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Invited review: Milk fat globule membrane—A possible panacea for neurodevelopment, infections, cardiometabolic diseases, and frailty

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ABSTRACT

Milk is an evolutionary benefit for humans. For infants, it offers optimal nutrients for normal growth, neural development, and protection from harmful microbes. Humans are the only mammals who drink milk throughout their life. Lipids in colostrum originate mostly from milk fat globule membrane (MFGM) droplets extruded from the mammary gland. The MFGM gained much interest as a potential nutraceutical, due to their high phospholipid (PL), ganglioside (GD), and protein contents. In this review, we focused on health effects of MFGM ingredients and dairy food across the life span, especially on neurodevelopment, cardiometabolic health, and frailty in older adults. The MFGM supplements to infants and children reduced gastrointestinal and respiratory tract infections and improved neurodevelopment due to the higher content of protein, PL, and GD in MFGM. The MFGM formulas containing PL and GD improved brain myelination and fastened nerve conduction speed, resulting in improved behavioral developments. Administration of MFGM-rich ingredients improved insulin sensitivity and decreased inflammatory markers, LDL-cholesterol, and triglycerides by lowering intestinal absorption of cholesterol and increasing its fecal excretion. The MFGM supplements, together with exercise, improved ambulatory activities, leg muscle mass, and muscle fiber velocity in older adults. There are great variations in the composition of lipids and proteins in MFGM products, which make comparisons of the different studies impossible. In addition, investigations of the individual MFGM components are required to evaluate their specific effects and molecular mechanisms. Although we are currently only beginning to understand the possible health effects of MFGM products, the current MFGM supplementation trials as presented in this review have shown significant clinical health benefits across the human life span, which are worth further investigation.
Key words: milk fat globule membrane, infection, neural development, cardiometabolic health, frailty

INTRODUCTION

Human milk (**HM**) is the solitary source of nutrients for infant's growth during the first months of life (Hettinga et al., 2011; Kramer and Kakuma, 2012). Human milk is rich in nutrients (carbohydrates, proteins, lipids, vitamins, minerals) and immune protections (oligosaccharides and antibodies; Willett and Ludwig, 2020). Milk fat provides about 50% of the total calories in the milk with milk fat globule (**MFG**) as one of the principle components, with highly complex structure and composition. The MFG is biosynthesized by packing triacylglycerol (**TAG**) into lipid droplets surrounded by a phospholipid (**PL**) and cholesterol monolayer in the endoplasmic reticulum of the alveolar epithelial cells of the mammary gland. These droplets migrate to the apical pole of the epithelial cells and fuse with an additional peripheral bilayer, leading to a triple layer membrane structure (Figure 1), and the mature MFG covered by membrane (**MFGM**) is secreted into the milk (Smoczyński, 2017). The main function of membranes is to stabilize the globule as an emulsion (Dewettinck et al., 2008). Structurally, the MFGM is a liquid lipid-protein mosaic, with proteins immersed or flowing in a liquid bilayer of spatially oriented lipids (Singer and Nicolson, 1972). The nonpolar environment resulting from inner monolayer of PL surround the TAG core and an outer PL bilayer. The external part of the bilayer is constituted mainly by PL, containing choline as well as glycolipids, cerebrosides, and gangliosides (**GD**), directed toward the aqueous environment, whereas the interior surface of the bilayer contains phosphatidylethanolamine (**PE**), phosphatidylinositol (**PI**) and phosphatidylserine (**PS**; Figure 1; Gallier et al., 2010; Donato et al., 2011).

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In this review, we summarize the recent interventions on MFGM and their possible health effects in different age groups in different organ systems, such as the central nervous, cardiovascular, metabolic, gastrointestinal, and motor systems. There are excellent recent reviews on milk and dairy food for human nutrition with respect to various diseases (Thorning et al., 2017; Willett and Ludwig, 2020) and MFGM in infant nutrition (Fontecha et al., 2020); we focus on the roles of MFGM on gastrointestinal infections, metabolic and cardiovascular systems, and frailty across the life span.

MFGM LIPIDS AND PROTEINS

The mean diameter of MFG in bovine milk is around 10 μm, enveloped by a 15-nm thick trilayer MFGM (Zheng et al., 2014). The MFGM contains 30 to 75% polar lipids and 25 to 70% protein of the MFGM weight (Holzmüller et al., 2016). Milk exosomes are additional membrane vesicles of endocytic origin with diameter of less than 0.12 μm (Figure 1). The exosomes (also called nanovesicles, lactosomes, or nanosomes) contain proteins, mRNA, microRNA, and lipids, which have

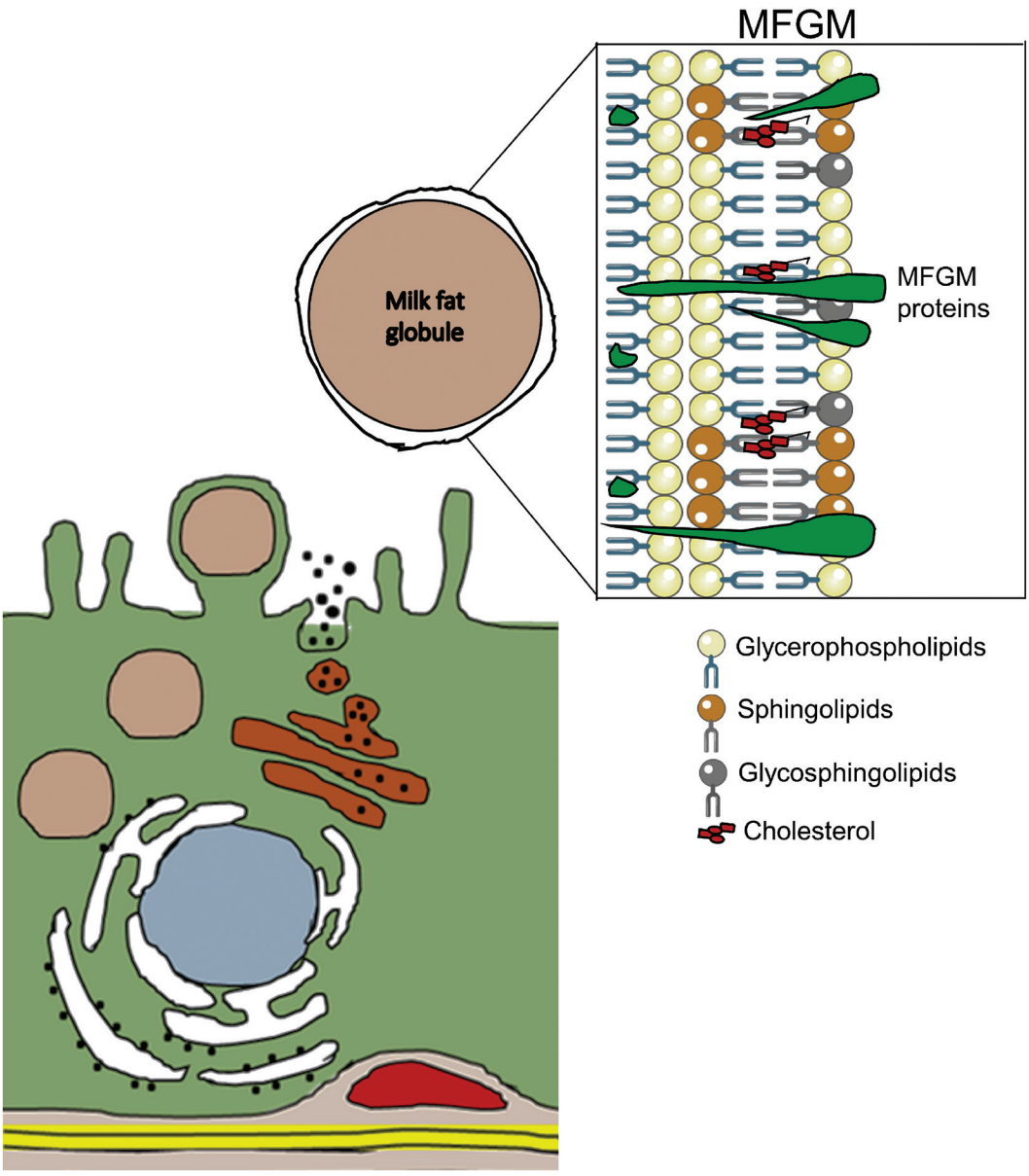


Figure 1. Schematic representation of milk fat globule membrane (MFGM) secretion and their contents. The diameter of the bovine MFGM is around 2.0 to 15 μm, and the MFGM is secreted from the endoplasmic reticulum of lactocytes. The MFGM has a 3-layer membrane surrounding the triacylglycerol core. The layers contain MFGM lipids and proteins. In addition, milk exosomes with a diameter of less than 0.12 μm are released.

cellular signaling and immune cell functions. Polar lipids of MFGM consist of 2 major classes: glycerophospholipids and sphingolipids (Table 1). The MFGM lipid fraction is highly abundant in glycerophospholipids and cholesterol, with a complex mixture of more than 30 different phospholipids. Glycerophospholipids contain a glycerol moiety comprised of 2 fatty acids and a phosphate group bound to a polar head, such as phosphatidylcholine (**PC**), PE, PS, PI, phosphatidyl-glycerol, or phosphatidic acid (Contarini and Povolo, 2013; Ortega-Anaya and Jiménez-Flores, 2019). Sphingolipids such as sphingomyelin (**SM**) have a phosphocholine residue bound to glycerol with 2 fatty acids (Verardo et al., 2017), whereas GD are sphingolipids with a complex polar head group of one or more sialic acids and oligosaccharides. The GD 3 gangliosides are the predominant form in human colostrum, with an inhibitory activity against innate immune functions (Rueda et al., 1998, 2007). Glycerophospholipids and sphingolipids in MFGM have similar concentrations in human and bovine milk (Cilla et al., 2016). In general, dairy PL are of particular interest as a nutritional source due to their higher content of SM and PS compared with, for example, egg yolk and soybean (Contarini and Povolo, 2013; Delplanque et al., 2015). Concentrations of PL and GD in bovine and human milk during the first day of lactation are shown in Table 1 (Garcia et al., 2012; Lee et al., 2018a).

Approximately 500 proteins have been identified in human milk and have recently gained increasing attention because of their clinical and biological functions (Cao et al., 2018). The MFG proteins account for approximately 1 to 4% of the total protein fraction in milk (Liao et al., 2011). The major proteins observed in various mammals include breast cancer proteins (BRCA1 and BRCA2), mucin I, xanthine oxidase, CD36, butyrophilin, adipophilin, lactadherin, proteose peptone 3, and fatty acid-binding protein (Yang et al., 2015; Cao et al., 2018; Fontecha et al., 2020). Butyrophilin and xanthine constitute approximately 40 and 12% of total MFGM proteins, respectively. These milk proteins are present in any laboratory or industry formulation of MFGM. Therefore, it is important for the investigation of potential clinical effects to consider the methods of isolation and the varying MFGM compositions among the given supplements in the various studies presented (Holzmüller et al., 2016; Holzmüller and Kulozik, 2016, in Tables 2 and 3). Other proteins such as milk alkaline phosphatase, carbonic anhydrase, lactoferrin, osteopontin, and lysozyme are also present in milk whey but in minor amounts in MFGM (Charlwood et al., 2002; Mudd et al., 2016).

Table 1. Concentration of phospholipids and gangliosides in bovine and human first-day milk

Phospholipid	Bovine milk (μg/mL)	Human milk (μg/mL)
Phosphatidylcholine (PC)	60	60
Phosphatidylethanolamine (PE)	62	42
Phosphatidylserine (PS)	21	22
Phosphatidylinositol (PI)	8	11
Sphingomyelin (SM)	46	78
PE plasmalogen (PLAS)	7	27
Gangliosides GD3	11–13	15–27

PRODUCTION OF MFGM-RICH INGREDIENTS

The MFGM fragments in dairy-based products are mainly divided in 2 groups: MFGM-enriched ingredients and phospholipid extracts. Various physical processes are used to prepare MFGM-enriched ingredients, whereas solvent extraction of MFGM-enriched ingredients is used for PL isolations (Price et al., 2018). The PL extracts rich in SM and PS have been shown to affect cell regulation and cognitive functions. The role of sphingolipids in food and human health has just recently been reviewed (Wang et al., 2020). The MFGM-enriched preparations are produced as potential nutraceuticals with possible health effects due to high concentrations of PL, GD, and glycoproteins (Contarini and Povolo, 2013; Delplanque et al., 2015; Figure 2).

The MFGM-enriched ingredients are produced by destabilizing the MFG natural emulsion (Huang et al., 2020). Starting material cream or subproducts during cheese processing are used for MFGM production (Figure 2). Cream is the raw material for anhydrous milk fat or butter manufacturing, produced by skimming whole milk. Churning of cream produces butter and buttermilk (an aqueous phase similar in composition to skim milk), which also contain MFGM fragments. Buttermilk contains maximal amounts of MFGM components, including minor lipids and MFGM proteins. Cheese whey, a subproduct from the cheese processes, is rich in MFGM ingredients due to its residual fat and MFGM proteins. This residual fat is removed from whey feed to produce whey protein concentrates or whey protein isolates. Finally, spray drying and evaporation processes are used to make a MFGM-rich powder from these different subproducts. The MFGM are vulnerable to disruption during industrial processing conditions, such as rapid air beating, intense turbulence, high velocity gradient, and temperature (Singh and Gallier, 2017). These processes make the milk fat susceptible to oxidation, hydrolytic rancidity, and coalescence. Heating denatured membrane proteins releases membrane PL into the serum phase (Houlihan et al., 1992); the cooling of milk causes about 20% of PL to release into milk serum. In addition, freezing and thawing has det-

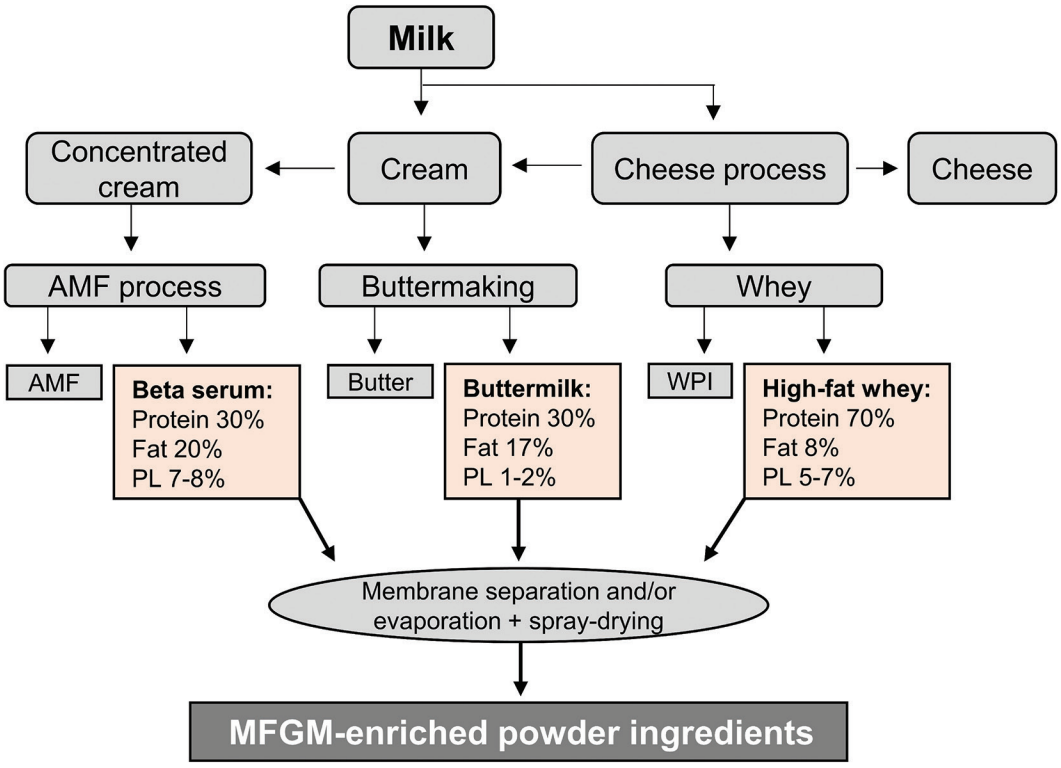


Figure 2. Milk fat globule membrane (MFGM) ingredients (modified using data from Gallier et al., 2018; Fontecha et al., 2020). AMF = anhydrous milk fat; PL = phospholipids; WPI = whey protein isolates.

rimental effects on MFGM compositions and stability. Industrial processing of MFGM promotes disruption of interfacial membrane and adsorption of soluble proteins, such as whey proteins and casein from the surrounding aqueous phase (Liang et al., 2017). Milk proteins can be grouped into 3 classes, namely casein, whey protein, and MFGM proteins. These membrane proteins have important roles in stabilizing MFG and MFGM. Casein and MFGM form a complex via calcium bridges between phosphorylated casein and the phosphate of PL (Spitsberg et al., 2019). The calcium-binding ability of MFGM inhibits protein (casein) flocculation and phase separation, rendering a stable MFGM-based food emulsions (Jukkola et al., 2019).

In the subsequent sections, we discuss the known health effects of MFGM products in human intervention organized into medical fields: gastrointestinal and respiratory infections, cardiometabolic diseases, neurological diseases, and frailty. The MFGM products consists of several components and are differently enriched in the various production lines, which makes the comparability of the different intervention studies almost impossible (Figure 2; Table 1). The amounts of MFGM and their contents described in the intervention studies are summarized in Tables 2 and 3.

MFGM AND GASTROINTESTINAL AND RESPIRATORY INFECTION

Mortality associated with infectious diarrhea is high in infants and young children in developing countries, and nutritional compounds would be of great advantage to alleviate this plight. Breastfeeding is the gold standard for infant nutrition, because HM contains biologically active components for growth, development, and protection against infections (Schack-Nielsen and Michaelsen, 2007). Anti-infectious factors in HM include immunoglobulins, antibacterial, and antiviral proteins, leukocytes, and oligosaccharides. Infant formula is mainly produced from skim milk powder and whey protein concentrates, resulting in a reduction of biologically important MFGM and their various components. Standard formula-fed infants may therefore be at a higher risk of gastrointestinal and respiratory infections and otitis media compared with breastfed infants (Ajetunmobi et al., 2015; Kørvel-Hanquist et al., 2017). To improve infant formulas, additions of different bioactive components have been investigated (Hernell, 2011). The MFGM contain numerous biologically active components with antimicrobial activities (Rueda, 2007), such as oligosaccharides (Triantis et al.,

Table 2. Effects of milk fat globule membrane (MFGM) supplementation in children with respect to gastrointestinal and respiratory infections and neurodevelopment

Subject	Study Period	MFGM supplement[1]	Outcome[2]	Reference
Infants (6–11 mo)	6 mo	Lacprodan MFGM-10 (7% PL + 0.2% GD; Arla Foods Ingredients)	Reduced diarrhea	Zavaleta et al., 2011
Premature infants with low birth weight	18 mo	SM-fortified milk (PL 200 mg containing 40 mg of SM)	Improved Behavior Rating Scale of the BSID-II, the Fagan test scores, the latency of VEP and sustained attention test	Tanaka et al., 2013
Infants (<2 mo)	12 mo	Lacprodan MFGM-10	Improved cognitive scores on testing with BSID-III	Timby et al., 2014
Infants (<2 mo)	12 mo	Lacprodan MFGM-10	Reduced antipyretic use and acute otitis media risk	Timby et al., 2015
Children (3 mo to 9 yr)	11 mo	MFGM + PUFA + choline + SM	PUFA, choline, and SM showed a significant association with early myelination	Deoni et al., 2018
Infants	365 d	Lacprodan MFGM-10 + lactoferrin (FrieslandCampina DMV)	Reduced diarrhea and improved cognitive, language, and motor test scores	Li et al., 2019
Newborn infants (2–8 wk)	6 mo	Anmum Infacare MFGM (9 mg of GD/100 g; Fonterra Co-operative Group)	Improved IQ scores in Hand and Eye Coordination, Performance, and General scores	Gurnida et al., 2012
Children (4.4 yr)	4 mo	MFGM Inpulse (500 mg of PL; Society Lactel)	Febrile period was shorter	Veereman-Wauters et al., 2012
Infants (8–24 mo)	12 wk	2 g of CML + 3 g of whole milk powder (150–300 mg of PL; Fonterra Co-operative Ltd.)	Mean duration of rotavirus diarrhea was shorter	Poppitt et al., 2014
Infants (21–28 d)	3 mo	3.88 g of Lacprodan MFGM-10/100 g of powder or standard formula + F19 strain (*Lactobacillus paracasei* 10^8 cfu/L; Chr. Hansen)	Fever episodes and days with fever were reduced with MFGM	Li et al., 2019
Infants (0–2 mo)	18 mo	MFGM (ORDESA Laboratories) + bioactive components (fructooligosaccharides and inulin, *Bifidobacterium* and *Lactobacillus*, PUFA, GD, nucleotides, and sialic acid)	Prolonged latencies and lower amplitudes of VEP	Nieto-Ruiz et al., 2019
Healthy infants (14 d old)	14 wk	MFGM-L (Fonterra Co-operative Group Limited; lipid-rich MFGM; 647 mg/L PL containing 141 mg of SM/L) or MFGM-P (Arla Foods Ingredients; protein-rich MFGM; 452 mg/L PL containing 106 mg of SM/L)	Both MFGM were well tolerated, eczema incidence was higher in MFGM-P	Billeaud et al., 2014

[1]PL = phospholipid; CML = complex milk lipid; GD = ganglioside; SM = sphingomyelin.

[2]BSID = Bayley Scale of Infants Development; VEP = visual evoked potential.

Table 3. Effect of milk fat globule membrane (MFGM) supplementation in older adult individuals

Subject	Study period	MFGM supplement[1]	Well-being[2]	Reference
Healthy adults (18–55 yr)	2 wk	MFGM Lacprodan PL-20 (Arla Foods Ingredients)	Reduced stool frequency and daily gastrointestinal complaint	Ten Bruggencate et al., 2016
Adults (18–65 yr)	4 wk	Butter milk MFGM (188 mg of PL containing 11.9 mg of SM; Westland Milk Products)	Reduced plasma LDL-C, triglyceride, ACE, and systolic BP	Conway et al., 2013, 2014
Overweight adults (20–70 yr)	8 wk	Whipping cream MFGM (19.8 mg of PL; Arla Foods Ingredients)	Reduced total, LDL-C, and Apo B/Apo A-1 ratio	Rosqvist et al., 2015
Overweight and obese adults (18–65 yr)	2 wk	MFGM BPC50 (13.7% PL + 0.63% GD + proteins; Fonterra Co-operative Group Ltd.)	Reduced postprandial LDL-C, total cholesterol, triglyceride, and iAUC insulin and increased IL-10	Demmer et al., 2016
Overweight and obese adults (50–76 yr)	8 wk	Milk PL (18.4% PL; Lipamin M20; Lecico GmbH)	Reduced waist circumference	Weiland et al., 2016
Postmenopausal women (<75 yr)	4 wk	Milk PL (3 or 5 g/100 g; Actalia Dairy Products)	Reduced fasting and postprandial plasma cholesterol, Apo B/Apo A1 ratio, and PCSK9 and increased fecal coprostanol	Vors et al., 2020
Healthy men (30–55 yr)	3 wk	Milk PL (13.5 g; Arla Foods Ingredients)	Shorter reaction time of working memory task and blunted psychological stress response at higher stress load	Hellhammer et al., 2010
Overweight and obese adults (51–59 yr)	4 d	HF dairy diet (250 mL of milk, 200 g of yogurt, 30 g of butter, 40 g of cheese, and 50 g of ice cream)	Plasma lyso-PC and lyso-PAF positively correlated with insulin sensitivity and inversely with insulin resistance	Nestel et al., 2014
Older women (>75 yr)	3 mo	1-g MFGM pill (33.3% PL containing 8.03% SM; Megmilk Snow Brand Co. Ltd.) and exercise twice weekly	Increased frailty reversal rate and improved walking speed and serum IGF-1	Kim et al., 2015
Women (50–67 yr)	10 wk	1 g of MFGM (18.4% PL containing 3.81% SM; Meiji Co.) and exercise 1 h twice weekly	Faster stepping and increased muscle fiber conduction velocity cross-section area in leg muscles	Ota et al., 2015
Adults (50–70 yr)	24 wk	1 g of MFGM (18.4% PL containing 3.81% SM; Kao Corporation)	Improved balance parameters	Kokai et al., 2018
Women (60–73 yr)	10 wk	1-g MFGM pill (Meiji Co.; 33.3% PL containing 8.03% SM) and exercise twice weekly	Improved chair test time and leg muscles cross-section area and increased leg muscle fiber conduction speed	Minegishi et al., 2016
Older individuals (71–75 yr)	8 wk	1-g MFGM pill (Kao Corporation; 16% PL containing 3.81% SM) and exercise daily	Increased foot tapping and open-close stepping score from baseline	Yoshinaka et al., 2018
Women (82–84 yr)	3 mo	1-g MFGM pill (Megmilk Snow Brand Co. Ltd.) and 1 h of exercise twice weekly	Exercise and MFGM improved walking speed	Kim et al., 2019

[1]PL = phospholipid; SM = sphingomyelin; BPC50 = cream-derived complex milk lipid fraction powder (Fonterra Co-operative Group Ltd.); GD = ganglioside; HF = high fat.

[2]LDL-C = low-density lipoprotein cholesterol; BP = blood pressure; Apo = apolipoproteins; iAUC = incremental area under curve; lyso-PC = lyso-phosphatidylcholine; lyso-PAF = lyso-platelet activating factor.

2018) and the glycoproteins butyrophilin, lactadherin, and mucin (Liao et al., 2011). An in vitro study demonstrated that the whey protein fraction MUC1 from bovine milk inhibited neuraminidase-sensitive rotavirus strain in cell culture lines (Kvistgaard et al., 2004). Preclinical studies showed that mucin, other proteins, and GD in MFGM inhibited the growth of various pathogen including rotavirus, and *Escherichia coli* (Laegreid et al., 1986; Yolken et al., 1992; Spitsberg, 2005). Clinical trials with MFGM supplementations to infants or children showed beneficial effects in gastrointestinal and respiratory infections (Zavaleta et al., 2011; Timby et al., 2015; Table 2). In a randomized double-blinded controlled trial, 550 infants (6–11 mo old) in a periurban community in Peru, received MFGM (Lacprodan, Arla Foods Ingredients) or a skim milk protein (control) formula for 6 mo (Zavaleta et al., 2011). Supplementation of MFGM significantly reduced the prevalence of diarrhea, including episodes of bloody diarrhea. The MFGM supplementation increased serum amino acids, zinc, and vitamin B12 levels, but decreased ketone bodies, trimethylamine-N-oxide and T-helper type 1 (**Th1**) response (Lee et al., 2018b). A Th1 response represents stimulation of proinflammatory immune cells, whereas a T-helper type 2 response is prevalent in allergy and counteracts the microbicidal actions mediated by Th1 cytokines (Kidd, 2003). The decreased Th1 response by MFGM supplementation was due to an IL-2 reduction in serum via docosahexaenoic and arachidonic acids (Chapkin et al., 2009). In addition, bioactive components in MFGM might affect intestinal maturation or activation of immune system. In contrast to protein-rich MFGM supplement (Zavaleta et al., 2011), a PL-rich MFGM supplement (INPULSE) failed to reduce diarrhea in children (Veereman-Wauters et al., 2012). 182 Belgian boys and girls (mean age 4.4 yr) received chocolate formula milk (Society Lactel) enriched with MFGM INPULSE for 4 mo (Veereman-Wauters et al., 2012). The daily PL intake was 500 mg in the MFGM supplementation and 60 mg in the control group. Febrile periods were significantly shorter in the MFGM compared with the control group (1.7 vs. 2.6 d), whereas diarrhea and cough were similar in both groups. The different outcome with PL-rich MFGM supplementation might be due to the different compositions of the supplements, length of intervention and age of the children. Furthermore, GD have been shown to affect gastrointestinal maturation and improve immune functions by modifying intestinal microflora and interfering with pathogenic binding in intestine (Rueda, 2007). The effect of GD on diarrhea was investigated in 450 North Indian infants, aged 8 to 24 mo, in a randomized controlled trial (**RCT**). Infants were given daily 5 g of whole milk powder (control) or complex milk lipid (**CML**; 2 g of spray-dried GD concentrate; Fonterra) plus 3 g of whole milk powder, and the diarrheal incidence was monitored for 12 wk (Poppitt et al., 2014). No significant difference in rotavirus diarrhea was found between the groups, but the mean duration of rotavirus diarrhea was shorter in the CML group. These studies demonstrate that the protein-rich fraction of MFGM and GD may be helpful in preventing diarrhea in infants, whereas PL seem to be ineffective on diarrheal outcome. The major drawback of the studies is that none of them included breastfed groups. In addition, further RCT are necessary to draw firm conclusions.

Specific changes in gut microbiota are associated with positive health outcomes (Pannaraj et al., 2017; Raza et al., 2019; Loftfield et al., 2020). In breastfed infants, bifidobacteria and lactobacilli are most prevalent, whereas formula-fed infants have a more diverse colonization, including bifidobacteria, *Bacteroidetes*, staphylococci, *E. coli*, and clostridia (Guaraldi and Salvatori, 2012; Chong et al., 2018). Several studies suggested that probiotic supplementation may be beneficial in preventing and treating upper-respiratory tract infections (Ozen et al., 2015) and infectious diarrhea (Szajewska et al., 2016), whereas others did not find an effect (Kuitunen et al., 2009; Abrahamsson et al., 2013). The different outcome with probiotics supplementation in the above studies might be due to varying strains of bacteria and their supplementation regimen. Recently, Li et al. (2019b) found that upper and lower respiratory tract infections were more prevalent in infants receiving lactobacillus strain F19 supplemented standard formula compared with breastfed in an RCT of 581 infants at several centers in Nanjing, China (Li et al., 2019b). The infants received a standard formula or standard formula with MFGM (3.88 g of Lacprodan MFGM 10/100 g powder), or with the lactobacillus F19 strain (*Lactobacillus paracasei* ssp. *paracasei* 10^8 cfu/L) for 12 mo (Li et al., 2019b). A reference group of 208 breastfed infants were included in the study. The number of diarrhea and fever episodes were not different in infants receiving formula supplemented with MFGM or *Lactobacillus* compared with breastfed infants, but the control group had more fever episodes during the 12-mo monitoring period.

To investigate if MFGM can increase resistance to diarrheagenic *E. coli*, 58 healthy adults received MFGM ingredients Lacprodan PL-20 (16% PL; Arla Foods Ingredients) or a Miprodan 30 powder (control; Arla Foods Ingredients) in a soy-milk drink for 2 wk followed by oral administration of live attenuated diarrheagenic *E. coli* strain (E1392/75–2A; Ten Bruggencate et al., 2016). Enterotoxigenic *E. coli* produces enterotoxins and is a leading bacterial cause of diarrhea in children

younger than 5 yr and travelers (WHO, 2006; Kotloff et al., 2013). Miprodan 30 is a sodium caseinate obtained from skim milk with a similar amino acid profile as Lacprodan PL-20. The MFGM supplementation significantly decreased *E. coli*-induced stool frequency and gastrointestinal symptoms. The authors speculated that MFGM possesses antimicrobial and decoy activities. In addition, certain components of MFGM such as unsaturated fatty acids (UFA), sphingolipids, mucin, and sialic acid, can affect survival of bacterial pathogens and prevent binding to the gastric epithelium (Sprong et al., 2001; Bode, 2009).

In summary, supplementation of different MFGM formulations have shown to reduce fever, respiratory and diarrhea symptoms, and length of the disease. The number of the reported studies are low, patient cohorts and outcomes significantly vary, which appears to thwart critical comparisons of the studies, but the positive results shown in Table 2 encourage in our opinion to further investigations of MFGM.

MFGM AND CARDIOMETABOLIC DISEASES

Metabolic and cardiovascular diseases (**CVD**) are a significant global burden and are increasing dramatically. Dyslipidemia, hypertension, and abdominal obesity are the major risk factors for cardiometabolic diseases (GBD 2016 Risk Factors Collaborators, 2017). Diets containing saturated fats have been shown to elevate serum cholesterol levels and increase cardiovascular diseases (Vessby et al., 2001). A recent systemic review and meta-analysis found that relative to reduced-fat cow milk, whole-fat cow milk consumption was associated with lower odds ratios for childhood overweight and obesity (Vanderhout et al., 2020). The authors speculate that replacement of calories from less healthy foods, satiety mechanisms or confounding by indication and reverse causality might explain the results. Milk fat, rich in saturated fatty acids (SFA; e.g., butter), increases plasma cholesterol compared with vegetable oils, which is rich in UFA (Tholstrup et al., 2004; Mozaffarian and Clarke, 2009). Howard and Marks (1979) appraised that the dairy product butter, but not cream, might be a cause for hypercholesterolemia. Controlled studies demonstrated that cholesterol levels increased more with the intake of butter compared with cheese, even with a similar intake of milk fat (Biong et al., 2004; Nestel et al., 2005; Sofi et al., 2010). The different outcomes after dairy food ingestions might be related to the amount of MFGM ingredients or their processing.

The MFGM gained much interest as a potential nutraceutical because of their high PL and sphingolipid contents (Bourlieu et al., 2018). In vitro and animal studies demonstrated that milk PL affected postprandial lipid metabolism by reduced intestinal cholesterol absorption and increased fecal excretion (Noh and Koo, 2004; Wat et al., 2009; Lecomte et al., 2015). Furthermore, it has been demonstrated that SM and sphingolipids supplementation reduced serum cholesterol and triglyceride concentrations in animals (Duivenvoorden et al., 2006; Yunoki et al., 2010; Chung et al., 2013). The clinical studies that investigated the effects of MFGM ingredients on metabolic and cardiovascular diseases are summarized in Table 3.

In healthy humans, acute and chronic studies with sphingolipids-enriched buttermilk found no changes in postprandial, but a trend toward lower cholesterol concentrations (Ohlsson et al., 2009, 2010). In contrast, reduced serum total cholesterol and triglycerides were observed in 34 healthy participants, ingesting PL-rich buttermilk (188 mg of PL; Westland Milk Products) for 4 wk in an RCT (Conway et al., 2013). The placebo consisted of the calcium caseinate, whey protein isolate, whey protein permeate, and butter powder to match the buttermilk composition except for its MFGM components. Buttermilk PL led to a significant decrease in serum total cholesterol and triglycerides compared with placebo, but the supplementation did not significantly reduce low-density lipoprotein cholesterol (**LDL-C**). The negative findings in the previous studies could be attributed to their small sample size and normal LDL-C levels of their study participants. In addition, in 34 participants receiving PL-rich buttermilk or placebo mean systolic blood pressure was significantly lower in those receiving buttermilk compared with those receiving placebo (108.3 vs. 110.9 mmHg) with no change in diastolic blood pressure (Conway et al., 2014). Plasma angiotensin-converting enzyme (**ACE**) levels were significantly reduced in participants receiving buttermilk without change in angiotensin II and aldosterone levels. The decrease in systolic blood pressure with buttermilk may be partly caused by a reduction in ACE and relaxation of vascular muscles. In contrast, no significant effects of milk PL or soy PL on plasma lipids were found in 62 overweight or obese men in an RCT (Weiland et al., 2016). Milk PL (Lipamin M20; Lecico) containing 18.4% PL for trial 1 and 31.2% PL for trial 2 was prepared from butter serum and soy PL preparation (de-oiled soy lecithin P 900 IPM; Lecico) containing 66.1% PL. The daily milk drink consisted of 2 g of milk PL or a control drink containing 2 g of milk fat (devoid of PL) for 8 wk in trial 1 and 3 g of milk PL or 2.8 g of soy PL for trial 2. Waist circumference was significantly reduced with milk PL, but not with soy PL. The lack of change in plasma lipids with either

with milk PL or soy PL might be due to the different source of PL, age, and body mass index characteristics of the participants. In contrast to Weiland et al. (2016), a randomized multicenter controlled trial demonstrated that milk PL reduced fasting and postprandial plasma cholesterol in 58 postmenopausal women (Vors et al., 2020). The participants received daily 100 g of full-cream cheese devoid of milk PL (control) or enriched with milk PL, 3 or 5 g containing SM 0.8 wt% and 1.3 wt%, respectively, with a higher cholesterol but lower TAG content compared with control. After 4 wk of supplementation, milk PL significantly reduced fasting and postprandial plasma cholesterol (Vors et al., 2020). Furthermore, 5 g/d of milk PL reduced LDL-C (8.7%) and TAG (15.6%), indicating that milk PL may reduce chylomicron-TAG synthesis and secretion and improve its hepatic clearance.

Various studies suggested that fat consumption is associated with insulin resistance (Maron et al., 1991; Parker et al., 1993). A diet rich in saturated fat decreases insulin sensitivity; however, dairy foods are exceptions to the hypothesis (Nestel, 2012). The effect of dairy fat on insulin sensitivity was investigated in 86 overweight or obese adults (Nestel et al., 2014). The participants consumed several dairy products (250 mL of milk, 200 g of yogurt, 30 g of cheese, 40 g of butter, and 50 g of ice cream per day) for 4 d. Plasma phospholipids, sphingolipids, and fatty acids were measured and correlated with insulin sensitivity and other metabolic parameters. The results showed that plasma lyso-phosphatidylcholine (**lyso-PC**) and lyso-platelet-activating factor (**lyso-PAF**) were directly associated with insulin sensitivity ($P < 0.02$) and inversely with insulin resistance ($P < 0.05$) after adjustment for confounding factors such as age, body mass index, and blood pressure (Nestel et al., 2014). In vitro and animal studies demonstrated that lyso-PC stimulates glucose uptake and induces insulin secretion from pancreas via G protein-coupled receptor 119, lowering blood glucose (Soga et al., 2005; Yea et al., 2009). In addition, human studies have shown that plasma lyso-PC concentrations are lower in obese, glucose-intolerant participants and individuals with type-2 diabetes compared with control (Zhao et al., 2010; Barber et al., 2012). These studies clearly demonstrate that lyso-PC plays an important role in insulin sensitivity. Plasma phospholipid species correlated with dairy food servings, indicating that dairy fats may induce the favorable health effects on metabolic parameters. In addition, in an RCT in 57 healthy overweight adults, the intake of an isocaloric diet, containing 40 g of milk fat/d as either whipping cream (19.8 mg of PL; MFGM diet) or butter oil (1.3 mg of PL; control diet) for 8 wk, did not increase plasma cholesterol (Rosqvist et al., 2015), whereas plasma cholesterol increased significantly in the control group. Plasma triglycerides and high-density lipoprotein cholesterol (**HDL-C**) were not significantly different, but apolipoprotein (**Apo**) B to A-1 ratio decreased significantly in the MFGM group, suggesting that milk fat enclosed by MFGM does not impair lipoprotein profiles. Fasting plasma glucose and insulin levels were not affected by the MFGM supplementation, which is in contrast with the previous study (Nestel et al., 2014). The different outcome with MFGM on plasma lipids and insulin sensitivity might be due to lower PL intake in the study of Rosqvist et al. (2015), the source of MFGM and their processing.

Meal fat content and composition affects postprandial inflammatory responses (Erridge et al., 2007; Deopurkar et al., 2010) and particularly SFA are detrimental. In vitro and animal studies found that MFGM fractions reduce inflammation (Dalbeth et al., 2010; Snow et al., 2011). Acute postprandial inflammatory response of a high-saturated fat meal with or without MFGM were investigated in 36 overweight participants in an RCT (Demmer et al., 2016). Participants with 2 or more traits of the metabolic syndrome (overweight, high waist circumference, elevated blood pressure, plasma triglycerides, HDL-C, or fasting plasma glucose) consumed a high-fat meal palm oil smoothie (control) or palm oil plus MFGM smoothie. The source of MFGM was BPC50, a cream derived CML fraction powder (Fonterra Co-operative Group Ltd.), containing 13.7% PL, 0.63% GD, and proteins such as butyrophihlin, lactadherin, adipophilin, mucin, and xantihine oxidase. The smoothies were consumed in the morning after fasting, and blood samples were taken before and at 1, 3, and 6 h after the meal. The MFGM decreased postprandial levels of LDL-C, total cholesterol, triglycerides, insulin, and increased IL-10 (anti-inflammatory) compared with control, suggesting that the MFGM diet attenuates unhealthy effects of saturated fats.

In summary, randomized intervention trials have shown that MFGM may provide cardiometabolic health benefits by reducing LDL-C and total cholesterol and improving insulin sensitivity. These findings confirm previous mass spectrometer analyses, which characterized dairy-derived molecules such as lyso-PC, Lyso-PAF, and trans-palmitoleate associated with reduced risk of metabolic and cardiovascular diseases (Warensjö et al., 2010; Mozaffarian et al., 2013). Sources, amounts of phospholipids, and patients' groups were different in the cited studies, yet they demonstrated that milk PL significantly affects postprandial lipid metabolism

by lowering intestinal absorption of cholesterol and increasing its fecal excretion. These findings might be of clinical relevance but need to be further investigated.

MFGM AND BRAIN DEVELOPMENT AND FUNCTIONS

The World Health Organization recommends exclusive breastfeeding up to 6 mo of age and possible continued breastfeeding along with appropriate foods up to 2 yr for proper development (Kramer and Kakuma, 2012). However, at 6 mo postpartum more than 50% of infants are formula fed (CDC, 2013) and several reports indicated poorer cognitive development in formula-fed infants compared with breastfed ones (Binns et al., 2016; Martin et al., 2016). These differences might be related to varying concentrations of GD, PL, proteins, oligosaccharides, immunoglobulins, and lactoferrins in breast milk and their lack in formulas (Rueda et al., 1998; Martin et al., 2016). Gangliosides are found in plasma membrane of cells, but they are more abundant in the nervous system, involved in neurogenesis, neural repair, learning, and memory (Ledeen, 1978; Ryan et al., 2013). Phospholipids are an integral part of plasma membrane and play a major role in brain development (Küllenberg et al., 2012). Sphingomyelins (**SM**) in the neural cell are important for cell adhesion, interactions, modulation of membrane receptors, signal transduction, and axon myelination (Babin et al., 1993). Recently, the current mechanisms of dietary sphingolipids in neuroprotection and neurogenesis have been reviewed (Wang et al., 2020). Dietary supplementation with GD and PL may be a viable approach to promote brain development in formula-fed infants. Several studies investigated the effects of MFGM supplementation on brain development in infants and children (Table 2).

Development of myelination in brain starts rapidly after the first months and begins to decrease at 40 mo of age. It has been shown that myelination trajectories are associated with cognitive abilities and outcomes (O'Muircheartaigh et al., 2014; Deoni et al., 2016). Long-chain PUFA, choline, cholesterol, iron, zinc, PL, and SM are key components of the myelin sheath and play an essential role in myelination (Oshida et al., 2003; Saher et al., 2005; Hadley et al., 2016). Infant formula provides many of these nutrients, but their concentrations often vary considerably from human milk (Ballard and Morrow, 2013). Traditionally, most of the studies investigated the effect of nutrition on human infant brain myelination indirectly via cognitive performance or using evoked potentials (Pivik et al., 2007).

In an RCT of 64 newborn infants, the effects of MFGM supplementation on cognitive development were investigated (Gurnida et al., 2012). The infants received standard formula (control) or standard formula supplemented with MFGM ingredient (CML supplemented by gangliosides GD3, Anmum Infacare; 9 mg/100 g in the MFGM formula; 6 mg/100 g in the standard formula) from 2 to 8 wk to 24 wk of age with a reference group of exclusive breastfed infants. Cognitive testing was performed before and after intervention using the Griffiths Mental Development Scales (**GMDS**; Luiz et al., 2001). The GMDS assess the neurobehavioral development in children from birth to 8 yr and are applicable to different cultural groups and populations. The GMDS cover locomotor, personal–social, hearing and speech, eye and hand coordination, and performance. A general intelligence quotient (**IQ**; total scale) is produced from these 5 scores. Infants receiving the MFGM formula had higher serum GD3 levels and achieved higher hand-eye coordination, performance score and general IQ scores than those receiving the standard formula. There were no significant changes in body weight, length, and head circumstance between the groups, and GD3-supplemented infants were comparable to breastfed infants. The results indicate that the GD-supplemented formula may provide advantages in infants' cognitive developments. Tanaka et al. (2013) investigated in a pilot study the effects of a SM-enriched milk formula on cognitive and motor functions in low birth weight infants (<1,500 g; Tanaka et al., 2013). Twenty-four premature infants were nasogastrically fed either SM-fortified milk (SM 20% of milk PL, 200 mg) or a control formula (SM 13% of eggs PL, 200 mg) in addition to the breast milk, and a battery of neurobehavioral tests such as Bayley Scale of Infant Development II (**BSID-II**), Fagan test, and visual evoked potential test were performed up to 18 mo of age. The BSID-II mental scale assesses the child's age-appropriate level of cognitive, language, and personal and social development, whereas BSID-II motor scale evaluates fine and gross motor development. The Behavior Rating Scale (**BRS**) assesses orientation skills, such as interest, attention, and social skills. In the Fagan test, novel objects are shown, and a higher novelty preference rate indicates better intellectual development. Visual evoked potential measures neurotransmission speed via the optic nerve. The latency of 16-Hz pattern stimulation was measured to evaluate the level of axon myelinization. The BRS of the BSID-II, the Fagan test, and the latency of visual evoked potential were all significantly higher in infants fed with the milk SM formula compared with those fed with egg SM at 18 mo. The findings suggest that higher milk SM-enriched formula might improve development of low birth weight infants in executive and learning functions. The authors suggested that SM may be transformed into ceramide or other metabolites

in the intestinal tract, entering the systemic circulation and subsequently the CNS. Myelinated nerve fibers process the information significantly faster than unmyelinated nerve cells. Shortening of the latency in the visual evoked test indicates that SM supplementation may have promoted myelination and neurotransmitter production in the brain. The results are in agreement with studies in which feeding GD-enriched formulas improved cognition development in infants (Gurnida et al., 2012). These are pilot studies and a larger trial would need to verify their results, yet the positive effects, especially with SM, give hopes for a catch-up development of premature infants who would need to be fed with a formula.

In an RCT, 160 Swedish infants aged <2 mo received a standard formula (66 kcal, 1.27 g proteins/100 mL) or standard formula low in energy and proteins (60 kcal, 1.2 g proteins/100 mL) supplemented with MFGM (Lacprodan MFGM-10, Arla Foods Ingredients) daily until 6 mo of age (Timby et al., 2014). Growth and neurodevelopment were analyzed by BSID-III at 12 mo. The BSID-III measures the child's developmental progress and is an advance version of BSID-II. The MFGM group ingested larger volumes of formula than standard formula to compensate for the lower energy density. Changes in growth, body weight, and head circumference were similar in MFGM and standard formula groups. Cognitive scores in the MFGM-supplemented group were significantly higher compared with the standard formula and comparable to the breastfed infants. The authors suggested that MFGM supplementation to infant formula may shorten the cognitive performance gap between breastfed and formula-fed infants. Similar findings on neurodevelopment were reported with MFGM plus lactoferrin (**LF**) in 451 healthy Chinese infants in an RCT (Li et al., 2019a). Infants received a cow's milk-based control formula (Mead Johnson Nutrition) or MFGM (Lacprodan MFGM-10, Arla Food Ingredients) plus LF formula (similar formula with added whey protein-lipid concentrate 5 g/L and LF 0.6 g/L; Friesland Campina DMV) for 365 d (Li et al., 2019a). Formula feeding started after the delivery and neurodevelopment was analyzed at d 365 and 545 using BSID-III. Cognitive, language and motor test scores were higher in the MFGM formula than in the control group at 365 d (143–148 infants). However, at 545 d no differences were found in those tests among the 2 different groups, which might be due to fewer participants at the later time point (88–95 infants). In addition, the incidence of adverse respiratory events and diarrhea were significantly lower in the MFGM formula than in the control group (193 vs. 168 cases and 156 vs. 121, respectively). The study indicated that MFGM plus LF improved neurodevelopment in infants, but unfortunately no comparisons to breastfed infants could be done because such a group was not included in the study. In another study, 170 Spanish infants, age 0 to 2 mo, received a standard infant formula or an enriched formula (MFGM, fructooligosaccharides and inulin, *Bifidobacterium* and *Lactobacillus*, PUFA, GD, nucleotides, and sialic acid) until 18 mo of age (Nieto-Ruiz et al., 2019). Neurodevelopment was assessed using General Movement test at 2, 3, and 4 mo of age, and visual function was recorded by Cortical Visual Evoked Potentials at 3 and 12 mo of age. The General Movement test measures a series of gross movements of variable speed and amplitude involving all body parts by videotaping the infants. No differences in growth and neurodevelopment were found between the groups. The breastfed infants showed better visual function, indicating better neuron myelination (shorter latencies) and higher amplitudes of visual evoked potentials than standard formula or enriched formula. The responses to visual stimulus were improved in infants receiving enriched formula, and they showed improved responses similar to the breastfed infants at 12 mo of age, suggesting that brain maturation was improved in infants fed with enriched formula compared with standard formula and similar to breastfed infants. However, the study had limitations, with 35.9% dropouts at 18 mo follow-up, and breastfed infants were not randomized, in contrast to the formula-fed infants.

There are very few neuroimaging studies performed throughout infancy and early childhood, which are cross-sectional and rely on parental recall of infant feeding (Deoni et al., 2013; Luby et al., 2016). A longitudinal study investigated the trajectories of brain myelination and neurocognitive development in children either exclusively breastfed or fed with different formulas for at least 3 mo (Deoni et al., 2018). The infant formulas used were commercially available in the United States and contained different amounts of nutrients, long-chain PUFA, folic acid, PC, and SM. Children were scanned and given a cognitive assessment at 6-mo increments from time of recruitment until 2 yr of age, and yearly thereafter, using multicomponent relaxometry technique multicomponent driven equilibrium single pulse observation of T_1 and T_2 (**mcDESPOT**). The cognitive skills were evaluated using the Mullen Scales of Early Learning (**MSEL**; Dumont et al., 2000) in each child under 6 yr of age within 7 d of scanning. The MSEL provides domain-level assessment of fine and gross motor control, receptive and expressive language, and visual reception. Longitudinal growth curves of brain myelination were higher in all brain areas in breastfed than formula-fed children. Breast-

fed children exhibited a significant increase in early leaning, verbal and nonverbal development quotients compared with formula-fed children, indicating that cognitive maturation is associated with myelination. Specific formulas containing long-chain PUFA, choline, folic acid, and SM were significantly associated with the highest myelin levels and cognitive scores. The authors concluded that breastfeeding plays an important role in early neurodevelopment and infant formulas containing long-chain PUFA, PC, and SM may improve the myelin trajectory toward breastfed infants. However, the study was unable to answer which nutrient or combination is better associated with myelination. A variety of other factors such as socioeconomic status, parent–child interaction, and physical activity might have affected the outcome. In addition, the nutritional composition was analyzed at a single time, and nutritional formulation may have changed in the 6 yr.

The MFGM ingredients were also investigated in adult individuals for the neuronal and psychological effects. In young students, PL increased cognitive functions (Ladd et al., 1993). In aged individuals (53–72 yr old) and patients with the early phase of Alzheimer's disease, PS from bovine brain or soy significantly improved cognition and memory functions (Crook et al., 1991; Küllenberg et al., 2012). An RCT investigated the effect of milk PL rich in PS and SM on working memory, allostatic load and acute stress response in 46 healthy men (Hellhammer et al., 2010). The individuals received daily 325 mL of milk drink containing 13.5 g of milk PL (5% SM, 5% PC, 4% PE, 2.3% PS, and 1.5% PI) or placebo for 3 wk before breakfast. Working memory performance, psychological, and endocrine responses to the Trier social stress test were studied. The test mainly contained 10 min of anticipation and a 10-min test period in front of an audience, during which the subject delivered a free speech and performed mental arithmetic (Kirschbaum et al., 1993). The reaction time of working memory task was shorter with PL supplementation, and a higher stress load showed a blunted psychological stress response. The Trier social stress test induced a significant increase in plasma ACTH and cortisol, which did not differ between the groups, suggesting that PL slightly improved memory and could be more effective in dampening the endocrine stress response in participants with a higher stress load. Cortisol is well known to interfere with memory and cognitive performance (Lupien et al., 2007; Wolf, 2008). It has been suggested that PL-induced downregulation of cortisol is linked with memory improvements (Monteleone et al., 1992; Lupien et al., 2005).

In summary, in RCT, MFGM-supplemented infant formulas were associated with an increased neurodevelopment and less respiratory and gastrointestinal infections. These results are encouraging but preliminary; concentrations and components of MFGM were not standardized, nor are the molecular mechanisms of action known. Standardization and mechanistic studies in animals would be necessary to elucidate their molecular mechanisms and to further develop the clinical usage of MFGM, and more clinical trials needed to establish their usefulness on neurodevelopment.

MFGM AND FRAILTY

Frailty is one of the fast-growing concerns in our aging societies, with various risk factors such as physical inactivity, chronic diseases, and impaired cognitive functions playing pivotal roles (Raji et al., 2010; Collard et al., 2012). Frailty is defined as the presence of 3 or more components, including weight loss, muscle weakness, exhaustion, slow walking speed, and low physical activity (Fried et al., 2001). Physical activity reduces the risk of disability (Pahor et al., 2014; Ikenaga et al., 2017; Yamada and Arai, 2017) and improves mental health and quality of life (Song et al., 2014; White et al., 2017). A decline in motor function and physical activity is commonly observed in older adults (Kimura et al., 2012; Kose et al., 2016; Ikenaga et al., 2017), and reduced motor function may cause a decline in physical activity or vice versa. Maintaining skeletal muscle mass and its functions is a key factor in frailty prevention and extending the healthy life expectancy of older adults. Several studies reported that milk intake along with physical training increased protein synthesis in the muscles, promoting muscle mass and maintenance (Elliot et al., 2006; Wilkinson et al., 2007; Josse et al., 2010). Furthermore, many studies in athletes have shown beneficial effects of colostrum whey (Buckley et al., 2002; Mero et al., 2002). During the last 5 yr, the effects of MFGM supplements and physical activity for improving skeletal muscle mass and function in aged individuals have been investigated (Table 3).

A reduction in frailty was reported with MFGM plus exercise in 131 frail Japanese women (age $\geq$75 yr) in an RCT (Kim et al., 2015). The participants received daily 1 g of MFGM pills (33.3% PL; Megmilk Snow Brand Co.) or placebo pills of whole milk powder (0.286% PL; Meiji Milk Products Co. Ltd.) and exercise for 3 mo. Supervised exercises included balances, gait training, sequences from seated to standing positions and resistance and strengthening trials for 1 h twice a week. The frailty was assessed based on Fried's frailty phenotype, which includes weight loss, weakness, slow walking, exhaustion, and low physical activity (Fried et al., 2001). The MFGM supplementation plus exercise

significantly improved the frailty components exhaustion, physical activity, and walking speed. Frailty reversal rate and plasma IGF-1 were significantly higher in participants receiving MFGM plus exercise compared with MFGM or placebo alone. The authors suggested that MFGM supplementation with exercise can improve frailty status in older women. Similar findings were reported with MFGM on muscle strength and mass in 44 middle-aged individuals (aged 50–67 yr) in an RCT (Ota et al., 2015). Participants ingested 1 g/d either MFGM (from buttermilk) containing 18.4% PL or placebo tablet (whole milk powder) containing 0.322% PL for 10 wk and engaged in an exercise training program twice per week (supervised exercise for 1 h: walking, cycle training sessions, step tests). Stepping to both sides, muscle fiber conduction velocity (**MFCV**) and leg muscle cross-section areas were significantly increased in the MFGM-supplemented group compared with the placebo group. Another randomized controlled study in 22 healthy Japanese adults (60–73 yr) reported comparable results with MFGM plus exercise (Minegishi et al., 2016). The participants received MFGM 1 g tablets/d containing 33.3% PL or placebo tablets from whole milk powder containing 0.286% PL and participated in light exercise programs twice weekly for 10 wk. Physical function tests, MRI, and surface electromyography for MFCV were performed at the baseline and after 5 and 10 wk of the study. The MFGM supplementation improved the chair test time (repeated standing and sitting), leg muscle cross-section area, and increased MFCV compared with baseline, but not in the placebo group. In another trial, 71 adult individuals (aged 72 yr) participated in light rhythmic exercises, supplemented with 1 g of MFGM containing 16% PL or placebo (whole milk powder) tablet containing 0.322% PL daily for 8 wk (Yoshinaka et al., 2018). Rhythmic gymnastics exercises were performed daily at home, consisting of arm and leg trainings and multiple body part movements. In the MFGM group, foot tapping, and open-close stepping scores were significantly increased from baseline to 8 wk. Recently, effects of a MFGM supplement and exercise on walking parameters were investigated in Japanese women in a 3-mo RCT (Kim et al., 2019). The participants (≥75 yr) were divided into 4 groups: exercise plus 1 g of MFGM (Megmilk Snow Brand Co. Ltd.), exercise (60 min twice weekly) plus placebo (Meiji Milk Products Co. Ltd.), 1 g of MFGM, and placebo. The exercise consisted of warming up, balance and gait training, stepping, chair exercise, and resistance band exercises. After 3 mo, walking speed and stride improved significantly in both exercise groups. Foot progression angles decreased in the exercise, but not in the MFGM or placebo group. The authors concluded that rhythmic exercise improved walking speed, due to improvements in stride and foot progression angle. However, they did not find any significant additive effects of MFGM on exercise. Various factors could have affected the outcome with MFGM in this study, such as the age of the participants or decline of their walking ability; about 64.7% of people had a history knee osteoarthritis, and 60.0% of those were undergoing knee osteoarthritis treatment. In contrast to the above findings, 113 healthy Japanese adults (50–70 yr) took 1 g of MFGM or placebo without any mandatory exercise, and muscle strength, agility, and balance were tested every 6 wk for 24 wk (Kokai et al., 2018). The compositions of MFGM and placebo tablets were similar to the results of a previous study by Ota et al. (2015). The MFGM improved balance without any mandatory exercise in a community-dwelling Japanese adult. However, the effects of MFGM on muscle strength and agility were not different compared with controls, which could be due to healthy participants and gender ratio.

In the present aging societies, the increase in frailty must be slowed to enable a healthy aging. The abovementioned studies shed some hope that MFGM supplementation might improve neural and ambulatory functions, yet the number of studies in this area are too few with encouraging results. More studies with similar MFGM are necessary.

MFGM SAFETY

The safety of 2 MFGM formulas (MFGM-L and MFGM-P) were investigated in 119 healthy infants aged <14 d in a randomized controlled noninferiority trial (Billeaud et al., 2014). The standard infant formula (PL 220 mg/L and SM 58 mg/L; NAN 1 Néstle Nutrition) was enriched with a bovine-derived lipid-rich MFGM fraction MFGM-L (PL 647 mg/L and SM 141 mg/L; Fonterra Group) or bovine-derived protein-rich MFGM fraction MFGM-P (PL 452 mg/L and SM 106 mg per L; Lacprodan MFGM-10, Arla Foods). The formulas were administered for 14 wk, keeping weight gain with noninferiority margin of 3 g/d. Both MFGM formulas were well tolerated, with no differences seen in parents' reports of vomiting, spitting up, fussing, crying, and colic, and overall adverse event reports did not reveal any major safety concerns. Both MFGM formulas had similar weight gains, but eczema incidence was significantly higher with protein-rich fraction Lacproan MFGM-10 than in the control group (10 vs. 2 cases). However, no eczema risk was reported in a separate clinical trial with MFGM-P fraction added to formula for infants between less than 2 mo and 6 mo of age (Timby et al., 2014). This variation could be due to its short duration and small sample size, as well as the

unequal allocation of participants among groups. The safety of MFGM pills (Megmilk Snow Brand Co.) was evaluated in healthy individuals by increasing 5 times the daily intake (6.5 g of MFGM) for 4 wk (Hari et al., 2015). No clinically significant changes in anthropometric measurements and blood tests were observed with higher amount of MFGM, indicating that MFGM is safe even with higher doses.

SUMMARY

The MFGM ingredients have been shown to be well tolerated across the life span (Billeaud et al., 2014; Hari et al., 2015). In infants and children, supplementation of MFGM containing phospholipids, sphingomyelins, gangliosides, sialic acid, PUFA, choline, or whey proteins shortened diarrhea and infections and improved growth and cognitive development. In adults, administrations of variable phospholipid amounts demonstrated beneficial health effects on metabolic parameters with decreased circulating LDL-C, total cholesterol, and triglycerides. The decrease in cholesterol appeared to be associated with the fecal loss of cholesterol metabolites. Administration of MFGM ingredients improved insulin sensitivity by decreasing plasma insulin in some of the studies but not all. Dairy fat (milk, yogurt, cheese, butter, and cream) for 4 d found significant associations between dairy-originated PL metabolites (lyso-PC) and insulin sensitivity (Nestel et al., 2014), demonstrating that dairy-derived PL metabolites improved cardiometabolic health. For prevention of cardiometabolic diseases in clinical studies, higher MFGM standardized concentrations may be needed. Yet, most of the studies did not describe the preparation of MFGM nor their ingredients, and the authors used commercial products, which did not describe the processing details of MFGM ingredients. In frail individuals, MFGM supplementation together with supervised exercises demonstrated significant improvements in walking speed, leg muscle mass, and muscle fiber velocity. To the best of our knowledge, no studies reported, the effects of MFGM ingredients on physical activity in young adults or in athletes.

The large intervention studies across the life span demonstrate clear beneficial health effects of MFGM ingredients in humans, but the mechanisms are still not known. Furthermore, sources, production, concentrations, and components of MFGM are not standardized (Brink et al., 2020), which make the comparison of the different clinical studies challenging. As outlined in the different studies summarized in the tables, MFGM have beneficial effects on different organ systems and might improve healthy aging, but more RCT and standardized MFGM compounds would be necessary.

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