

**Table 1. Effect of early CMF introduction on the development of CMA - Observational Studies (12)**

Source/year	Population	Interventions/collected data	Outcome	Results	comment	Verdict / Strength	
<b>Case-control studies (4)</b>							
Saarinen <sup>40</sup> 1995 Finland	150/236 infants	Prolonged BF - >6m Intermediate – 1-6m Short or no BF (<1m) Follow-up to age 17 y	Allergic diseases Food allergy per history	<1 month BF: highest prevalence of food allergy at age 1-3 years. Comparable rates at older ages	High rates of food allergy: 24% at age 3 years 7% at adolescence	<b>Verdict: C/U</b> <b>Strength: L</b>	
Sanchez-Valverde <sup>41</sup> 2009 Spain	IgE-CMA- 119 Non IgE CMA- 106	Duration of exclusive BF: Prolonged - ≥2m	Comparison of IgE- and non-IgE CMA	IgE CMA was associated with shorter duration of EBF	Comparison to non-allergic controls was not performed	<b>Verdict: C</b> <b>Strength: L</b>	
Liao <sup>42</sup> 2014 Taiwan	258 infants Unselected birth cohort	Feeding history collected at 6 m sIgE measured	Milk-sIgE at ages 6, 12, 18, 24, 36 m	Decreased risk of sensitization to CMP at ages 12, 18, 24 m in those EBF >4 m	No difference in milk-sIgE at age 36 m	<b>Verdict: U</b> <b>Strength: M</b>	
Onizawa <sup>43</sup> 2016 Japan	CMA - 51 Control -102	Parent reported Early regular CM once daily within the first m until 6m or CMA	<b>CMF</b> Any at Maternity: EBF Early CM Early Reg Cont CMF	<b>CMA</b> 31(60.8%) 35(68.6%) 6(11.8%) 2(3.9)	<b>Control</b> 73(70.6%) 24(23.5) 60(58.8%) 52(51%)	0.273 P<0.001 P<0.001 P<0.001	<b>Verdict: P</b> <b>Strength: M</b>

Source/year	Population	Interventions/collected data	Outcome	Results	comment	Verdict / Strength
<b>Population-based studies (8)</b>						
Host <sup>45,46</sup> 1988, 1991 Denmark	1749 infants	Feeding history in the 1 <sup>st</sup> month of life CMI – various symptoms which resolved with elimination diet and appeared on re-introduction CMA – CMI+CM sensitization	CMA/CMI in the first year of life	EBF – 1.7% CMF± BF – 4.5%	The difference was only in CMI while for CMA the rates were similar	<b>Verdict: C/U</b> <b>Strength: L</b>
Katz <sup>24</sup> 2011 Israel	13,019 infants followed from birth	Age of regular CMF introduction Parent reported feeding	CMA (diagnosed in 0.5%) SPT and OFC	CMA prevalence: 0-14 d- 0.05% 15-104 d- 0.5% >105 d -1.75%	CMF might be accompanied with BF	<b>Verdict: P</b> <b>Strength: H</b>
Goldsmith <sup>48</sup> 2016 Australia "HealthNuts"	5276 infants Examined at age 1 Y	Record of EBF duration Parent reported	FA- 11.3% CMA- 0.6%	No effect of age of exposure to CMF on FA	Age of diagnosis of CMA and duration of EBF was not reported	<b>Verdict: U</b> <b>Strength: M</b>
Tran <sup>49</sup> 2017 Canada "CHILD"	2124 infants	Questionnaire at 3,6,12,18, 24m, 1y – SPT	Delay introduction of CMF increases the odds of sensitization to CMP		Milk allergy was not reported	<b>Verdict: P</b> <b>Strength: M</b>
Peters <sup>50</sup> 2019 Australia "HealthNuts"	5276 infants Examined at age 1 Y 2715 skin tested	Parent reported Exposure to CMF in 1 <sup>st</sup> 3m	CMA rates based on exposure to CMF at 0-3m	Exposed – 0.4% Not exposed-1.3%	CMA diagnosed as parent reported event + SPT≥2mm	<b>Verdict: P</b> <b>Strength: H</b>

Lachover <sup>51</sup> 2021 Israel	635/1560 (40.7%) newborn infants	-Exclusive BF -BF with $\geq 1$ CMF daily CMF only	Milk allergy at age 1 y	Exclusive BF – 9 (1.77%) CMF $\pm$ BF – 0 RR=1.96	Abstract form	<b>Verdict: P</b> <b>Strength: M</b>
Tezuka <sup>52</sup> 2021 Japan "JECS"	80,408 infants	CMF consumption at age <3 months, 3-6 months, 6-12 months	Physician diagnosed CMA prior to age 6 or 12 m	CMF <3 m – reduction of CMA 6m – aRR 0.42 12m - aRR 0.44	The protective effect was lost if infants discontinued regular CMP consumption at 3-6 m	<b>Verdict: P</b> <b>Strength: H</b>
Switkowski <sup>44</sup> 2022 USA	1298/2128 infants Milk sIgE measured in 505 infants	Exposure to CMP: -<2weeks – 32% -2w<6m – 38% ->6m- 30%	Parent-reported CM adverse reaction (CMAR) CM-sIgE CMA = sensitization + EpiPen carriage	CMAR age 2-5 y: <2weeks -3%, 2w<6m – 5% >6m- 7.5% <2w and formula at delivery – 1.8% <2w and no formula at delivery – 8.0%	No association between CMP introduction and CM sensitization and allergy in the subset tested	<b>Verdict: P</b> <b>Strength: H</b>

Verdict on early introduction of CMP: C=Con, U=Undetermined, P=Pro

Strength: L=Low, M=Medium, H=High

(E)BF – (Exclusive)Breastfeeding, CM(A)=Cow milk (allergy), CMF=Cow milk formula

**Table 2. Effect of early CMF introduction on the development of CMA – interventional studies (4)**

Source/year	Population	Interventions/collected data	Outcome	Results	comment	Verdict / Strength
Perkin <sup>53</sup> 2016 UK, Wales "EAT"	Singleton 3 month-old exclusively breastfed infants	-Early Introduction group (EIG): 2 g of CMF twice weekly -Avoidance: EBF until 6 m	food allergy to one or more of the six foods between 1 year and 3 years of age	CMA rates: Control- 3/525 EIG- 1/415	The definition of CMP avoidance was a daily formula intake of less than 300 ml (9 grams of CMP)	<b>Verdict: U</b> <b>Strength: M</b>
Sakihara <sup>55</sup> 2021 Japan	Newborns from 4 hospitals in Japan	-Ingestion group: At least 10 ml cm from ≤1 m until 3m (n=242) -Avoidance group: BF±Soy (n=249)	CMA based on SPT and OFC at 3m, 6m	CMA: Ingestion- 0.8% Avoidance- 6.8%	The 2 CMA patients in the ingestion group ingested only small amounts of CMF. BF was not impaired	<b>Verdict: P</b> <b>Strength: H</b>
Quake <sup>56</sup> 2022 USA	180 infants Age 4-6 m	Food avoidance until age 12 m Milk early introduction groups: -Single milk -Milk/egg, milk/peanut Mixture of 10 foods + milk *low protein (total 300 mg) *medium protein (900 mg) *high protein (3000 mg)	OFC 2-4 years after the start of the study	None of the infants in the consumption groups, developed CMA	It is not specified how many infants who received milk early as a single food or a 2-food combination developed CMA.	<b>Verdict: P</b> <b>Strength: M</b>
Skjerven <sup>57</sup> 2022 Norway and Sweden "PreventADALL"	2397 newborns	Intervention type: -None=597 -Skin emollient =575 -Early food at 3 m=642 -Combined= 583 Foods– Peanut, CMP, wheat, egg	Any food allergy at age 36 m	Food allergy/CMA: None- 2.3%/0.34% Skin- 3.0%/17% Food- 0.9%/0.17% Comb.-1.2%/0%	Food intervention was started at 3 months	<b>Verdict: U</b> <b>Strength: M</b>

Verdict on early introduction of CMP: C=Con, U=Undetermined, P=Pro

Strength: L=Low, M=Medium, H=High

(E)BF – (Exclusive)Breastfeeding, CM(A)=Cow milk (allergy), CMF=Cow milk formula

**Table 3. Effect of early CMF introduction on the development of CMA in high risk patients (2)**

Source/year	Population	Interventions/collected data	Outcome	Results	comment	Verdict / Strength																				
Sakihara <sup>59</sup> 2016 Japan	374 patients with egg allergy	Retrospective cohort study CMF ingestion during the first 3 months of life	CMA at age 3-24 m	<table border="1"> <thead> <tr> <th>CMA (171)</th> <th>#(%)</th> <th>OFC (84)</th> <th>persist(90)</th> </tr> </thead> <tbody> <tr> <td>Bf =75</td> <td>46(61.3)</td> <td>22</td> <td>24(32)</td> </tr> <tr> <td>Temporary =177</td> <td>95(53.6)</td> <td>44</td> <td>48(27.2)</td> </tr> <tr> <td>Nondaily= 47</td> <td>19(40.4)</td> <td>12</td> <td>8(17.02) *</td> </tr> <tr> <td>Continuous=75</td> <td>11(14.7)</td> <td>6</td> <td>4(0.5)*</td> </tr> </tbody> </table>	CMA (171)	#(%)	OFC (84)	persist(90)	Bf =75	46(61.3)	22	24(32)	Temporary =177	95(53.6)	44	48(27.2)	Nondaily= 47	19(40.4)	12	8(17.02) *	Continuous=75	11(14.7)	6	4(0.5)*	Exposed 0-3m – 0.4% CMA	<b>Verdict: P</b> <b>Strength: M</b>
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Nishimura <sup>60</sup> 2022 Japan	163 infants with AD at age 3-4 m	Interventional Placebo: PP (n=80) Mixed powder (MP) containing milk, soy, buckwheat, wheat, peanut, egg (n=83)	Food allergy at age 18 m	<table border="1"> <thead> <tr> <th>All foods: PP- 19/80</th> <th>MP-7/83</th> <th>p=0.0066</th> </tr> </thead> <tbody> <tr> <td>For milk: PP-6/80</td> <td>MP-2/83</td> <td>ns</td> </tr> </tbody> </table>	All foods: PP- 19/80	MP-7/83	p=0.0066	For milk: PP-6/80	MP-2/83	ns	CMP was gradually increased but reached only 20 mg	<b>Verdict: P/U</b> <b>Strength: M</b>														
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Verdict on early introduction of CMP: C=Con, U=Undetermined, P=Pro  
CMA=Cow milk allergy, OFC=Oral food challenge

**Table 4. Effect of temporary neonatal exposure to cow's milk on the development of CMA (10)**

Source/year	Pop.	Study design	Interventions/ collected data	Outcome	Results	comment	Effect/ Strength/ Timing
Lindofrs <sup>29</sup> 1988 Sweden	General	<b>Interventional</b> -BF -Up to 60 ml CMF at 6 h and until mother's lactation started	BF- 112 CMF- 104	Atopic diseases at ages 3,6,18 m	Lower in CMF at 18 m		<b>Effect: I/U</b> <b>Strength: M</b> <b>Timing: T</b>
Lindofrs <sup>62</sup> 1992 Sweden			BF- 95 CMF- 88	Atopic disease at age 5 y CM sensitization at age 5 y	No difference in atopic diseases BF= no CM sensitization CMF=3 CM sensitization		<b>Effect: I/U</b> <b>Strength: M</b> <b>Timing: T</b>
Juvonen <sup>63</sup> 1996 Sweden	General	<b>Interventional</b> randomly assigned at birth for supplements in the first 3 d of life followed by exclusive BF	HM- 53 CMF- 39 CHF- 37	CMA at age 3y	Human milk -0/53 CMF -1/39 Casein hydrolysate formula -0/37	Interested mothers who volunteered at the beginning of pregnancy	<b>Verdict: I/U</b> <b>Strength: M</b> <b>Timing: T</b>
Saarinen <sup>66</sup> 1999 Finland	General	<b>Interventional,</b> randomly assigned to Specific supplements for 4 days followed by BF with CMF as required	BF- 824 CMF- 1789 HM- 1859 EHF- 1737	Adverse reaction to OFC with CM at age 18-34 m	Exposure to CM while in the hospital increased the risk of CMA (OR, 1.54; $P = .03$ )	In the CM group the subsequently allergic infants had been given smaller daily amounts of formula than the tolerant infants.	<b>Verdict: I</b> <b>Strength: M</b> <b>Timing: T</b>

Source/year	Pop.	Study design	Interventions/collected data	Outcome	Results	comment	Verdict/ Strength/ Timing
Saarinen <sup>72</sup> 2000 Finland	IgE (+) CMA- 75 IgE (-) CMA- 43	<b>Case control</b>	Exposure to cow's milk at hospital, and at home during the first 8 weeks of life	IgE(+) CMA	IgE(+) CMA was increased by exposure to CM at hospital, and by no or minimal exposure at home during the first 8 weeks	symptoms suggestive of CMA included a broad range of symptoms not necessarily reflecting CMA	<b>Verdict: I</b> <b>Strength: M</b> <b>Timing: T</b>
de Jong <sup>64,65</sup> 2002 Netherlands "BOKKAL"	General	<b>Interventional</b> DBPC Supplements in the first 3 d of life	CMF- 758 No CMF- 775	Allergic disease CM sIgE (2y, 5Y)	No differences	~50% of participants were not exclusively breastfed despite their intention	<b>Verdict: U</b> <b>Strength: M</b> <b>Timing: T</b>
Urashima <sup>67</sup> 2019 Japan	General	<b>Interventional</b> BF±AA for the first 3 days followed by BF±CMF  BF+CMF >5ml /day for 5 months	n=151 for each group	Cow's milk sensitization at 24 m CMA	Sensitization: BF±EF = 16.8% BF+CMF = 32.2% CMA: BF±EF = 0.7% BF+CMF = 6.6% Switching from BF/EF to BF+CMF at any time did not increase CMA	Mothers in the BF+CMF group could ignore the protocol to skip feeding CMF for a while, e.g., 2 weeks, because of enough amounts of BF	<b>Verdict: I</b> <b>Strength: M</b> <b>Timing: T</b>
Kelly <sup>70</sup> 2019 Ireland	CMA- 55 Control- 55	<b>Retrospective case control</b> Feeding pattern in first 24h in	-BF -BF + formula -Formula	CMA	Rate of CMA in exclusive BF was lower compared to BF + formula but comparable to exclusively formula	Data on the type of feeding beyond the first 24 hours of life was not provided	<b>Verdict: U</b> <b>Strength: M</b> <b>Timing: na</b>

Source/year	Pop.	Study design	Interventions/collected data	Outcome	Results	comment	Verdict/ Strength/ Timing
Garcette <sup>71</sup> 2022 France	CMA- 554 Conts- 211	<b>Retrospective case control</b> recruited at age 6-9 months Bf at least 1m	Records of supplemental feeding at maternity	CMA	Feeding bottle at maternity hospital (OR = 1.81 [1.27;2.59]) and avoidance of dairy products during pregnancy or breast feeding (OR = 5.62 [1.99; 15.87]) were independent risk factors of CMA	39% received at least 1 complementary bottle at maternity. In 62.2% it was CMF	<b>Verdict: I</b> <b>Strength: M</b> <b>Timing: T</b>
Sakihara <sup>73</sup> 2022 Japan	General	Observational	CMF consumption in the first 3 days of life followed by: -consume at least 10 mL of CMF daily -avoiding CMF between 1 and 2 m of age	CMA at age 6 m	Dis. <1m -7/17 (41.2%) Dis. 1-2m 3/26 (11.5%) Dis. 3-5m 7/69 (10.1%) Cont. 2/319 (0.6%)		<b>Verdict: I</b> <b>Strength: H</b> <b>Timing: T</b>

Effect of **very** early introduction of CMP on CMA: I=Increase, U=Unchanged, D=Decrease  
Timing: T=Transient, P=Persistent