <sup>1</sup>)<sup>2</sup> = 3.82         <sup>1</sup></li> <li>0.03         <sup>0</sup></li> <li>0.03         <sup>0</sup></li> <li>0.04         <sup>0</sup></li> <li>0.05         <sup>0</sup></li> <li>0.05         <sup>0</sup></li> <li>0.06         <sup>0</sup></li> <li>0.07         <sup>0</sup></li> <l< td=""><td>df = 18 i)) . df = 3 ( . df</td><td>P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.09 0.85 0.0004); F 0.88 1.13 1.04 1.09 0.85 0.88 1.13 1.04 0.85 0.88 1.13 1.04 0.88 1.13 1.04 0.85 0.85 0.85 0.88 1.13 1.04 0.85 0.</td><td>P<sup>I</sup> = 21.6% pht gain (n SD 0.13 0.05 0.03 0.01 0.13 0.07 0.13 0.01 0.62 0.01 0.62 0.01 0.13 0.13 0.13 0.13 0.13 0.43 0.13 0.13 0.43 0.43 0.43 0.43 0.43 0.44</td><td>5 Total 82 82 82 82 82 82 82 82 82 82</td><td>Weinht 7.0% 7.0% 9.0% 8.1% 3.9% 8.6% 3.8% 9.3% 5.8% 5.9.5% 5.4% 15.7%</td><td>N. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.04 [0.03, 0.05]           -0.01 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.06]           -0.03 [-0.08, 0.08]           0.04 [0.02, 0.06]           0.03 [-0.04, 0.08]           0.03 [-0.04, 0.08]           0.03 [-0.04, 0.08]           0.03 [-0.04, 0.08]           0.03 [-0.04, 0.12]           0.07 [0.02, 0.12]           0.04 [-0.02, 0.07]</td><td>Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl</td></l<></ul>	df = 18 i)) . df = 3 ( . df	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.09 0.85 0.0004); F 0.88 1.13 1.04 1.09 0.85 0.88 1.13 1.04 0.85 0.88 1.13 1.04 0.88 1.13 1.04 0.85 0.85 0.85 0.88 1.13 1.04 0.85 0.	P <sup>I</sup> = 21.6% pht gain (n SD 0.13 0.05 0.03 0.01 0.13 0.07 0.13 0.01 0.62 0.01 0.62 0.01 0.13 0.13 0.13 0.13 0.13 0.43 0.13 0.13 0.43 0.43 0.43 0.43 0.43 0.44	5 Total 82 82 82 82 82 82 82 82 82 82	Weinht 7.0% 7.0% 9.0% 8.1% 3.9% 8.6% 3.8% 9.3% 5.8% 5.9.5% 5.4% 15.7%	N. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.04 [0.03, 0.05]           -0.01 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.06]           -0.03 [-0.08, 0.08]           0.04 [0.02, 0.06]           0.03 [-0.04, 0.08]           0.03 [-0.04, 0.08]           0.03 [-0.04, 0.08]           0.03 [-0.04, 0.08]           0.03 [-0.04, 0.12]           0.07 [0.02, 0.12]           0.04 [-0.02, 0.07]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
Heterogeneity: Tau" = Test for overall effect : Test for suboroup L2.1 4m - pro < 1.8 Dropeza-Ceja 2018 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect Z 1.2.2 4m - pro 1.8-2.0 Breij 2019 Daniels 2008 Liotto 2018 Dropeza-Ceja 2018 Videt 2016 Raiha 2002 Frabulsi 2010 Turck 2006 Jantotal 016% CI) Heterogeneity: Tau" = ( Fest for overall effect Z 1.2.3 4m - pro 2.1-2.2 Dropeza-Ceja 2018 Raiha 2002 Frabulsi 2010 Subtotal (95% CI) Heterogeneity: Tau" = ( Fest for overall effect Z L.3.3 4m - pro 2.1-2.2 Diabtotal (95% CI) Heterogeneity: Tau" = ( Fest for overall effect Z L.2.4 4m - pro > 2. Jointo 2018	Z = 7.61 (P erences: Cr Mean 0.83 0licable Z = 3.11 (P = 1.11 1.06 1.13 1.09 1.09 1.09 1.09 1.12 0.88 0.00; Chi <sup>2</sup> = Z = 3.36 (P = 1.13	<ul> <li>&lt; 0.000(0)</li> <li>gain (m</li> <li>SD</li> <li>0.03</li> <li>0.02)</li> <li>0.04</li> <li>0.04</li> <li>0.03</li> <li>0.02</li> <li>0.04</li> <li>0.03</li> <li>0.16</li> <li>0.03</li> <li>0.16</li> <li>0.12</li> <li>0.09</li> <li>0.17</li> <li>0.11</li> <li>2.09, cfr-1</li> <li>0.008)</li> <li>0.04</li> </ul>	df = 18 i)) . df = 3 ( . df	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.09 0.85 0.0004); F 0.88 1.13 1.04 1.09 0.85 0.0004); F 0.88 1.13 1.04 1.14	Pr         = 21.6%           pht gain (n         SD           0.13         0.13           0.05         0.03           0.13         0.07           0.13         0.07           0.13         0.07           0.13         0.07           0.01         0.07           0.01         0.01           *= 72%         0.13           0.11         0.11           %         0.01	5 mm/d) <u>Total</u> 82 82 65 56 65 65 65 65 65 65 65 53 110 220 50 50 50 53 110 220 50 50 50 53 10 53 53 53 53 53 53 53 53 53 53	Weight 7.0% 9.0% 9.3% 3.9% 3.8% 3.8% 3.8% 3.8% 3.8% 9.3% 59.5% 59.5% 15.7%	N. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.01 [-0.00, 0.02]           0.04 [0.03, 0.05]           -0.01 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.06]           -0.04 [-0.10, 0.02]           0.03 [-0.02, 0.06]           0.03 [-0.2, 0.04]           0.03 [-0.2, 0.04]           0.03 [0.02, 0.04]           0.07 [0.02, 0.12]           0.04 [-0.04, 0.12]           0.03 [0.02, 0.07]           0.04 [0.02, 0.07]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect : Test for suboroup diffe L2.1 4m - pro < 1.8 Dropeza-Ceja 2018 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect Z L2.2 4m - pro 1.8-2.0 Breij 2019 Daniels 2008 Lotto 2018 Dropeza-Ceja 2018 Puet 2016 Raiha 2002 Trabulsi 2010 Furck 2006 Yandenplas 2020 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0 Fest for overall effect Z L2.3 4m - pro 2.1-2.2 Dropeza-Ceja 2018 Raiha 2002 Trabulsi 2010 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0 Fest for overall effect Z L2.3 4m - pro 2.1 L2.4 4m - pro > 2.2 Lotto 2018 Puet 2016	Z = 7.61 (P erences: Cf Mean 0.83 01cable Z = 3.11 (P = 1.11 1.06 1.13 1.09 1.13 1.09 1.17 1.07 0.88 0.00; Chi <sup>2</sup> = Z = 3.36 (P = 1.13 1.15	<ul> <li>&lt; 0.000(0)</li> <li>a)<sup>µ</sup> = 3.82</li> <li>gain (m</li> <li>SD</li> <li>0.03</li> <li>0.03</li> <li>0.04</li> <li>0.04</li> <li>0.04</li> <li>0.04</li> <li>0.06</li> <li>0.12</li> <li>0.03</li> <li>0.06</li> <li>28.40, di</li> <li>0.001)</li> <li>0.09</li> <li>0.17</li> <li>0.11</li> <li>2.09, df<sup>2</sup></li> <li>0.008)</li> <li>0.04</li> <li>0.04</li> <li>0.004</li> <li>0.04</li> <li>0.04</li> <li>0.04</li> <li>0.04</li> <li>0.04</li> <li>0.04</li> <li>0.04</li> </ul>	df = 18 in) . df = 3 ( . df	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.09 1.13 1.04 1.09 0.85 0.0004); F 0.888 1.13 1.04 0.85 0.0004); F 0.888 1.13 1.04 0.355; P = 4 1.14 1.09	Pr =         21.6%           st         st           0.13         0.05           0.03         0.01           0.13         0.01           0.13         0.01           0.13         0.13           0.14         0.03           0.01         0.13           0.13         0.11           0.61         0.01           0.13         0.11           %         0.01           0.01         0.62	5 Total 82 82 65 56 65 56 82 82 82 100 25 81 82 82 82 82 82 82 82 82 82 82	Weight 7.0% 9.0% 9.3% 8.1% 3.8% 5.9.5% 59.5% 59.5% 59.5% 15.7%	N. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.01 [-0.00, 0.02]           0.04 [0.03, 0.05]           -0.01 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.06]           -0.04 [-0.02, 0.06]           0.03 [-0.24, 0.30]           0.03 [-0.24, 0.30]           0.03 [-0.24, 0.30]           0.03 [0.02, 0.04]           0.07 [0.02, 0.12]           0.03 [0.02, 0.04]           0.03 [0.02, 0.07]           0.04 [0.02, 0.07]           0.05 [0.04, [0.02, 0.07]           -0.01 [-0.02, 0.00]           0.06 [-0.21, 0.33]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
Heterogeneity: Tau" = Test for overall effect: : Test for suboroup diffe L2.1 4m - pro < 1.8 Dropeza-Ceja 2018 Subtotal (95% CI) Heterogeneity: Not app Fest for overall effect: Z L2.2 4m - pro 1.8-2.0 Breij 2019 Janiels 2008 Lotto 2018 Dropeza-Ceja 2018 Judet 2016 Trabulsi 2010 Furck 2006 Aradhenglas 2020 Subtotal (95% CI) Heterogeneity: Tau" = ( Test for overall effect: Z Dropeza-Ceja 2018 Raiha 2002 Trabulsi 2010 Furck 2006 Subtotal (95% CI) Heterogeneity: Tau" = ( Test for overall effect: Z L2.4 4m - pro > 2.2 Lotto 2018 Judet 2016 Lick 2016 Lick 2016 Subtotal (95% CI)	Z = 7.61 (P erences: Cr Mean 0.83 0licable Z = 3.11 (P = 1.11 1.06 1.13 1.09 1.09 1.09 1.09 1.12 0.88 0.00; Chi <sup>2</sup> = Z = 3.36 (P = 1.13	<ul> <li>&lt; 0.000(0)</li> <li>gain (m</li> <li>SD</li> <li>0.03</li> <li>0.02)</li> <li>0.04</li> <li>0.04</li> <li>0.03</li> <li>0.02</li> <li>0.04</li> <li>0.03</li> <li>0.16</li> <li>0.03</li> <li>0.16</li> <li>0.12</li> <li>0.09</li> <li>0.17</li> <li>0.11</li> <li>2.09, cfr-1</li> <li>0.008)</li> <li>0.04</li> </ul>	df = 18 i)) . df = 3 ( . df	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.09 0.85 0.0004); F 0.88 1.13 1.04 1.09 0.85 0.0004); F 0.88 1.13 1.04 1.14	Pr         = 21.6%           pht gain (n         SD           0.13         0.13           0.05         0.03           0.13         0.07           0.13         0.07           0.13         0.07           0.13         0.07           0.01         0.07           0.01         0.01           *= 72%         0.13           0.11         0.11           %         0.01	5 mm/d) <u>Total</u> 822 82 82 82 86 85 85 85 85 85 85 85 85 85 85	Weiaht 7.0% 7.0% 9.0% 8.1% 0.3% 9.3% 0.3% 9.3% 59.5% 15.7% 9.2% 0.3% 7.3%	N. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.04 [0.03, 0.05]           -0.01 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.06]           -0.03 [-0.04, 0.08]           0.03 [-0.02, 0.06]           0.03 [-0.02, 0.06]           0.03 [-0.02, 0.04]           0.03 [0.02, 0.04]           0.07 [0.02, 0.12]           0.04 [-0.02, 0.01]           0.03 [0.02, 0.12]           0.04 [-0.02, 0.07]           -0.01 [-0.02, 0.07]           -0.01 [-0.02, 0.00]           0.06 [-0.21, 0.33]           0.08 [0.06, 0.10]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
Heterogeneity. Tau" = C Test for overall effect : Test for suborous diffe AL2.1 4m - pro < 1.8 Dropeza-Ceja 2018 Subtotal (95% CI) Heterogeneity. Not app Test for overall effect Z L2.2 4m - pro1.8-2.0 Breij 2019 Dropeza-Ceja 2018 Dropeza-Ceja 2018 Dropeza-Ceja 2018 Dropeza-Ceja 2018 Dropeza-Ceja 2018 Videt 2016 Raiha 2002 Trabulsi 2010 Trabulsi 2010 Trabulsi 2010 Subtotal (95% CI) Heterogeneity. Tau" = C Test for overall effect Z L.2.4 m - pro 2.1-2.2 Dropeza-Ceja 2018 Subtotal (95% CI) Alta 2016 Subtotal (95% CI)	Z = 7.61 (P erences: Cf Mean 0.83 0.83 0.83 0.83 0.83 0.83 0.83 0.83	<ul> <li>&lt; 0.000(0)</li> <li>m<sup>2</sup> = 3.82</li> <li>gain (m</li> <li>SD</li> <li>0.03</li> <li>0.03</li> <li>0.04</li> <li>0.04</li> <li>0.04</li> <li>0.03</li> <li>0.03</li> <li>0.04</li> <li>0.04</li> <li>0.03</li> <li>0.16</li> <li>0.12</li> <li>0.03</li> <li>0.06</li> <li>28.40, dt</li> <li>0.00</li> <li>0.17</li> <li>0.11</li> <li>2.09, dt<sup>2</sup></li> <li>0.04</li> <li>0.04</li> <li>0.04</li> <li>0.09</li> <li>0.17</li> <li>0.11</li> <li>2.09, dt<sup>2</sup></li> <li>0.04</li> <li>0.04</li> <li>0.06</li> </ul>	df = 18 (df = 3 (df =	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.09 1.13 1.04 1.09 0.85 0.0004); F 0.888 1.13 1.04 1.04 0.85 0.888 1.13 1.04 0.355; P = 4 1.14 1.09 1.09	pri gain (n           st           0.13           0.05           0.03           0.14           0.15           0.13           0.14           0.15           0.15           0.16           0.17           0.18           0.19           0.11           0.12           0.13           0.14           0.15           0.16           0.07	5 Total 82 82 82 82 82 82 82 82 82 82	Weiaht 7.0% 7.0% 9.0% 8.1% 0.3% 9.3% 0.3% 9.3% 59.5% 15.7% 9.2% 0.3% 7.3%	N. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.01 [-0.00, 0.02]           0.04 [0.03, 0.05]           -0.01 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.06]           -0.04 [-0.02, 0.06]           0.03 [-0.24, 0.30]           0.03 [-0.24, 0.30]           0.03 [-0.24, 0.30]           0.03 [0.02, 0.04]           0.07 [0.02, 0.12]           0.03 [0.02, 0.04]           0.03 [0.02, 0.07]           0.04 [0.02, 0.07]           0.05 [0.04, [0.02, 0.07]           -0.01 [-0.02, 0.00]           0.06 [-0.21, 0.33]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
Heterogeneity: Tau" = Test for overall effect : Test for suboroup diffe L2.1 4m - pro < 1.8 Dropeza-Ceja 2018 Subtotal (95% CI) deterogeneity: Not app Test for overall effect Z L2.2 4m - pro 1.8 - 2.0 Breij 2019 Daniels 2008 L010 2018 Dropeza-Ceja 2018 Putel 2016 Tabulsi 2010 Subtotal (95% CI) deterogeneity: Tau" = C Test for overall effect Z L2.3 4m - pro 2.1 - 2.2 Dropeza-Ceja 2018 Tabulsi 2010 Subtotal (95% CI) deterogeneity: Tau" = C Test for overall effect Z L3.3 4m - pro 2.1 - 2.2 Dropeza-Ceja 2018 Tabulsi 2010 Subtotal (95% CI) deterogeneity: Tau" = C Test for overall effect Z L2.4 4m - pro > 2.2 L010 2018 Putet 2016 Turck 2006 Subtotal (95% CI) deterogeneity: Tau" = C	Z = 7.61 (P erences: Cr Mean 0.83 blicable = 3.11 (P = 1.11 1.06 1.13 0.9 1.13 1.09 1.03 1.09 1.12 0.88 0.00; Chi <sup>2</sup> = Z = 3.18 (P = 0.95 1.17 1.00; Chi <sup>2</sup> = 3.36 (P = 1.13 1.15 1.17 0.00; Chi <sup>2</sup> =	< 0.000(0) gain (m SD 0.03 0.03 0.04 0.04 0.04 0.04 0.04 0.04 0.04 0.04 0.04 0.04 0.04 0.06 28.40, di 0.17 0.17 0.17 0.17 0.17 0.17 0.17 0.11 0.09 0.17 0.17 0.01 0.09 0.17 0.11 0.09 0.43 0.00 0.04 0.0008 0.004 0.046 0.46 0.46 0.46 0.46 51.39, di	df = 18 (df = 3 (df =	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.09 1.13 1.04 1.09 0.85 0.0004); F 0.888 1.13 1.04 1.04 0.85 0.888 1.13 1.04 0.355; P = 4 1.14 1.09 1.09	pri gain (n           st           0.13           0.05           0.03           0.14           0.15           0.13           0.14           0.15           0.15           0.16           0.17           0.18           0.19           0.11           0.12           0.13           0.14           0.15           0.16           0.07	5 mm/d) <u>Total</u> 822 82 82 82 86 85 85 85 85 85 85 85 85 85 85	Weiaht 7.0% 7.0% 9.0% 8.1% 0.3% 9.3% 0.3% 9.3% 59.5% 15.7% 9.2% 0.3% 7.3%	N. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.04 [0.03, 0.05]           -0.01 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.06]           -0.03 [-0.04, 0.08]           0.03 [-0.02, 0.06]           0.03 [-0.02, 0.06]           0.03 [-0.02, 0.04]           0.03 [0.02, 0.04]           0.07 [0.02, 0.12]           0.04 [-0.02, 0.01]           0.03 [0.02, 0.12]           0.04 [-0.02, 0.07]           -0.01 [-0.02, 0.07]           -0.01 [-0.02, 0.00]           0.06 [-0.21, 0.33]           0.08 [0.06, 0.10]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
Heterogeneity: Tau" = 0 Test for overall effect : Test for suboroup diffe L2.1 4m - pro < 1.8 Dropeza-Ceja 2018 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect Z L2.2 4m - pro 1.8-2.0 Breij 2019 Daniels 2008 Joito 2018 Dropeza-Ceja 2018 Putel 2016 Tabulsi 2000 Subtotal (95% CI) Heterogeneity: Tau" = 0 Fest for overall effect Z L2.3 4m - pro 2.1-2.2 Dropeza-Ceja 2018 Raina 2002 Tabulsi 2010 Subtotal (95% CI) Heterogeneity: Tau" = 0 Test for overall effect Z L2.4 4m - pro > 2.2 Joito 2018 Putel 2016 Turck 2006 Subtotal (95% CI) Heterogeneity: Tau" = 0 Fest for overall effect Z L2.4 4m - pro > 2.2 Joito 2018 Putel 2016 Turck 2006 Subtotal (95% CI) Heterogeneity: Tau" = 0 Fest for overall effect Z	Z = 7.61 (P erences: Cr Mean 0.83 blicable = 3.11 (P = 1.11 1.06 1.13 0.9 1.13 1.09 1.03 1.09 1.12 0.88 0.00; Chi <sup>2</sup> = Z = 3.18 (P = 0.95 1.17 1.00; Chi <sup>2</sup> = 3.36 (P = 1.13 1.15 1.17 0.00; Chi <sup>2</sup> =	< 0.000(0) gain (m SD 0.03 0.03 0.04 0.04 0.04 0.04 0.04 0.04 0.04 0.04 0.04 0.04 0.04 0.06 28.40, di 0.17 0.17 0.17 0.17 0.17 0.17 0.17 0.11 0.09 0.17 0.17 0.01 0.09 0.17 0.11 0.09 0.43 0.00 0.04 0.0008 0.004 0.046 0.46 0.46 0.46 0.46 51.39, di	df = 18 in) . df = 3 ( . df	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.09 1.13 1.04 1.09 0.85 0.0004); F 0.888 1.13 1.04 1.04 0.85 0.888 1.13 1.04 0.355; P = 4 1.14 1.09 1.09	pri gain (n           st           0.13           0.05           0.03           0.14           0.15           0.13           0.14           0.15           0.15           0.16           0.17           0.18           0.19           0.11           0.12           0.13           0.14           0.15           0.16           0.07	5 Total 82 82 65 56 56 50 82 82 82 100 25 82 28 100 25 50 531 100 25 65 54 100 25 82 82 82 82 82 82 82 82 82 82	Weight 7.0% 9.0% 9.3% 8.1% 8.8% 3.8% 9.3% 8.8% 9.3% 9.3% 9.3% 9.3% 9.3% 9.3% 9.3% 9.3	N. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.04 [0.03, 0.05]           -0.01 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.06]           -0.03 [-0.04, 0.08]           0.04 [0.02, 0.06]           0.03 [-0.00, 0.06]           0.03 [-0.02, 0.04]           0.03 [0.02, 0.04]           0.04 [0.02, 0.04]           0.07 [0.02, 0.12]           0.04 [-0.02, 0.07]           0.04 [0.02, 0.07]           -0.01 [-0.02, 0.07]           -0.01 [-0.02, 0.07]           -0.01 [-0.02, 0.01]           0.06 [0.02, 0.12]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
Heterogeneity: Tau <sup>2</sup> = Test for overall effect : Test for suboroup diffe Study of Suboroup diffe Subtotal (95% CI) Heterogeneity: Total 2018 Subtotal (95% CI) Heterogeneity: Total 2018 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = C Test for overall effect Z Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = C Test for overall effect Z Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = C Test for overall effect Z Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = C L2.4 4m - pro > 2.2 Jointo 2018 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = C Fest for overall effect Z Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = C Fest for overall effect Z Subtotal (95% CI)	Z = 7.61 (P erences: Cr IF-height Mean 0.83 olicable 2 = 3.11 (P = 1.11 1.06 1.13 0.9 1.17 1.09 1.07 1.12 0.88 0.00; Chip = 2 = 3.36 (P = 1.13 1.15 1.17 0.00; Chip = 2 = 3.06 (P = 2 = 0.85 (P = 2 = 0.85 (P = 2) 2	<ul> <li>&lt; 0.000(0)</li> <li>a,82</li> <li><b>gain (m</b></li> <li><b>SD</b></li> <li>0.03</li> <li>0.02)</li> <li>0.04</li> <li>0.03</li> <li>0.02</li> <li>0.04</li> <li>0.03</li> <li>0.06</li> <li>28.40, dt</li> <li>0.06</li> <li>28.40, dt</li> <li>0.09</li> <li>0.17</li> <li>0.19</li> <li>0.17</li> <li>0.11</li> <li>0.09</li> <li>0.17</li> <li>0.01</li> <li>0.09</li> <li>0.12</li> <li>0.09</li> <li>0.14</li> <li>0.06</li> <li>51.39, dt</li> <li>0.39</li> </ul>	df = 18 i)) . df = 3 ( . df	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.09 1.13 1.04 1.09 0.85 0.0004); F 0.88 1.13 1.04 0.85 0.0004); F 0.88 1.13 1.04 0.85 0.0004); F 0.88 1.13 1.04 0.35); P = 4	Pr = 21.6% SD 0.13 0.05 0.03 0.01 0.13 0.07 0.13 0.07 0.13 0.17 0.13 0.07 0.13 0.07 0.01 0.62 0.01 0.13 0.13 0.72% 0.13 0.72% 0.13 0.72% 0.13 0.72% 0.13 0.72% 0	5 mm/d) <u>Total</u> 822 82 665 566 560 228 500 531 822 282 282 100 255 500 531 100 250 531 110 220 500 556 140 973	Weiaht 7.0% 7.0% 9.0% 9.0% 8.1% 0.3% 9.3% 0.3% 9.3% 59.5% 15.7% 9.2% 0.3% 7.0%	N. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.04 [0.03, 0.05]           -0.01 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.06]           -0.03 [-0.04, 0.08]           0.03 [-0.02, 0.06]           0.03 [-0.02, 0.06]           0.03 [-0.02, 0.04]           0.03 [0.02, 0.04]           0.07 [0.02, 0.12]           0.04 [-0.02, 0.01]           0.03 [0.02, 0.04]           0.04 [-0.02, 0.07]           -0.01 [-0.02, 0.00]           0.06 [-0.21, 0.33]           0.08 [0.06, 0.10]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
Heterogeneiky: Tau" = C Test for overall effect : Test for suboroup diffe L2.1 4m - pro < 1.8 Dropeza-Ceja 2018 Subtotal (95% CI) Heterogeneiky: Not app Fest for overall effect Z L2.2 4m - pro1.8-2.0 Breij 2019 Dropeza-Ceja 2018 Dropeza-Ceja 2018 Dropeza-Ceja 2018 Dropeza-Ceja 2018 Dropeza-Ceja 2018 Putel 2016 Raiha 2002 Frabulsi 2010 Turck 2006 Subtotal (95% CI) Heterogeneiky: Tau" = C Fest for overall effect Z L2.3 4m - pro2.1-2.2 Dropeza-Ceja 2018 Raiha 2002 Trabulsi 2010 Subtotal (95% CI) Heterogeneiky: Tau" = C Fest for overall effect Z L2.4 4m - pro > 2.2 Liotto 2018 Dutota (95% CI) Heterogeneiky: Tau" = C Fest for overall effect Z Fotal (95% CI)	Z = 7.61 (P erences: Cf Mean 0.83 0.83 0.83 0.83 0.83 0.83 0.83 0.83	<ul> <li>&lt; 0.000(0)</li> <li>a, a = 3, a ≤ 3, a &lt; 3, a &lt;</li></ul>	df = 18 i)) . df = 3 ( . df	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.09 1.13 1.04 1.09 0.85 0.0004); F 0.88 1.13 1.04 0.85 0.0004); F 0.88 1.13 1.04 0.85 0.0004); F 0.88 1.13 1.04 0.35); P = 4	Pr = 21.6% SD 0.13 0.05 0.03 0.01 0.13 0.07 0.13 0.07 0.13 0.17 0.13 0.07 0.13 0.07 0.01 0.62 0.01 0.13 0.13 0.72% 0.13 0.72% 0.13 0.72% 0.13 0.72% 0.13 0.72% 0	5 mm/d) <u>Total</u> 822 82 665 566 560 228 500 531 822 282 282 100 255 500 531 100 250 531 110 220 500 556 140 973	Weight 7.0% 9.0% 9.3% 8.1% 8.8% 3.8% 9.3% 8.8% 9.3% 9.3% 9.3% 9.3% 9.3% 9.3% 9.3% 9.3	N. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.04 [0.03, 0.05]           -0.01 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.06]           -0.03 [-0.04, 0.08]           0.04 [0.02, 0.06]           0.03 [-0.00, 0.06]           0.03 [-0.02, 0.04]           0.03 [0.02, 0.04]           0.04 [0.02, 0.04]           0.07 [0.02, 0.12]           0.04 [-0.02, 0.07]           0.04 [0.02, 0.07]           -0.01 [-0.02, 0.07]           -0.01 [-0.02, 0.07]           -0.01 [-0.02, 0.01]           0.06 [0.02, 0.12]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% Cl
tudy or Subaroup rest for overall effect : rest for subaroup diffe 2.1 4m - pro < 1.8 ropeza-Ceja 2018 uiutotal (95% CI) deterogeneity: Not app rest for overall effect Z 2.2 4m - pro 1.8-2.0 reij 2019 vaniels 2008 joto 2018 vopeza-Ceja 2018 uiutotal (95% CI) deterogeneity: Tau <sup>2</sup> = C 2.3 4m - pro 2.1-2.2 vopeza-Ceja 2018 uiutotal (95% CI) deterogeneity: Tau <sup>2</sup> = C z.4 4m - pro 2.2 ioto 2018 uiuto 2016 uiutotal (95% CI) deterogeneity: Tau <sup>2</sup> = C z.4 4m - pro 2.2 ioto 2018 uiuto 2018 uiuto 2010 uiutotal (95% CI) deterogeneity: Tau <sup>2</sup> = C z.4 4m - pro 2.2 ioto 2018 uiuto 2018 uiuto 2018 uiuto 2010 uiutotal (95% CI) deterogeneity: Tau <sup>2</sup> = C rest for overall effect Z sotal (95% CI)	Z = 7.61 (P) erences: CP $IF-height Mean 0.83 blicable = 3.11 (P = 1.11 1.06 1.13 0.9 1.13 1.09 1.13 1.09 1.12 0.88 0.00; Chi2 = Z = 3.18 (P = 0.95 1.17 1.00; Chi2 = 1.13 1.15 1.17 0.00; Chi2 = 2.36 (P = 1.13 1.15 1.17 0.00; Chi2 = 2.26 (P = 0.00; Chi2 = 2.266 (P = 0.00; Chi2 = 2.266 (P = 0.00; Chi2 = 0$	< 0.000( ) <sup>µ</sup> = 3.82 0.03 0.03 0.04 0.04 0.04 0.04 0.04 0.04 0.03 0.06 28.40, d1 2.09, df: 0.001) 0.09 0.17 0.11 0.09 0.17 0.11 0.09 0.17 0.01 1.13, 74, 1 0.01)	df = 18 in) . df = 3 ( . df = 5 ( . df	P = 0.28). HM - heig Mean 0.88 1.1 1.02 1.14 0.88 1.09 0.85 0.0004); F 0.88 1.13 1.04 0.35; I <sup>2</sup> = 4 1.14 1.09 0.35; I <sup>2</sup> = 4	P <sup>i</sup> = 21.6%           pht gain (n           SD           0.13           0.05           0.01           0.03           0.01           0.03           0.01           0.03           0.01           0.03           0.01           0.03           0.01           0.02           0.03           0.01           0.62           0.01           0.13           0.13           0.13           0.14           0.62           0.07           %           0.01           0.62           0.07           P <sup>a</sup> = 96%           1); P <sup>a</sup> = 879	5 Total 822 82 655 566 20 255 500 551 100 255 500 551 822 282 282 100 255 500 551 100 200 551 100 200 551 100 200 551 100 200 551 100 200 551 100 200 551 200 555 550 550 550 550 550 550	Weight 7.0% 9.0% 9.3% 8.1% 8.8% 3.8% 9.3% 8.8% 9.3% 9.3% 9.3% 9.3% 9.3% 9.3% 9.3% 9.3	N. Random, 95% Cl           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           -0.05 [-0.08, -0.02]           0.04 [0.03, 0.05]           -0.01 [-0.03, 0.01]           0.02 [-0.04, 0.08]           0.04 [0.02, 0.06]           -0.03 [-0.04, 0.08]           0.04 [0.02, 0.06]           0.03 [-0.00, 0.06]           0.03 [-0.02, 0.04]           0.03 [0.02, 0.04]           0.04 [0.02, 0.04]           0.07 [0.02, 0.12]           0.04 [-0.02, 0.07]           0.04 [0.02, 0.07]           -0.01 [-0.02, 0.07]           -0.01 [-0.02, 0.07]           -0.01 [-0.02, 0.01]           0.06 [0.02, 0.12]	Favors human milk Favors infant formula

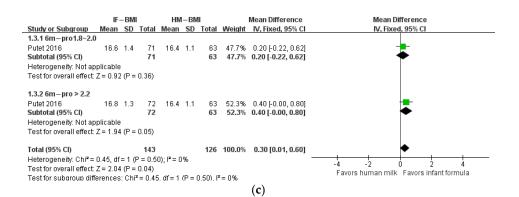
Figure 5. Cont.

	IF	-BMI		HN	I-BM			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.3.1 4m–pro1.8~2.0	)								
Putet 2016	16	1.4	71	15.7	1.1	65	19.9%	0.30 [-0.12, 0.72]	
Raiha 2002	16.62	1.45	56	16.25	1.21	28	10.3%	0.37 [-0.22, 0.96]	
Turck 2006	16.9	1.16	51	16.02	1.47	25	8.2%	0.88 [0.22, 1.54]	
Subtotal (95% CI)			178			118	38.4%	0.44 [0.14, 0.75]	◆
Heterogeneity: Chi² =	2.19, df	= 2 (P	= 0.33	); I <sup>z</sup> = 99	6				
Test for overall effect:	Z = 2.85	5 (P = 0	0.004)						
1.3.2 4m-pro2.1~2.2	2								
Raiha 2002	16.78	1.32	29	16.25	1.21	28	8.2%	0.53 [-0.13, 1.19]	
Sinahal 2010	17.4	1.66	200	16.6	1.6	101	23.6%	0.80 [0.41, 1.19]	+
Subtotal (95% CI)			229			129	31.8%		◆
Heterogeneity: Chi <sup>2</sup> =	0.48, df	= 1 (P	= 0.49)	); I <sup>2</sup> = 09	6				
Test for overall effect:	Z=4.29	) (P < (	0.0001)						
1.3.3 4m–pro > 2.2									
Putet 2016	16.3	1.3	74	15.7	1.1	65	22.2%	0.60 [0.20, 1.00]	
Turck 2006	16.66	1.31	50	16.02	1.47	25	7.6%	0.64 [-0.04, 1.32]	
Subtotal (95% CI)			124			90	29.9%	0.61 [0.27, 0.95]	◆
Heterogeneity: Chi <sup>2</sup> =	0.01, df	= 1 (P	= 0.92)	); <b>I</b> ² = 09	6				
Test for overall effect:	Z = 3.47	' (P = (	).0005)						
Total (95% CI)			531			337	100.0%	0.58 [0.40, 0.77]	•
Heterogeneity: Chi <sup>2</sup> =	4.28. df	= 6 (P	= 0.64)	): <b> </b> ² = 09	6				<u> </u>
Test for overall effect:									-4 -2 0 2 4
Test for subaroup diff					<sup>o</sup> = 0.4	5), I <sup>2</sup> =	0%		Favors human milk Favors infant formula
								(a)	
								( <b>c</b> )	

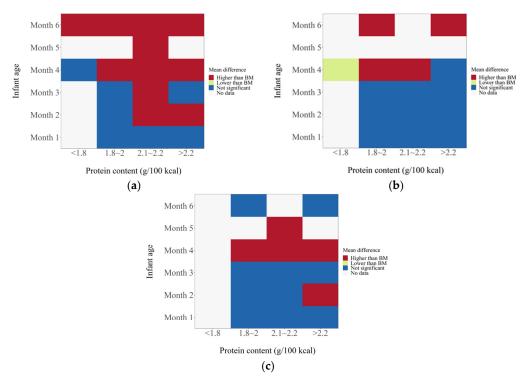
**Figure 5.** Forest plot of the effects of protein content of infant formula on the weight gain, height gain, and BMI of infants at 4 months of age. (a) The effects on weight gain. (b) The effects on height gain. (c) The effects on BMI.

Study or Subgroup	IF – weigl Mean	π gain SD	(g/a) Total	HM–weig Mean	gnt gain ( SD			Mean Difference V, Random, 95% Cl	Mean Difference IV, Random, 95% Cl
1.1.1 6m–pro < 1.8									
Kouwenhoven 2019	24	2.4	88	22	2.9	65	24.1%	2.00 [1.13, 2.87]	
Subtotal (95% CI)			88			65	24.1%	2.00 [1.13, 2.87]	•
Heterogeneity: Not ap									
Test for overall effect: .	Z = 4.53 (P ·	< 0.000	01)						
1.1.2 6m–pro1.8~2.0									
Putet 2016	23.4	2.2	71	22.4	2.1	63	26.3%	1.00 [0.27, 1.73]	-
Subtotal (95% CI)			71			63	26.3%	1.00 [0.27, 1.73]	◆
Heterogeneity: Not ap	plicable								
Test for overall effect: .	Z = 2.69 (P =	= 0.007	)						
1.1.3 6m–pro2.1~2.2									
Kouwenhoven 2019	24.8	2.1	82	22	2.9	65	24.6%	2.80 [1.96, 3.64]	
Subtotal (95% CI)			82			65	24.6%	2.80 [1.96, 3.64]	◆
Heterogeneity: Not ap	plicable								
Test for overall effect:		< 0.000	01)						
1.1.4 6m–pro > 2.2									
Putet 2016	24.8	2.7	72	22.4	2.1	63	25.0%	2.40 [1.59, 3.21]	
Subtotal (95% CI)			72			63	25.0%	2.40 [1.59, 3.21]	•
Heterogeneity: Not ap	plicable								
Test for overall effect: .	Z = 5.80 (P ·	< 0.000	01)						
Test for overall effect: . Total (95% CI)	Z = 5.80 (P ·	< 0.000				256	100.0%	2 03 [1 24 2 83]	•
Total (95% CI)			313	- 0.009)- 6	<sup>2</sup> = 74%	256	100.0%	2.03 [1.24, 2.83]	<b>♦</b>
Total (95% Cl) Heterogeneity: Tau² =	0.49; Chi <sup>2</sup> =	11.65,	313 df=3 (P	= 0.009); F	<sup>2</sup> =74%	256	100.0%	2.03 [1.24, 2.83]	-10 -5 0 5 10
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: .	0.49; Chi <sup>z</sup> = Z = 5.00 (P ·	11.65, < 0.000	<b>313</b> df = 3 (P 01)				100.0%	2.03 [1.24, 2.83] -	-10 -5 0 5 10 Favors human milk Favors infant formula
Total (95% Cl) Heterogeneity: Tau² =	0.49; Chi <sup>z</sup> = Z = 5.00 (P ·	11.65, < 0.000	<b>313</b> df = 3 (P 01)					2.03 [1.24, 2.83] -	
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: .	0.49; Chi <sup>z</sup> = Z = 5.00 (P ·	11.65, < 0.000	<b>313</b> df = 3 (P 01)				100.0% (a)	2.03 [1.24, 2.83] -	
Total (95% CI) Heterogeneity: Tau² = Test for overall effect: .	0.49; Chi² = Z = 5.00 (P erences: Ch	11.65, ≤ 0.000 i² = 11.i	313 df= 3 (P 01) 65. df= 3	(P = 0.009	3). I <sup>z</sup> = 74	3%		· · · · -	Favors human milk Favors infant formula
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect . Test for suboroup diffe	0.49; Chi <sup>z</sup> = Z = 5.00 (P ·	11.65, ≤ 0.000 i² = 11.i	313 df= 3 (P 01) 65. df= 3		3). I <sup>z</sup> = 74	3% mm/d)	(a)	2.03 [1.24, 2.83] - - Mean Difference IV. Random, 95% Cl	
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect. Test for subarous diffe Study or Subgroup 1.2.1 6m – pro 1.8–2.0	0.49; Chi <sup>a</sup> = Z = 5.00 (P erences: Ch IF – height <u>Mean</u>	11.65, < 0.000 i² = 11.1 gain (n SD	313 df = 3 (P 01) 65. df = 3 mm/d) Total	(P = 0.009 HM-heig Mean	3),  ² = 74 ]ht gain (1 SD	3% nm/d) Total	(a)	Mean Difference IV, Random, 95% Cl	Favors human milk Favors infant formula Mean Difference IV, Random, 95% CI
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect. Test for subaroup diffe Study or Subgroup 1.2.1 6m – pro1.8 – 2.0 Putet 2016	0.49; Chi <sup>a</sup> = Z = 5.00 (P erences: Ch IF – height <u>Mean</u>	11.65, < 0.000 i² = 11.1 gain (m	<b>313</b> df = 3 (P 01) 65. df = 3 mm/d) <u>Total</u> 71	(P = 0.009 HM-heig	3).  ² = 74 )ht gain (1	3% mm/d) <u>Total</u> 63	(a)	Mean Difference IV. Random, 95% Cl 0.03 (0.02, 0.04)	Favors human milk Favors infant formula Mean Difference IV, Random, 95% Cl
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect. Test for subaroup diffe Study or Subgroup 1.2.1 6m – pro1.8–2.0 Putet 2016 Subtotal (95% CI)	0.49; Chi <sup>a</sup> = Z = 5.00 (P erences: Ch IF – height <u>Mean</u> 0.98	11.65, < 0.000 i² = 11.1 gain (n SD	313 df = 3 (P 01) 65. df = 3 mm/d) Total	(P = 0.009 HM-heig Mean	3),  ² = 74 ]ht gain (1 SD	3% nm/d) Total	(a)	Mean Difference IV, Random, 95% Cl	Favors human milk Favors infant formula Mean Difference IV, Random, 95% CI
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect. Test for subarous diffe Study or Subgroup 1.2.1 6m – pro1.8–2.0 Putet 2016 Subtotal (95% CI) Heterogeneity: Not api	0.49; Chi² = Z = 5.00 (P erences: Ch IF – height <u>Mean</u> 0.98 plicable	11.65, × 0.000 i <sup>≈</sup> = 11.1 gain (m <u>SD</u> 0.01	<b>313</b> df = 3 (P 01) 65. df = 3 mm/d) <u>Total</u> 71 71	(P = 0.009 HM-heig Mean	3),  ² = 74 ]ht gain (1 SD	3% mm/d) <u>Total</u> 63	(a)	Mean Difference IV. Random, 95% Cl 0.03 (0.02, 0.04)	Favors human milk Favors infant formula Mean Difference IV, Random, 95% Cl
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect Test for suboroup diffe Study or Subgroup 1.2.1 6m – pro1.8–2.0 Putet 2016 Subtotal (95% CI) Heterogeneity: Not api	0.49; Chi² = Z = 5.00 (P erences: Ch IF – height <u>Mean</u> 0.98 plicable	11.65, × 0.000 i <sup>≈</sup> = 11.1 gain (m <u>SD</u> 0.01	<b>313</b> df = 3 (P 01) 65. df = 3 mm/d) <u>Total</u> 71 71	(P = 0.009 HM-heig Mean	3),  ² = 74 ]ht gain (1 SD	3% mm/d) <u>Total</u> 63	(a)	Mean Difference IV. Random, 95% Cl 0.03 (0.02, 0.04)	Favors human milk Favors infant formula Mean Difference IV, Random, 95% Cl
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect. Test for subaroup diffe Study or Subaroup 1.2.1 6m – pro 1.8 - 2.0 Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect. : 1.2.2 6m – pro > 2.2	0.49; Chi≇ = Z = 5.00 (P erences: Ch IF – height Mean 0.98 plicable Z = 5.79 (P ∘	11.65, × 0.000 i <sup>≈</sup> = 11.1 gain (m SD 0.01 × 0.0000	313 df = 3 (P 01) 65. df = 3 mm/d) <u>Total</u> 71 71 11)	HM – heig <u>Mean</u> 0.95	3),  ² = 74 ht gain (r <u>SD</u> 0.04	3% mm/d) Total 63 63	(a)	Mean Difference IV, Random, 95% Cl 0.03 (0.02, 0.04) 0.03 (0.02, 0.04)	Favors human milk Favors infant formula Mean Difference IV, Random, 95% Cl
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect. Test for subaroup diffe Subdy or Subaroup 1.2.1 6m – pro1.8–2.0 Putet 2016 Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect : 1.2.2 6m – pro > 2.2 Putet 2016	0.49; Chi² = Z = 5.00 (P erences: Ch IF – height <u>Mean</u> 0.98 plicable	11.65, × 0.000 i <sup>≈</sup> = 11.1 gain (m <u>SD</u> 0.01	<b>313</b> df = 3 (P 01) 85. df = 3 mm/d) <u>Total</u> 71 71 11)	(P = 0.009 HM-heig Mean	3),  ² = 74 ]ht gain (1 SD	3% mm/d) <u>Tota</u> 63 63	(a)	Mean Difference IV, Random, 95% Cl 0.03 [0.02, 0.04] 0.03 [0.02, 0.04] 0.06 [0.04, 0.08]	Favors human milk Favors infant formula Mean Difference IV, Random, 95% Cl
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Test for subaroup diff Study or Subaroup 1.2.1 6m – pro 1.8~2.0 Putel 2016 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect : 1.2.2 6m – pro > 2.2 Putel 2016 Subtotal (95% CI)	0.49; Chi¤ = Z = 5.00 (P erences: Ch IF – height Mean 0.98 plicable Z = 5.79 (P ≪ 1.01	11.65, × 0.000 i <sup>≈</sup> = 11.1 gain (m SD 0.01 × 0.0000	313 df = 3 (P 01) 65. df = 3 mm/d) <u>Total</u> 71 71 11)	HM – heig <u>Mean</u> 0.95	3),  ² = 74 ht gain (r <u>SD</u> 0.04	3% mm/d) Total 63 63	(a)	Mean Difference IV, Random, 95% Cl 0.03 (0.02, 0.04) 0.03 (0.02, 0.04)	Favors human milk Favors infant formula Mean Difference IV, Random, 95% Cl
Total (95% CI) Heterogeneity. Tau <sup>2</sup> = Test for overall effect. Test for subaroup diffe Study or Subaroup diffe Subtotal (95% CI) Heterogeneity. Not ap Putet 2016 Subtotal (95% CI) Heterogeneity. Not ap	0.49; Chi <sup>≇</sup> = Z = 5.00 (P erences: Ch IF-height Mean 0.98 plicable Z = 5.79 (P ≈ 1.01 plicable	11.65, < 0.000 i <sup>#</sup> = 11.1 gain (m SD 0.01 0.0000 0.06	<b>313</b> df = 3 (P 01) 85. df = 3 <b>mm/d)</b> <b>Total</b> 71 71 11) 72 72	HM – heig <u>Mean</u> 0.95	3),  ² = 74 ht gain (r <u>SD</u> 0.04	3% mm/d) <u>Tota</u> 63 63	(a)	Mean Difference IV, Random, 95% Cl 0.03 [0.02, 0.04] 0.03 [0.02, 0.04] 0.06 [0.04, 0.08]	Favors human milk Favors infant formula Mean Difference IV, Random, 95% CI
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect. Test for subaroup diffe Study or Subaroup 1.2.1 6m – pro 1.8 - 2.0 Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect. : 1.2.2 6m – pro > 2.2	0.49; Chi <sup>≇</sup> = Z = 5.00 (P erences: Ch IF-height Mean 0.98 plicable Z = 5.79 (P ≈ 1.01 plicable	11.65, < 0.000 i <sup>#</sup> = 11.1 gain (m SD 0.01 0.0000 0.06	<b>313</b> df = 3 (P 01) 85. df = 3 <b>mm/d)</b> <b>Total</b> 71 71 11) 72 72	HM – heig <u>Mean</u> 0.95	3),  ² = 74 ht gain (r <u>SD</u> 0.04	3% mm/d) <u>Tota</u> 63 63	(a)	Mean Difference IV, Random, 95% Cl 0.03 [0.02, 0.04] 0.03 [0.02, 0.04] 0.06 [0.04, 0.08]	Favors human milk Favors infant formula Mean Difference IV, Random, 95% CI
Total (95% CI) Heterogeneity. Tau <sup>2</sup> = Test for overall effect. Test for subaroup diffe Subtoral (95% CI) Heterogeneity: Not ap Test for overall effect : 2.2.2 6m – pro > 2.2 Putet 2016 Subtotal (95% CI) Heterogeneity. Not ap Test for overall effect : Total (95% CI)	0.49; Chi <sup>#</sup> = Z = 5.00 (P erences: Ch <u>IF – height</u> 0.98 plicable Z = 5.79 (P ∘ 1.01 plicable Z = 6.91 (P ∘	11.65, < 0.000 <b>gain (m</b> SD 0.01 0.000 0.06 ≤ 0.0000	313 df = 3 (P 01) 65. df = 3 mm/d) Total 71 71 71 01) 72 72 72 01) 143	HM-heig Mean 0.95	3).   <sup>2</sup> = 74 <b>ht gain (r <u>SD</u> 0.04 0.04</b>	.3% mm/d) Total 63 63 63	(a)	Mean Difference IV, Random, 95% Cl 0.03 [0.02, 0.04] 0.03 [0.02, 0.04] 0.06 [0.04, 0.08]	Favors human milk Favors infant formula Mean Difference IV, Random, 95% Cl
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect. Test for subaroup diffe Study or Subaroup diffe 1.2.1 6m—pro 1.8~2.0 Putet 2016 Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect : Jutet 2016 Subtotal (95% CI) Heterogeneity: Not ap; Test for overall effect : Total (95% CI)	0.49; Chi <sup>#</sup> = Z = 5.00 (P erences: Ch <u>IF-height</u> 0.98 plicable Z = 5.79 (P = 1.01 plicable Z = 6.91 (P = 0.00; Chi <sup>#</sup> =	11.65, < 0.000 i <sup>2</sup> = 11.1 0.01 0.001 0.06 € 0.0000 8.81, dt	313 313 317 317 317 317 317 317	HM-heig Mean 0.95	3).   <sup>2</sup> = 74 <b>ht gain (r <u>SD</u> 0.04 0.04</b>	.3% mm/d) Total 63 63 63	(a) Weight 52.7% 52.7% 52.7% 47.3%	Mean Difference IV, Random, 95% Cl 0.03 [0.02, 0.04] 0.03 [0.02, 0.04] 0.06 [0.04, 0.08] 0.06 [0.04, 0.08]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% CI
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Testfor overall effect. Test for subaroup diffe Study or Subaroup diffe Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect : 1.2.2 6m – pro > 2.2 Putet 2016 Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect : Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect :	0.49; Chi <sup>#</sup> = Z = 5.00 (P erences: Ch IF - height Mean 0.98 plicable Z = 5.79 (P = 1.01 plicable Z = 6.91 (P = 0.00; Chi <sup>#</sup> = Z = 2.95 (P =	11.65, < 0.000 i <sup>≠</sup> = 11.1 0.01 0.01 0.06 0.000 0.06 8.81, dt 0.003)	<b>313</b> df = 3 (P 01) 65. df = 3 <b>mn/d)</b> <b>Total</b> 71 71 01) 11) 72 72 72 01) 143 i = 1 (P =	HM—heig HM—heig <u>Mean</u> 0.95 0.95	<ol> <li>i<sup>a</sup> = 74</li> <li>i<sup>bit</sup> gain (i SD</li> <li>0.04</li> <li>0.04</li> <li>89%</li> </ol>	3% nm/d) Total 63 63 63 63	(a) Weight 52.7% 52.7% 52.7% 47.3%	Mean Difference IV, Random, 95% Cl 0.03 [0.02, 0.04] 0.03 [0.02, 0.04] 0.06 [0.04, 0.08] 0.06 [0.04, 0.08]	Favors human milk Favors infant formula Mean Difference N. Random, 95% CI
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect. Test for subaroup diffe Study or Subaroup diffe 1.2.1 6m—pro 1.8~2.0 Putet 2016 Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect : Jotal (95% CI) Heterogeneity: Not ap; Test for overall effect : Total (95% CI)	0.49; Chi <sup>#</sup> = Z = 5.00 (P erences: Ch IF - height Mean 0.98 plicable Z = 5.79 (P = 1.01 plicable Z = 6.91 (P = 0.00; Chi <sup>#</sup> = Z = 2.95 (P =	11.65, < 0.000 i <sup>≠</sup> = 11.1 0.01 0.01 0.06 0.000 0.06 8.81, dt 0.003)	<b>313</b> df = 3 (P 01) 65. df = 3 <b>mn/d)</b> <b>Total</b> 71 71 01) 11) 72 72 72 01) 143 i = 1 (P =	HM—heig HM—heig <u>Mean</u> 0.95 0.95	<ol> <li>i<sup>a</sup> = 74</li> <li>i<sup>bit</sup> gain (i SD</li> <li>0.04</li> <li>0.04</li> <li>89%</li> </ol>	3% nm/d) Total 63 63 63 63	(a) Weight 52.7% 52.7% 52.7% 47.3%	Mean Difference IV, Random, 95% Cl 0.03 [0.02, 0.04] 0.03 [0.02, 0.04] 0.06 [0.04, 0.08] 0.06 [0.04, 0.08]	Favors human milk Favors infant formula Mean Difference IV. Random, 95% CI

Figure 6. Cont.



**Figure 6.** Forest plot of the effects of protein content of infant formula on the weight gain, height gain, and BMI of infants at 6 months of age. (**a**) The effects on weight gain. (**b**) The effects on height gain. (**c**) The effects on BMI.



**Figure 7.** Heat map of the effects of protein content of infant formulas on the growth of infants. (a) The effects on weight gain. (b) The effects on height gain. (c) The effects on BMI.

## 4. Discussion

Our study analyzed the relationship between the protein content of infant formulas and infant growth in a longitudinal manner in the first 6 months of life. We found that, in the first month of life, growth was not different between formula- and breastfed infants. During 2–3 months of life, growth was faster in infants who consumed formulas with protein content higher than 2.0 g/100 kcal. After 3 months, formula-fed infants grew faster than breastfed infants. To our best knowledge, our study was the first systematic review and meta-analysis that investigated the association between the protein content of infant formulas and infant growth in the first 6 months of life.

We included a total of 19 papers in our study by applying the inclusion and exclusion criteria in the PICOS table (Supplementary Table S1). Some studies that were included by others were not included by us because they did not meet our standards. For example, studies by P.M. Akeson et al. did not meet our standards because the subjects were not exclusively breastfed or exclusive formula fed [39,40]. Another example is that a study

by Weber et al. was not included because the study did not identify anthropometric assessments of infants during the first 6 months of life [41].

The difference in protein concentrations between human milk and infant formulas may explain the faster growth trajectory in formula-fed infants than in breastfed infants. Human milk protein concentrations decrease gradually from 2.13 to 1.14 g/dL in the first 90 days of lactation and remain stable thereafter [42]. By contrast, formula-fed infants, in the first 6 months of life, consume the same formulas, which typically range from 1.4 to 1.5 g of protein/dL. Accordingly, infant formulas may provide 30% more protein than human milk after the infant is 2 months old [42]. Because the digestibility, amino acid profile, and protein efficiency of human milk protein are superior to those of other protein sources such as bovine milk, it is rational for infant formula to provide higher concentrations of protein. It is possible that the food calories introduced by excessive protein in infant formula cause the faster growth velocity in formula-fed infants. Studies have also suggested that excessive protein may raise the levels of IGF-1, which may mediate faster weight gain.

The findings of our work agreed with other reviews. Patro-Gołąb et al. concluded that different formula protein concentrations did not affect mean weight at 3 months as observed in a meta-analysis of four studies. Lower mean weight and weight z scores obtained from the infants fed lower-protein formulas were observed only from 6 to 12 months of age [17]. Aurore Camier et al. determined whether the variability in the protein content of infant formula used in France over the period 2003-2012 was significantly associated with early growth in children. Their findings confirmed the positive association between infant formula protein content and weight- and BMI-for-age z-scores up to 18 months. Among formula-fed infants, the lowest protein-content group had the lowest anthropometric zscores, although these scores remained higher than those for breastfed infants [43]. A review by Hornell et al. published in 2013 focused on protein intake in the diet (not only in milk formula) of children of different ages (0 to 18 years) and its relation to health. The authors concluded that higher protein intake during infancy was associated with increased growth, a higher BMI during childhood, and an increased risk of being overweight later in life [44]. Fenton et al. found that low-certainty evidence suggested that higher protein intake  $(\geq 3.0 \text{ g/kg/d} \text{ but } < 4.0 \text{ g/kg/d})$  from formula accelerates weight gain of preterm or low birth weight infants [45].

Our study and others described above showed that protein content of infant formula was associated with early growth in children. However, there is insufficient direct evidence to evaluate the effects of reducing protein concentrations in infant formula on long term outcomes related to decreased risk of later obesity. According to the "early protein hypothesis", however, reducing early protein intake is a potential lever for obesity prevention. Therefore, a relatively lower protein/energy ratio in infant formula may reduce the risk of overweight and obesity in children. In fact, many studies have investigated the safety of infant formulas with reduced protein levels in order to simulate human milk. More notably, when reducing the protein content of infant formula, attention should be paid to the composition of amino acids. Otherwise, unreasonable amino acid patterns may lead to limited protein synthesis during the rapid growth of infants. For this reason, using a low-protein formula with an amino acid composition modified according to the estimated infant requirements has been suggested [46].

This review had some limitations. Because we separated protein contents into four levels and categorized the postnatal life into six stages, the number of studies in each category was limited. For example, at the age of under 1 month, there was only one study in each of the protein levels of <1.8, 1.8–2.0, 2.1–2.2, and >2.2 g/100 kcal. The limited number of studies diminished the power of the meta-analysis. Nevertheless, our results highlighted the dose-dependent effects of formula protein content on infant growth and the effects of formula feeding on growth in different postnatal ages, which could encourage future investigations by using animal models, human studies, and systematic reviews and meta-analysis. Additionally, we only analyzed the infants' growth during first six months of the life, because nutrient intake during this time is provided only by breast or formula.

Other sources of nutrition in the diet also play an important role after the introduction of complementary feeding. This review included studies of exclusive breastfeeding and exclusive formula feeding patterns, but mixed milk feeding (MMF) was not considered. MMF defined as the combination of breastfeeding and formula feeding during the same period in term infants [47]. There may be some changes in the growth performance of differently fed infants. Feng et al. conducted a longitudinal study of Chinese breastfeeding infant growth and development. It showed that infants who were nonexclusively breastfed had lower weights than those who were exclusively breastfed but that the difference was not statistically significant. However, there was an interaction between feeding patterns and age. The average weight of babies who were nonexclusively breastfed increased faster than those who were exclusively breastfed with age [48]. MMF is a widespread feeding reality. It is very important to evaluate MMF's influence on infants' nutritional status, growth, development, and health status in the short and long terms. Energy deposition as a percentage of total energy requirements decreases from 40% at age 1 month to 1-2%from 12 months until midadolescence. Therefore, weight gain during infancy is more closely related to energy intake than is weight gain in childhood or in later life [49]. Energy intake in early infancy is mainly from breast milk or formula, so breast milk or formula intake is closely related to weight gain during infancy. Eight of the twenty articles included in this systematic review reported infant formula intake (Supplementary Table S2). The results showed no difference between groups, except that the studies of Turck and Putet showed higher intakes of infants in the high-protein powder group [22,24]. Because of the limited evidence, it was unclear whether protein content affected infant formula intake. Studies have shown that breast milk or formula intake is associated with infant appetite traits. Appetitive traits are thought to be largely innate and stable. Infant appetitive profiles characterized by high food responsiveness and low satiety responsiveness are prospectively associated with more rapid weight gain. However, parental attitudes to following healthy infant feeding guidelines attenuate the effects of infant appetitive traits on infant milk intake and body weight [11].

Human milk is the most effective and natural food for infants. Therefore, many ingredients are being taken to create an infant formula mimicking the composition of the human milk as closely as possible for infants who cannot be breastfed. The growth outcomes of infants fed formula supplemented with these ingredients are worth evaluating. Some systematic reviews about comparisons between infants fed with standard formula and those fed with milk fat globule membrane-supplemented formulas, palm olein-containing formulas, prebiotic-supplemented formulas, or taurine-containing formulas revealed no differences in anthropometric measurements [50–53]. A meta-analysis by Wang et al. indicated that nucleotide supplementation could increase the rate of weight gain; however, it could not conclude that it affected other anthropometric measurements [54]. A meta-analysis by Sun et al. showed that there was lower weight gain in the probiotics group than in the control group but that this difference was not statistically significant [55]. Therefore, even if the relevant components of infant formula milk powder underwent the aforementioned changes, the impact on infants' weight and other relevant anthropometric parameters would be very small.

## 5. Conclusions

Our meta-analysis indicated that exclusively formula-fed infants would have visibly higher weight gain starting from four months of age. The growth outcomes of infants fed with infant formula with a relatively low protein/energy ratio, compared with those of infants fed with infant formula with a relatively high protein/energy ratio, were close to those of breastfed infants. To our knowledge, we collated the largest number of studies on the effects of breastfeeding and feeding with formulas with different protein/energy ratios on the growth outcomes of infants during the first six months the life. The findings of this review were similar to those of other reviews addressing the effect of the intake of low-protein formula by infants on growth. In addition, the protein content of infant formula is not the only factor that may affect infant growth. Therefore, we also discussed the influence of feeding patterns, formula intake, ingredients of infant formula, and other factors on infant growth. However, we analyzed the infants' growth only during the first six months of life. There is insufficient direct evidence to evaluate the effects of reducing protein concentrations in infant formula on long-term outcomes related to decreased risk of later obesity. In view of the limited available evidence, more studies demonstrating effects on long-term health outcomes are needed.

**Supplementary Materials:** The following supporting information can be downloaded at: https: //www.mdpi.com/article/10.3390/nu14112255/s1, Figure S1: Risk of bias in the included studies; Table S1: Inclusion and exclusion criteria for selecting articles (PICOS); Table S2: Characteristics of included studies.

**Author Contributions:** Conceptualization, Y.X. and S.J.; methodology, Q.R. and K.L.; investigation, Q.R., K.L., H.S. (Han Sun) and C.Z.; writing—original draft preparation, Q.R. and W.Z.; writing—review and editing, Y.Z., Y.L., W.Y. and H.S. (Hanxu Shi); visualization, Q.R., K.L. and C.Z.; supervision, Y.X., S.J. and W.Z.; project administration, Y.X., S.J. and W.Z.; funding acquisition, Y.X., W.Z. and S.J. All authors have read and agreed to the published version of the manuscript.

**Funding:** This study was supported by the National Natural Science Foundation of China (NSFC, Grant No. 82173500), the Chinese Human Milk Project (CHMP) Study grant (funded by Heilongjiang Feihe Co., Ltd., Tsitsihar, China, to K.L., W.Z. and S.J.), and the "Bai-Qian-Wan Engineering and Technology Master Project" (Grant #2019ZX07B01, funded by the Government of Heilongjiang Province of the People's Republic of China, to W.Z. and S.J.).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

**Conflicts of Interest:** Q.R., K.L., H.S., C.Z., W.Z. and S.J. are employed by Feihe Dairy Co., Ltd., Tsitsihar, China. The other authors declare no conflicts of interest. Feihe Dairy Co., Ltd., Tsitsihar, China provided the funding.

## References

- 1. Duale, A.; Singh, P.; Al Khodor, S. Breast Milk: A Meal Worth Having. Front. Nutr. 2022, 8, 800927. [CrossRef] [PubMed]
- 2. World Health Organization. *Protecting, Promoting, and Supporting Breastfeeding in Facilities Providing Maternity and Newborn Services: The Revised Baby-Friendly Hospital Initiative;* WHO: Geneva, Switzerland, 2018.
- 3. World Health Organization; UNICEF. Global Nutrition Targets 2025: Breastfeeding Policy Brief; WHO: Geneva, Switzerland, 2014.
- North, K.; Gao, M.; Allen, G.; Lee, A.C. Breastfeeding in a Global Context: Epidemiology, Impact, and Future Directions. *Clin. Ther.* 2022, 44, 228–244. [CrossRef] [PubMed]
- Beggs, B.; Koshy, L.; Neiterman, E. Women's Perceptions and Experiences of Breastfeeding: A scoping review of the literature. BMC Public Health 2021, 21, 2169. [CrossRef] [PubMed]
- 6. Tomori, C. Overcoming barriers to breastfeeding. Best Pract. Res. Clin. Obstet. Gynaecol. 2022, in press. [CrossRef]
- Dewey, K.G.; Heinig, M.J.; Nommsen-Rivers, L.A. Differences in morbidity between breast-fed and formula-fed infants. *J. Pediatr.* 1995, 126, 696–702. [CrossRef]
- Victora, C.G.; Bahl, R.; Barros, A.J.; França, G.V.; Horton, S.; Krasevec, J.; Murch, S.; Sankar, M.J.; Walker, N.; Rollins, N.C. Lancet Breastfeeding Series Group. Breastfeeding in the 21st century: Epidemiology, mechanisms, and lifelong effect. *Lancet* 2016, 387, 475–490. [CrossRef]
- 9. Gillman, M.W. Developmental origins of health and disease. N. Engl. J. Med. 2005, 353, 1848–1850. [CrossRef]
- 10. Ong, K.K.; Loos, R.J. Rapid infancy weight gain and subsequent obesity: Systematic reviews and hopeful suggestions. *Acta Paediatr.* **2006**, *95*, 904–908. [CrossRef]
- Clifton, E.A.D.; Ahern, A.L.; Day, F.R.; Sharp, S.J.; Griffin, S.J.; Ong, K.K.; Lakshman, R. Positive maternal attitudes to following healthy infant feeding guidelines attenuate the associations between infant appetitive traits and both infant milk intake and weight. *Appetite* 2021, *161*, 105124. [CrossRef]
- 12. Giugliani, E.R.J. Growth in exclusively breastfed infants. J. Pediatr. 2019, 95, 79-84. [CrossRef]
- 13. Dewey, K.G. Growth characteristics of breast-fed compared to formula-fed infants. *Biol. Neonate* **1998**, *74*, 94–105. [CrossRef] [PubMed]
- 14. WHO; FAO; United Nations University. Protein and Amino Acid Requirements in Human Nutrition. Report of a Joint FAO/WHO/UNU Expert Consultation; WHO Technical Report Series 935; WHO: Geneva, Switzerland, 2007.

- 15. Lönnerdal, B.; Erdmann, P.; Thakkar, S.K.; Sauser, J.; Destaillats, F. Longitudinal evolution of true protein, amino acids and bioactive proteins in breast milk: A developmental perspective. *J. Nutr. Biochem.* **2017**, *41*, 1–11. [CrossRef] [PubMed]
- 16. Abrams, S.A.; Hawthorne, K.M.; Pammi, M. A systematic review of controlled trials of lower-protein or energy-containing infant formulas for use by healthy full-term infants. *Adv. Nutr.* **2015**, *6*, 178–188. [CrossRef] [PubMed]
- Patro-Gołąb, B.; Zalewski, B.M.; Kouwenhoven, S.M.; Karaś, J.; Koletzko, B.; Bernard van Goudoever, J.; Szajewska, H. Protein Concentration in Milk Formula, Growth, and Later Risk of Obesity: A Systematic Review. J. Nutr. 2016, 146, 551–564. [CrossRef]
- 18. Moher, D.; Shamseer, L.; Clarke, M.; Ghersi, D.; Liberati, A.; Petticrew, M.; Shekelle, P.; Stewart, L.A.; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst. Rev.* 2015, *4*, 1. [CrossRef]
- 19. Higgins, J.P.T.; Thomas, J.; Chandler, J.; Cumpston, M.; Li, T.; Page, M.J.; Welch, V.A. (Eds.) *Cochrane Handbook for Systematic Reviews of Interventions*, 2nd ed.; John Wiley & Sons: Chichester, UK, 2019.
- Davis, A.M.; Harris, B.J.; Lien, E.L.; Pramuk, K.; Trabulsi, J. Alpha-lactalbumin-rich infant formula fed to healthy term infants in a multicenter study: Plasma essential amino acids and gastrointestinal tolerance. *Eur J. Clin. Nutr.* 2008, 62, 1294–1301. [CrossRef]
- Singhal, A.; Kennedy, K.; Lanigan, J.; Clough, H.; Jenkins, W.; Elias-Jones, A.; Stephenson, T.; Dudek, P.; Lucas, A. Dietary nucleotides and early growth in formula-fed infants: A randomized controlled trial. *Pediatrics* 2010, 126, 946–953. [CrossRef]
- 22. Turck, D.; Grillon, C.; Lachambre, E.; Robiliard, P.; Beck, L.; Maurin, J.L.; Kempf, C.; Bernet, J.P.; Marx, J.; Lebrun, F.; et al. Adequacy and safety of an infant formula with a protein/energy ratio of 1.8 g/100 kcal and enhanced protein efficiency for term infants during the first 4 months of life. *J. Pediatr. Gastroenterol. Nutr.* 2006, 43, 364–371. [CrossRef]
- Meli, F.; Puccio, G.; Cajozzo, C.; Ricottone, G.L.; Pecquet, S.; Sprenger, N.; Steenhout, P. Growth and safety evaluation of infant formulae containing oligosaccharides derived from bovine milk: A randomized, double-blind, noninferiority trial. *BMC Pediatr.* 2014, 14, 306. [CrossRef]
- 24. Putet, G.; Labaune, J.M.; Mace, K.; Steenhout, P.; Grathwohl, D.; Raverot, V.; Morel, Y.; Picaud, J.C. Effect of dietary protein on plasma insulin-like growth factor-1, growth, and body composition in healthy term infants: A randomised, double-blind, controlled trial (Early Protein and Obesity in Childhood (EPOCH) study). *Br. J. Nutr.* **2016**, *115*, 271–284. [CrossRef]
- Litmanovitz, I.; Davidson, K.; Eliakim, A.; Regev, R.H.; Dolfin, T.; Arnon, S.; Bar-Yoseph, F.; Goren, A.; Lifshitz, Y.; Nemet, D. High Beta-palmitate formula and bone strength in term infants: A randomized, double-blind, controlled trial. *Calcif. Tissue Int.* 2013, 92, 35–41. [CrossRef] [PubMed]
- 26. Trabulsi, J.; Capeding, R.; Lebumfacil, J.; Ramanujam, K.; Feng, P.; McSweeney, S.; Harris, B.; DeRusso, P. Effect of an αlactalbumin-enriched infant formula with lower protein on growth. *Eur. J. Clin. Nutr.* **2011**, *65*, 167–174. [CrossRef] [PubMed]
- Kennedy, K.; Fewtrell, M.S.; Morley, R.; Abbott, R.; Quinlan, P.T.; Wells, J.C.; Bindels, J.G.; Lucas, A. Double-blind, randomized trial of a synthetic triacylglycerol in formula-fed term infants: Effects on stool biochemistry, stool characteristics, and bone mineralization. *Am. J. Clin. Nutr.* 1999, 70, 920–927. [CrossRef] [PubMed]
- Breij, L.M.; Abrahamse-Berkeveld, M.; Vandenplas, Y.; Jespers, S.N.J.; de Mol, A.C.; Khoo, P.C.; Kalenga, M.; Peeters, S.; van Beek, R.H.T.; Norbruis, O.F.; et al. An infant formula with large, milk phospholipid-coated lipid droplets containing a mixture of dairy and vegetable lipids supports adequate growth and is well tolerated in healthy, term infants. *Am. J. Clin. Nutr.* 2019, *109*, 586–596. [CrossRef] [PubMed]
- Liotto, N.; Orsi, A.; Menis, C.; Piemontese, P.; Morlacchi, L.; Condello, C.C.; Giannì, M.L.; Roggero, P.; Mosca, F. Clinical evaluation of two different protein content formulas fed to full-term healthy infants: A randomized controlled trial. *BMC Pediatr.* 2018, 18, 18, 59, Erratum in: *BMC Pediatr.* 2018, 18, 135. [CrossRef]
- Oropeza-Ceja, L.G.; Rosado, J.L.; Ronquillo, D.; García, O.P.; Caamaño, M.D.C.; García-Ugalde, C.; Viveros-Contreras, R.; Duarte-Vázquez, M.Á. Lower Protein Intake Supports Normal Growth of Full-Term Infants Fed Formula: A Randomized Controlled Trial. Nutrients 2018, 10, 886. [CrossRef]
- 31. Daniels, L.; Gibson, R.A.; Simmer, K.; van Dael, P.; Makrides, M. Selenium status of term infants fed selenium-supplemented formula in a randomized dose-response trial. *Am. J. Clin. Nutr.* **2008**, *88*, 70–76. [CrossRef]
- 32. Räihä, N.C.; Fazzolari-Nesci, A.; Cajozzo, C.; Puccio, G.; Monestier, A.; Moro, G.; Minoli, I.; Haschke-Becher, E.; Bachmann, C.; Van't Hof, M.; et al. Whey predominant, whey modified infant formula with protein/energy ratio of 1.8 g/100 kcal: Adequate and safe for term infants from birth to four months. *J. Pediatr. Gastroenterol. Nutr.* **2002**, *35*, 275–281. [CrossRef]
- Timby, N.; Domellöf, M.; Holgerson, P.L.; West, C.E.; Lönnerdal, B.; Hernell, O.; Johansson, I. Oral Microbiota in Infants Fed a Formula Supplemented with Bovine Milk Fat Globule Membranes—A Randomized Controlled Trial. *PLoS ONE*. 2017, 12, e0169831. [CrossRef]
- Roggero, P.; Liotto, N.; Pozzi, C.; Braga, D.; Troisi, J.; Menis, C.; Giannì, M.L.; Berni Canani, R.; Paparo, L.; Nocerino, R.; et al. Analysis of immune, microbiota and metabolome maturation in infants in a clinical trial of Lactobacillus paracasei CBA L74fermented formula. *Nat. Commun.* 2020, 11, 2703. [CrossRef]
- 35. Hanning, R.M.; Paes, B.; Atkinson, S.A. Protein metabolism and growth of term infants in response to a reduced-protein, 40:60 whey: Casein formula with added tryptophan. *Am. J. Clin. Nutr.* **1992**, *56*, 1004–1011. [CrossRef] [PubMed]
- Wu, S.L.; Ding, D.; Fang, A.P.; Chen, P.Y.; Chen, S.; Jing, L.P.; Chen, Y.M.; Zhu, H.L. Growth, Gastrointestinal Tolerance and Stool Characteristics of Healthy Term Infants Fed an Infant Formula Containing Hydrolyzed Whey Protein (63%) and Intact Casein (37%): A Randomized Clinical Trial. *Nutrients* 2017, *9*, 1254. [CrossRef] [PubMed]

- Kouwenhoven, S.M.P.; Antl, N.; Finken, M.J.J.; Twisk, J.W.R.; van der Beek, E.M.; Abrahamse-Berkeveld, M.; van de Heijning, B.J.M.; Schierbeek, H.; Holdt, L.M.; van Goudoever, J.B.; et al. A modified low-protein infant formula supports adequate growth in healthy, term infants: A randomized, double-blind, equivalence trial. *Am. J. Clin. Nutr.* 2020, *111*, 962–974. [CrossRef] [PubMed]
- 38. Vandenplas, Y.; de Halleux, V.; Arciszewska, M.; Lach, P.; Pokhylko, V.; Klymenko, V.; Schoen, S.; Abrahamse-Berkeveld, M.; Mulder, K.A.; Porcel Rubio, R.; et al. A Partly Fermented Infant Formula with Postbiotics Including 3'-GL, Specific Oligosaccharides, 2'-FL, and Milk Fat Supports Adequate Growth, Is Safe and Well-Tolerated in Healthy Term Infants: A Double-Blind, Randomised, Controlled, Multi-Country Trial. *Nutrients* 2020, *12*, 3560. [CrossRef] [PubMed]
- Karlsland Akeson, P.K.; Axelsson, I.E.; Räihä, N.C.; Warm, A.; Minoli, I.; Moro, G. Protein intake and metabolism in formula-fed infants given Swedish or Italian weaning foods. *Acta Paediatr.* 2000, *89*, 158–164. [CrossRef]
- 40. Akeson, P.M.; Axelsson, I.E.; Räihä, N.C. Growth and nutrient intake in three- to twelve-month-old infants fed human milk or formulas with varying protein concentrations. *J. Pediatr. Gastroenterol. Nutr.* **1998**, *26*, 1–8. [CrossRef]
- 41. Weber, M.; Grote, V.; Closa-Monasterolo, R.; Escribano, J.; Langhendries, J.P.; Dain, E.; Giovannini, M.; Verduci, E.; Gruszfeld, D.; Socha, P.; et al. Lower protein content in infant formula reduces BMI and obesity risk at school age: Follow-up of a randomized trial. *Am. J. Clin. Nutr.* **2014**, *99*, 1041–1051. [CrossRef]
- 42. Ren, Q.; Sun, H.; Zhao, M.; Xu, Y.; Xie, Q.; Jiang, S.; Zhao, X.; Zhang, W. Longitudinal Changes in Crude Protein and Amino Acids in Human Milk in Chinese Population: A Systematic Review. J. Pediatr. Gastroenterol. Nutr. 2020, 70, 555–561. [CrossRef]
- 43. Camier, A.; Davisse-Paturet, C.; Scherdel, P.; Lioret, S.; Heude, B.; Charles, M.A.; de Lauzon-Guillain, B. Early growth according to protein content of infant formula: Results from the EDEN and ELFE birth cohorts. *Pediatr. Obes.* **2021**, *16*, e12803. [CrossRef]
- 44. Hörnell, A.; Lagström, H.; Lande, B.; Thorsdottir, I. Protein intake from 0 to 18 years of age and its relation to health: A systematic literature review for the 5th Nordic Nutrition Recommendations. *Food Nutr. Res.* **2013**, *57*, 21083. [CrossRef]
- 45. Fenton, T.R.; Al-Wassia, H.; Premji, S.S.; Sauve, R.S. Higher versus lower protein intake in formula-fed low birth weight infants. *Cochrane Database Syst. Rev.* 2020, *6*, CD003959. [CrossRef] [PubMed]
- 46. Liotto, N. Protein content of infant formula for the healthy full-term infant. *Am. J. Clin. Nutr.* **2020**, *111*, 946–947. [CrossRef] [PubMed]
- 47. Monge-Montero, C.; van der Merwe, L.F.; Papadimitropoulou, K.; Agostoni, C.; Vitaglione, P. Mixed milk feeding: A systematic review and meta-analysis of its prevalence and drivers. *Nutr. Rev.* **2020**, *78*, 914–927. [CrossRef] [PubMed]
- 48. Feng, W.; Huang, X.; Wang, H.; Xu, Y.; Pan, X.; Jin, X. Determinants of growth for 4 months old infants in rural areas. *Chin. J. Child Health Care* **2017**, *25*, 18–20.
- Lakshman, R.; Sharp, S.J.; Whittle, F.; Schiff, A.; Hardeman, W.; Irvine, L.; Wilson, E.; Griffin, S.J.; Ong, K.K. Randomised controlled trial of a theory-based behavioural intervention to reduce formula milk intake. *Arch. Dis. Child* 2018, 103, 1054–1060. [CrossRef]
- Ambrożej, D.; Dumycz, K.; Dziechciarz, P.; Ruszczyński, M. Milk Fat Globule Membrane Supplementation in Children: Systematic Review with Meta-Analysis. Nutrients 2021, 13, 714. [CrossRef]
- 51. Bronsky, J.; Campoy, C.; Embleton, N.; Fewtrell, M.; Mis, N.F.; Gerasimidis, K.; Hojsak, I.; Hulst, J.; Indrio, F.; Lapillonne, A.; et al. Palm Oil and Beta-palmitate in Infant Formula: A Position Paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition. J. Pediatr. Gastroenterol. Nutr. 2019, 68, 742–760. [CrossRef]
- 52. Skórka, A.; Pieścik-Lech, M.; Kołodziej, M.; Szajewska, H. Infant formulae supplemented with prebiotics: Are they better than unsupplemented formulae? An updated systematic review. *Br. J. Nutr.* **2018**, *119*, 810–825. [CrossRef]
- 53. Bazzano, A.N.; Kaji, A.; Felker-Kantor, E.; Bazzano, L.A.; Potts, K.S. Qualitative Studies of Infant and Young Child Feeding in Lower-Income Countries: A Systematic Review and Synthesis of Dietary Patterns. *Nutrients* **2017**, *9*, 1140. [CrossRef]
- 54. Wang, L.; Mu, S.; Xu, X.; Shi, Z.; Shen, L. Effects of dietary nucleotide supplementation on growth in infants: A meta-analysis of randomized controlled trials. *Eur. J. Nutr.* 2019, *58*, 1213–1221. [CrossRef]
- Sun, J.; Marwah, G.; Westgarth, M.; Buys, N.; Ellwood, D.; Gray, P.H. Effects of Probiotics on Necrotizing Enterocolitis, Sepsis, Intraventricular Hemorrhage, Mortality, Length of Hospital Stay, and Weight Gain in Very Preterm Infants: A Meta-Analysis. *Adv. Nutr.* 2017, *8*, 749–763. [CrossRef] [PubMed]