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Nutritional programming in early life: the role of dietary lipid quality for future health☆

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Abstract – Worldwide, overweight and obesity have increased dramatically, not only in high income countries. Clearly, unhealthy diets and sedentary lifestyle are important drivers of the increased obesity rates, but increasing evidence indicates that the vulnerability for later life non-communicable diseases is set during the first 1000 days, the period from conception until 2 years of age. The growth during this period is faster than during any other period in life. Dietary fats provide energy for growth, but also supply essential fatty acid (FA) precursors for long chain polyunsaturated FA that are building blocks and signals for adipose tissue development. Both epidemiological and experimental data support the notion that specific improvements in dietary fat quality, *e.g.* specific changes in the fatty acid composition as well as the structural organization of dietary lipids, may reduce the risk of obesity and other adverse outcomes in later life, but clinical evidence is limited and largely inconclusive. We anticipate that effects of such relatively small improvements in nutrient quality may be difficult to measure on the short term and have limited impact in healthy children. However, for children that already experience challenging conditions in the womb and have a higher risk profile based on deviations in birthweight and postnatal growth, the potential protective effects of improved dietary lipid quality in early life could be more substantial. Results from randomized clinical studies testing improved lipid quality concepts will help to develop specific strategies to adapt infant nutrition based on the need with the aim to improve long term outcomes.

Keywords: LA-ALA ratio / fatty acid composition / dietary fat structure / metabolic programming / obesity risk

Résumé – Programmation nutritionnelle en début de vie : le rôle de la qualité des lipides alimentaires pour la santé future. Au niveau mondial, la fréquence du surpoids et de l'obésité a augmenté de façon spectaculaire, et pas seulement dans les pays à hauts revenus. Il est clair que les régimes alimentaires déséquilibrés et la sédentarité sont des facteurs importants de ces augmentations, mais des preuves de plus en plus nombreuses indiquent que la vulnérabilité aux maladies non transmissibles à un âge plus avancé se détermine durant les 1000 premiers jours de la vie, c'est-à-dire la période allant de la conception à l'âge de 2 ans. La croissance pendant cette période est plus rapide que pendant toute autre période de la vie. Les graisses alimentaires fournissent l'énergie nécessaire à la croissance, mais aussi des précurseurs d'acides gras (AG) essentiels pour les AG polyinsaturés à longue chaîne qui sont des éléments constitutifs et des signaux pour le développement du tissu adipeux. Les données épidémiologiques et expérimentales confirment l'idée que des améliorations spécifiques de la qualité des graisses alimentaires, par exemple des modifications spécifiques de leur composition en acides gras ainsi que de leur organisation structurelle, peuvent réduire le risque d'obésité ainsi que d'autres effets néfastes pour la santé à un âge avancé, mais les preuves cliniques sont limitées et très peu concluantes. Il est à envisager que les effets de faible intensité de ces améliorations de la qualité des nutriments pourraient être difficiles à mesurer à court terme et donc avoir un impact limité sur les enfants en bonne santé. Toutefois, pour les enfants qui connaissent déjà des conditions difficiles *in utero* et qui peuvent présenter un profil de risque beaucoup plus élevé en raison des écarts de poids à la naissance et de croissance postnatale, les effets protecteurs potentiels d'une amélioration de la qualité des lipides alimentaires en début de vie pourraient être plus importants. Les résultats d'études

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cliniques randomisées testant les concepts d'une meilleure qualité lipidique aideront à développer des stratégies spécifiques pour adapter l'alimentation des nourrissons en fonction des besoins, dans l'objectif d'améliorer les résultats à long terme.

Mots clés : rapport LA-ALA / composition en acides gras / structure des graisses alimentaires / programmation métabolique / risque d'obésité

1 Early life, obesity & non-communicable disease

Obesity poses a global economic and health burden due to high medical costs, loss of productivity and loss of health-related quality of life (Wang *et al.*, 2011; OECD report, 2019). Obesity increasingly emerges at an early age, and the prevalence of childhood obesity is increasing worldwide (Jackson-Leach and Lobstein, 2006). In 2010, 43 million children under the age of 5 were overweight or obese and numbers are expected to increase to 60 million by the year 2020 (De Onis *et al.*, 2010; WHO Fact Sheet Obesity & Overweight, 2012; NCD Risk Factor Collaboration (NCD-RisC), 2017). This is particularly alarming because early onset obesity is strongly associated with adult obesity risk (Lobstein *et al.*, 2004) and with early onset and more severe metabolic disease (Lobstein and Jackson-Leach, 2006).

Excess intake of energy-dense foods and sedentary lifestyle are considered the two most important contributors to the energy imbalance underlying obesity (Nishida *et al.*, 2004, Crombie *et al.*, 2009). However, neither contemporary lifestyle factors nor established genetic factors can fully explain the rapid increase in (childhood) obesity over the past few decades (Eisenmann, 2006; Crombie *et al.*, 2009). Early life environmental factors have been suggested to contribute to (childhood) obesity including pharmaceutical agents, endocrine disruptors, reduced sleep duration and nutrition (McAllister *et al.*, 2009). Since weight management programs show only moderate and short term effectiveness (Bond *et al.*, 2009), prevention is key.

2 Programming later health

The Developmental Origins of Adult Health and Disease (DOHaD) concept originated from the "fetal origins of adult health" hypothesis. This notion was based on the observation that low birth weight, suggested as a proxy for impaired fetal growth, was associated with increased mortality due to ischemic heart disease at middle age (Barker *et al.*, 1989). Since then, many epidemiological and experimental studies confirmed that nutritional disturbances during critical periods of early life development predispose to obesity and metabolic disease later in life (Barker *et al.*, 1993; Uvena-Celebrezze *et al.*, 2002; Ehrenberg *et al.*, 2004; Gluckman *et al.*, 2005, 2007; Lillycrop *et al.*, 2005; Hernandez-Valencia and Patti, 2006; Lambin *et al.*, 2007; Taylor and Poston, 2007; Godfrey *et al.*, 2010; Schwarzenberg *et al.*, 2018). Current thinking is that developmental adaptations to nutritional signals are a normal part of development in anticipation of the future (nutritional) environment. Consequently, a specific genotype can generate a variety of different phenotypes depending on environmental cues during critical periods of development, *i.e.* periods of developmental plasticity. Adaptation can only be induced during these critical periods and changes in phenotype are considered irreversible when the period of developmental plasticity ends (McMillen and Robinson, 2005).

It has become increasingly acknowledged that the window for programming extends into the (early) postnatal period (Singhal and Lucas, 2004; Guilloteau *et al.*, 2009; Symonds *et al.*, 2009). Observational studies investigating postnatal growth velocity provide evidence that the period after birth can be considered a critical window of plasticity, independent of the prenatal period. A meta-analysis of individual-level data of more than 47 thousand individuals from 10 cohort studies showed independent positive association of weight gain in the first year of life with childhood obesity (Druet *et al.*, 2011). Postnatal growth velocity across all birth weight tertiles predicted abdominal adiposity at 2 years of age in a prospective birth cohort (Durmus *et al.*, 2010) and enhanced postnatal weight gain rather than birth weight was strongly associated with abdominal fat mass in a pediatric obese population (Wells *et al.*, 2011).

Although the timing of this critical period for individual organs is not fully clarified, the development of many (metabolic) organs including gastrointestinal tract (Le Huerou-Luron *et al.*, 2010), brain (Alamy and Bengelloun, 2012), pancreas (Fowden and Hill, 2001) and adipose tissue (Symonds *et al.*, 2010; Hauner *et al.*, 2013) continues for a considerable time after birth.

Several mechanisms, including (irreversible) changes in organ and tissue structure, epigenetic regulation of gene expression, altered set-points for homeostatic neuroendocrine systems and changes in cellular mitochondrial capacity may contribute to these long term effects of early life nutritional programming (Godfrey *et al.*, 2011; Waterland, 2014).

3 Breast feeding & obesity risk

Epidemiological studies indicate that breastfeeding is associated with a moderately reduced risk of later life obesity and metabolic disease (Fall *et al.*, 1992; Owen *et al.*, 2006, 2008; Ryan, 2007). Specifically longer duration (> 6 months) of breastfeeding is associated with a reduced risk of childhood obesity (Harder *et al.*, 2005). It has been hypothesized that the reduced growth velocity of breastfed (BF) infants compared to formula fed (FF) infants might underlie the reduced obesity risk (Gale *et al.*, 2012). The PIAMA birth cohort showed that infants who were BF for more than 16 weeks had a lower Body Mass Index (BMI) at 1 year of age, suggesting slower growth, compared to FF infants. BMI at 1 year of age was positively associated with BMI at 7 years of age (Scholtens *et al.*, 2007). A systematic review and meta-analysis by Gale and colleagues showed that differences in weight gain between BF and FF were accompanied by differences in body composition trajectories (Gale *et al.*, 2012). BF infants had lower lean body mass throughout infancy compared to FF infants, whereas fat mass was higher before 6 months of age but lower

between 6 and 12 months of age. Additionally, breastfeeding for more than 4 months was associated with lower visceral adiposity at 2 years of age (Durmus *et al.*, 2011). Long-term implications of these different growth trajectories remain to be elucidated, but the reduced growth velocity and altered lean and fat mass development are compatible with a better "quality of growth" in BF infants, resulting in less deposition of visceral adipose tissue.

Many other factors associated with infant feeding have been suggested to contribute to obesity risk, including milk volume and intake patterns, timing of weaning, energy density, protein content, n-6/n-3 PUFA content and bioactive compounds such as leptin, ghrelin and adiponectin (Bartok and Ventura, 2009; Thompson, 2012). It should be noted, however, that the contribution of these factors to obesity risk has often been extrapolated from their effects on early growth trajectories rather than clearly demonstrated through direct association with (childhood) obesity or through intervention studies. Clearly, since almost all of the studies examining the association between breast feeding and later outcomes are observational, there is a high risk of confounding by socioeconomic and other environmental circumstances. For instance, the choice to breast feed exclusively and/or for longer duration is strongly influenced by maternal education level.

4 Dietary lipids in early life

Human Milk (HM) lipid content and composition is affected by maternal diet and body composition, stage of lactation (colostrum, transitional or mature milk), interval between feeds during 24 h and volume ingested per feed, but even changes during a single feed (fore- versus hind-milk) (Emmett and Rogers, 1997; Mitoulas *et al.*, 2002; Minda *et al.*, 2004; Carlson and Colombo, 2016; van de Heijning *et al.*, 2017).

The average lipid content of mature milk is 39 g/L, but can vary between 25 and 59 g/L. HM lipid globules comprise of a core consisting of triglycerides and cholesteryl-esters surrounded by a native biological membrane composed mainly of phospholipids, proteins and enzymes, free cholesterol and glycoproteins. The lipid globule size ranges between 1 and 10 μm. HM contains between 0.1 and 0.35 g/L cholesterol and between 0.1 and 0.4 g/L phospholipids (Koletzko *et al.*, 2001, 2005; Michalski *et al.*, 2005; Gallier *et al.*, 2015). In contrast, the lipid composition in Infant Milk Formula (IMF) is maintained constant and uniform to adhere to (inter)national legislation (see EU Commission Directive, 2006) (Innis, 1992, 2007; Koletzko *et al.*, 2005). IMF encompasses small lipid globules triglycerides with milk proteins adhering to the globule surface and the majority of the lipid content is comprised of triglycerides (Gallier *et al.*, 2015; Bourlieu *et al.*, 2017).

During the first 4–6 months of life, HM (or IMF) is the sole source of nutrition for the infant. Both provide 40–55% energy as fat. Dietary fats provide energy for growth, supply the essential fatty acids (EFA) linoleic acid (LA; C18:2 n-6) and α-linolenic acid (ALA; C18:3 n-3), and ensure adequate absorption of the fat-soluble vitamins required for a healthy growth and development. EFA play an important role in growth and development during the last months of gestation and the first months of postnatal life (Innis, 1991; Koletzko *et al.*, 2008). Between 6 months and 2 years of age, the WHO recommends 30–40% energy from fat, although it has been suggested that the energy derived from fat should be gradually reduced to maximal 30% to better match energy requirements and reduce weight gain velocity according to new WHO reference growth standards (Uauy and Dangour, 2009).

The LA and ALA coming from the diet (Le *et al.*, 2009) need to be converted to 20 to 22-carbon long chain polyunsaturated fatty acids (LC-PUFA) by (delta-5 and delta-6) desaturases and elongases (Guillou *et al.*, 2009). Because LA and ALA compete for the same set of enzymes, the absolute amount of dietary EFA as well as the n-6/n-3 ratio determines the relative abundance of the LCPs arachidonic acid (ARA; C20:4 n-6) and docahexanoic acid (DHA, C22:6 n-3) and their incorporation in biological membranes (Jensen *et al.*, 1997; Makrides *et al.*, 2000), as well as the ARA and n-3 eicosapentaenoic acid (EPA; C22:6 n-3) derived eicosanoid metabolites (Broughton and Wade, 2002). LC-PUFAs can be considered conditionally essential during this period of rapid growth, because synthesis capacity may be too limited to obtain tissue LC-PUFA levels as high as found in infants fed preformed DHA and ARA (Salem *et al.*, 1996; Fleith and Clandinin, 2005; Brenna *et al.*, 2009).

The European Food Safety Authority (EFSA) set adequate nutrient intakes of LC-PUFA for infants from birth to 6 months at 100 mg DHA/day and 140 mg ARA/day (EFSA Scientific Opinion, 2013), supported by a systematic review of the available scientific evidence (Koletzko *et al.*, 2014). However, according to the latest adopted European Union compositional requirements, all infant and follow-on formula should contain relatively high amounts of 20–50 mg DHA/100 kcal (approximately 0.5–1% of FA), but providing ARA is no longer considered necessary, thus allowing levels that are significantly deviating from levels typically found in human milk. To preserve in vivo conversion of the precursors LA and ALA to their respective LC-PUFAs, minimal LA addition levels were increased, whereas ALA addition levels were set lower resulting in a clearly higher LA/ALA ratio than before without a maximum (*e.g.* range n6/n3 set to 5–15 previously) (EFSA Scientific Opinion, 2014). These changes in the recommendations are a topic of fierce scientific debate based on the scarcity of data to support these directions (Delplanque *et al.*, 2015; Koletzko *et al.*, 2015). A recently published position paper of the European Academy of Paediatrics and Child Health Foundation strongly advocates addition of ARA to similar levels as DHA and highlights the need for well designed clinical studies to evaluate optimal intakes of DHA and AA based on relevant outcomes including safety (Koletzko *et al.*, 2020).

As indicated earlier, the IMF recommendations are based on the composition of HM. However, changes in food processing, sourcing of dietary lipids and dietary intake patterns have resulted in a global contemporary increase in exposure to dietary LA and a decrease in n-3 LC-PUFA over the last decades (Sanders, 2000; Wolmarans, 2009; Blasbalg *et al.*, 2011; Guyenet and Carlson, 2015; Wood *et al.*, 2015) also considerably affecting HM FA composition (Ailhaud *et al.*, 2006; Gibson *et al.*, 2011). The net result is a higher dietary (and HM) n-6/n-3 ratio, which has been hypothesized to contribute to the pathogenesis of cardiovascular disease, cancer, inflammatory and auto-immune diseases (Hibbeln *et al.*, 2006; Simopoulos, 2008; Ramsden *et al.*, 2013).

5 Dietary lipid composition and adipose tissue development

Ailhaud and colleagues hypothesized that the contemporary high dietary LA intake and the concomitant increased n-6/n-3 ratio, is a key determinant in obesity development (Ailhaud and Guesnet, 2004; Ailhaud *et al.*, 2006; Massiera *et al.*, 2006, 2010). The proposed underlying mechanism includes the stimulatory effect of high ARA, synthesized from dietary LA, on adipose tissue expansion through enhanced adipogenesis and lipogenesis especially during early development (Massiera *et al.*, 2003, 2006, 2010; Muhlhausler and Ailhaud, 2012).

Adipose tissue growth is regulated by the concerted actions of several transcription factors such as peroxisome proliferator-activated receptor γ (PPARγ γ), which heterodimerizes upon activation with retinoid X receptor α (RXRα), and the CCAAT/enhancer binding protein (C/EBP) family members (Darlington *et al.*, 1998; Berger and Moller, 2002). N-6 and n-3 polyunsaturated fatty acids (PUFA) and their eicosanoid metabolites act as endogenous PPAR ligands (Waku *et al.*, 2009), enabling sensing of nutritional signals and translating these into a metabolic response to maintain homeostasis. ARA is a precursor of prostacyclin, a very potent adipogenic factor (Massiera *et al.*, 2003). After its release from preadipocytes, prostacyclin binds to its receptor, which activates the protein kinase A pathway through cAMP production, thereby enhancing C/EBPβ and C/EBPδ expression (Madsen *et al.*, 2005, 2008; Ailhaud *et al.*, 2006). N-3 LCPs EPA and to a lesser extent DHA, inhibit ARA effects on cAMP production and can thereby counteract pro-adipogenic effects of ARA. Apart from adipogenesis, n-3 and n-6 LC-PUFAs have differential effects on transcription factors involved in white adipose tissue (WAT) lipogenesis with n-3 inhibiting and n-6 PUFA stimulating expression of lipogenic transcription factors (Muhlhausler *et al.*, 2010a). Although PUFAs could exert their effects on WAT transcription factors throughout life, early life exposure may enhance their effects due to the high capacity of adipocyte precursors to proliferate and differentiate in this period (Hauner *et al.*, 2013). Moreover, early LC-PUFA exposure may program lipogenic genes towards enhanced expression, for instance through modulation of DNA-methylation (Milagro *et al.*, 2013).

6 Dietary FA composition in early life & later obesity risk

Based on the notion that a high dietary n-6/n-3 ratio may contribute to the current obesity incidence, changing dietary FA quality, reaching a level and composition closer to ancient diets (Kuipers *et al.*, 2005; Muskiet *et al.*, 2006), might decrease obesity risk. Preclinical studies in mice showed that early postnatal exposure to a diet containing identical levels of fat but containing either more n-3 LC-PUFA (5% of total fatty acid content) or a 50% reduction in LA content, both effectively decreasing the total n-6/n-3 ratio, protected against excessive fat accumulation in response to a mild western style diet challenge in adulthood (Oosting *et al.*, 2010, 2015a). These two manipulations in early life in the dietary PUFA composition resulted in a comparable reduction in fat accumulation: 30% (n-3 LC-PUFA increase) and 27% (LA reduction) respectively. Possible effect size of such dietary manipulations may be very different in humans but warrant further research since a 5% reduction in body fat percentage already improves cardio-metabolic risk profile in obese children (Going *et al.*, 2011).

Although these mouse studies demonstrated that both increased postnatal n-3 LC-PUFA or reduced LA decreased adult fat accumulation following an western diet challenge, the mechanisms by which these diets decreased adult obesity risk are likely different. Supplementation with the n-3 enriched diet resulted in reduced fat mass and smaller adipocytes (Oosting *et al.*, 2010), supporting altered homeostatic control of lipid metabolism resulting in enhanced lipolysis or reduced lipogenesis (Kopecky *et al.*, 2009). Lowering the relative contribution of n-6 LA to the diet, however, increased adipocyte size and showed a trend towards a lower adipocyte number (Oosting *et al.*, 2015a), suggesting a reduction in preadipocyte differentiation (adipogenesis) and thereby decreasing longer term lipid storage capacity. In addition, other mechanisms may contribute to the observed effects. The reduced fat accumulation, despite enhanced adult food intake in mice fed the low LA diet (Oosting *et al.*, 2015a), suggest programming effects on adult energy partitioning and feed efficiency. In line with this suggestion, a fat balance study in mice showed that LA tended towards enhanced energy storage in WAT and towards a lower energy expenditure compared to saturated fatty acids, n-3 PUFA or conjugated LA (Javadi *et al.*, 2004). Additionally, altered hypothalamic regulation of energy homeostasis could also play a role, considering the lipid sensing ability of the hypothalamus (Pocai *et al.*, 2006; Avram *et al.*, 2007). Indeed, in a separate study we showed that both reducing LA and increasing n-3 LCP reduced the outgrowth of orexogenic and anorexogenic neuronal projections in the developing hypothalamus with potential consequences for the central regulation of satiety and energy (Schipper *et al.*, 2013).

Our data suggest that the balance of n-6 and n-3 EFA and LC-PUFAs in the early postnatal diet is relevant for the observed programming effects on adult obesity development in mice and rats. The net balance of n-6 and n-3 PUFA in tissues is determined by dietary intake of LA and ALA and the respective LC-PUFAs produced, knowing that the enzymes for conversion of LA and ALA are shared, and dietary LC-PUFAs inhibit endogenous LC-PUFA synthesis. Consequently, supplementation of ALA to a high LA diet may have very limited effects on n-3 LC-PUFA status and metabolic health, because LA inhibits both n-3 LC-PUFA synthesis from ALA and its incorporation in biological membranes (Gibson *et al.*, 2011, 2013). Apart from the n-6/n-3 balance, absolute amounts of LA and ALA are important, as high amounts of LA can inhibit ALA conversion to EPA irrespective of the relative dietary LA/ALA ratio (Goyens *et al.*, 2006). In addition, the total dietary fat content modulates the PUFA effects. N-3 LC-PUFA concentrations ranging from 0 to 1.5%wt combined with fat content ranging from 5 to 20%wt of total diet under a constant LA concentration result in differential patterns of ARA derived eicosanoids in mice (Broughton and Wade, 2002). These data support the notion that adipogenic, lipogenic and proinflammatory effects of ARA and its eicosanoid metabolites are modulated by total fat content and n-3 LC-PUFA abundance (Broughton and Wade, 2002; Ailhaud *et al.*, 2006; Muhlhausler *et al.*, 2010a). Finally, also the macronutrient

composition of the diet may modulate adipogenic effects of ARA during early development. The combination of high LA with high sucrose (43%wt) was pro-adipogenic, whereas the combination of high LA and high protein (50%wt) was anti-adipogenic in adult mice (Madsen *et al.*, 2008).

Taken together, these data indicate that (programming) effects of early life PUFAs as demonstrated in rodent models depend on overall dietary EFA and LC-PUFA content and ratio, total dietary fat content and overall macronutrient composition, which may explain some of the ambiguous results from the few animal and human intervention studies that have investigated metabolic programming by dietary lipids.

7 Dietary physical lipid structure in early life & later obesity risk and metabolic health

Apart from FA composition, the physical structure of dietary lipids in HM can be considered a key feature of early life dietary lipid quality. We have shown that exposure of preweaning mice to a diet containing a physical lipid structure closer to that of HM, *i.e.* with an increased lipid droplet size and a phospholipid (PL) coating (Nuturis®, Gallier *et al.*, 2015) protected against excessive fat mass accumulation in adolescence and young adulthood (Oosting *et al.*, 2012, 2014; Baars *et al.*, 2016) although effects may decrease and disappear after longer HFD exposure (Oosting *et al.*, 2012; Ronda *et al.*, 2019). The effect size of this programming diet on body composition was in fact comparable to those resulting from the adjustments in early life PUFA composition (Oosting *et al.*, 2010, 2015a), namely 30% lower adult fat mass after feeding Nuturis® compared to a standard IMF based diet.

The underlying mechanism of this so called "lipid matrix" effect remains elusive to some extent. Postnatal exposure to the altered physical lipid structure had sustained effects on adipocyte size, indicating programming towards reduced lipid and storage. This notion was supported by reduced expression of lipogenic transcription factors in adulthood (Oosting *et al.*, 2014) as well as enhanced gene and protein expression of specific mitochondrial oxidative capacity markers, indicative of increased substrate oxidation in white adipose tissue and skeletal muscle (Kodde *et al.*, 2017). These results suggest that the physical lipid structure may have modulated the homeostatic set point of adipocyte lipid metabolism, thereby limiting lipid storage. Alternatively, as suggested for n-6 and n-3 PUFAs, lipid structure may have programmed adult energy partitioning and feed efficiency towards enhanced energy expenditure for instance due to higher basal metabolic rate or enhanced heat production. Indeed, experimental studies showed that physical properties of dietary lipids, including lipid droplet size and surface composition, modulate acute absorption and digestion kinetics as well as metabolic fate of lipids (Michalski *et al.*, 2013; Bourlieu *et al.*, 2017). For instance, small lipid droplets are hydrolyzed faster, but also delay gastric emptying compared to larger lipid droplets in healthy adults. In contrast, large lipid droplets with a native milk fat globule membrane (MFGM) on the lipid/water interface are hydrolyzed faster than small droplets with proteins on the interface in preterm infants. In adult rats, large MFGM coated lipid droplets decreased plasma triglyceride appearance and increased β-oxidation compared to small droplets with proteins at the interface (Michalski *et al.*, 2013). Taken together, these data indicate that differences in lipid digestion and absorption may preferentially target lipids towards either β-oxidation or storage in WAT. However, data on in vivo lipid digestion and absorption kinetics are scarce and apart from the studies mentioned above, little is known about the effect of physical lipid structure on utilization of dietary lipids. Whether the effects found in human adults and adult rodents are applicable to infants is presently unknown since absorption and digestion kinetics differ between infants and adults due to immaturity of the infant digestive system (Armand *et al.*, 1996; Abrahamse *et al.*, 2012; Bourlieu *et al.*, 2015; Baumgartner *et al.*, 2017). An exploratory study in healthy 8-week old infants did indicate some distinct differences in postprandial kinetics between HM and IMF (Teller *et al.*, 2017). If and how differences in absorption and digestion kinetics may contribute to the programming effects as observed in the mouse studies is topic of further research. It is tempting to speculate that differential postprandial FA kinetics and bioavailability due to the physical lipid structure modulates the functional development of metabolic organs during the postnatal period of plasticity, affecting later life obesity risk. Future studies dedicated to measurement of energy balance, nutrient partitioning and feed efficiency are pivotal to determine the potential value of these initial findings.

8 Critical periods in mice and men

The contribution of lipids in HM to later cardiometabolic outcomes has not been investigated in great depth apart from studies focusing on correlations between milk ARA and DHA content and body composition in (early) childhood. These studies have provided conflicting data on association between HM DHA and/or ARA and childhood adiposity (Muhlhausler *et al.*, 2010a, b, 2016; Innis, 2011; Pedersen *et al.*, 2012; van Rossem *et al.*, 2012; Hauner *et al.*, 2013). The few randomized clinical trials that have been performed, with focus on supplementing n-3 LC-PUFA during pregnancy and/or lactation, investigating later life body mass index and fat mass show inconsistent results (Muhlhausler *et al.*, 2010a, b, 2016; Hauner *et al.*, 2013; Vinding *et al.*, 2018). These inconsistencies could be due to the focus on and differences in dose, timing and duration of n-3 LC-PUFA supplementation and background diet including LA and ALA intake levels and the n6/n3 ratio in case of maternal interventions and/or use of BMI as indirect growth variable rather than actual body composition measurements (Muhlhausler *et al.*, 2010b; 2011; Rodriguez *et al.*, 2012; Hauner *et al.*, 2013; Vinding *et al.*, 2018). Differences in sociodemographic variables, number of recruited subjects, different age at the time of measurement and the lack of precise techniques to measure body composition probably also limits the power of these studies. In addition, most of these studies were performed in healthy subjects who may be too resilient to current environmental challenges to have an increased disease risk and reveal any (in)adequate nutritional programming. Obviously, if the later life environment is relatively healthy and does not challenge the system, for instance by means of high fat feeding and/or sedentary lifestyle, adverse early life nutritional programming may not (yet) become manifest. Indeed, several experimental studies

have shown that an adverse phenotype due to perinatal malnutrition only became apparent after exposure to an obesogenic adult environment (Bayol *et al.*, 2005; Velkoska *et al.*, 2005; Souza-Mello *et al.*, 2007; Oosting *et al.*, 2010, 2012).

Lipid quality in early life may be particularly critical in individuals with an increased obesity risk due to their prenatal environment. Prenatal factors predisposing to later life obesity include maternal obesity, unbalanced diet, smoking, gestational diabetes, gestational weight gain and psychosocial stress (Liao *et al.*, 2019). Nutritional quality of the early postnatal diet could (partially) alleviate detrimental effects of an adverse prenatal environment. The few n-3 LC-PUFA programming studies performed in animal models (as reviewed in Muhlhausler *et al.*, 2011) support the notion that n-3 LC-PUFA may ameliorate unfavorable metabolic outcome due to an adverse perinatal environment, *i.e.* fetal dexamethasone exposure or neonatal overfeeding (Wyrwoll *et al.*, 2006; Hou *et al.*, 2012; Hidaka *et al.*, 2018; Kerling *et al.*, 2019). Indeed, we recently showed that an early diet containing large, PL coated lipids droplets (Nuturis®, Gallier *et al.*, 2015) in early life improved long term metabolic outcomes in growth restricted rats when challenged with a western style diet later in life (Teller *et al.*, 2018). Clinical studies investigating the role of n-3 LC-PUFAs in growth and brain development also support this notion: n-3 LC-PUFA supplementation is consistently effective in preterm or small-for-gestational-age infants whereas effects in healthy term infants are less evident (Fleith and Clandinin, 2005; Makrides *et al.*, 2011).

When extrapolating findings in mouse models to human development one needs to take into account that rodents are born relatively immature compared humans. Humans are born with a mature hypothalamus-pituitary-adrenal (HPA) axis, important in regulation of adipose tissue development, which starts in the third trimester of gestation (Kuzawa, 1998). In rodents, WAT development starts after birth and coincides with maturation of the HPA axis in the first two weeks of life (Schmitz and Ecker, 2008). Based on these species comparisons, it seems reasonable to assume that the PUFA interventions in our rodent studies starting at postnatal day (PN) 2 can correspond to a nutritional intervention during late gestation in humans continuing into early postnatal life as we extended the diet intervention even beyond weaning of the pups. Effectiveness of moderate FA composition changes for humans may therefore not only depend on postnatal but also on late fetal nutritional environment. Effectiveness of in particular reduced LA or enhanced n-3 LC-PUFA on body composition in human adult life might by enhanced when provided throughout (late) pregnancy and lactation and beyond. There are several arguments to support this approach: Firstly, it could potentially modulate fetal WAT development in the last trimester beneficially. The critical window for hyperplastic and hypertrophic WAT development in humans is not well defined, but it has been suggested that human preadipocytes have highest proliferation and differentiation capacity during the 1st year of life (Hauner *et al.*, 2013), suggesting that the critical period for adipogenesis is still open during infancy and that nutritional signals could influence adipocyte development during this period. Secondly, it could increase the n-3 PUFA and decrease n-6 PUFA content in human milk, since experimental data indicate that only one-third of the milk DHA content is determined by dietary PUFA during lactation (Oosting *et al.*, 2015b; Schipper *et al.*, 2016) and the rest is derived from maternal fat depots.

In line with the reports that indicate that breastfeeding duration is associated with protective effects on (childhood) obesity (Harder *et al.*, 2005), we could hypothesize that the protective effects of HM are (at least partially) mediated by the milk lipid structure. In our experimental studies, we simply extended exposure to the improved lipid structure (closer to that in mouse milk) beyond lactation into the early weaning period by providing a diet containing the large PL-coated lipid droplets (Oosting *et al.*, 2012, 2014, Baars *et al.*, 2016; Ronda *et al.*, 2019). The observed reduction in adiposity in young adulthood following the western style diet challenge may indeed support the idea that the physical structure of HM lipids may explain some of the positive associations reported between the duration of BF and later overweight (Harder *et al.*, 2005).

9 Health implications and future directions

Altogether the published preclinical data demonstrate that quality of nutrition during infancy, more specifically different aspects of lipid quality, such as FA composition and physical lipid structure, are important determinants for adult life metabolic health and disease risk. Since in humans mother's milk or infant formula is the only source of food in early postnatal life, defining appropriate milk lipid composition and matrix is crucial for early development and adult health. That to date clinical data are limited and show positive, negative or no effects of intervention during pregnancy and/or lactation. These inconclusive outcomes could be related to a number of factors. Most studies focused on N3 LCPUFA supplementation but dose, duration and timing differ as well as the specific outcome measured and the timing of assessment differed considerably. In addition, most studies were performed in healthy term born infants. For these infants, such improvements in nutrient quality may only have small impact that is difficult to measure on the short term. Much of the risk profile may in fact be determined by later exposures as is also clear from the preclinical data that show that a challenge with a western style diet was often needed to show beneficial results of the early diet exposure. Yet, many children already experience challenging conditions in the womb that may impact their birth weight and/or postnatal growth and development in whom effects of such nutritional concepts could be more substantial. For instance, today, obesity among pregnant women is becoming one of the most important women's health issues (NCD Risk Factor Collaboration, 2017; Poston *et al.*, 2011). Maternal obesity is associated with higher birth weights and more body fat, forming a risk factor for unbalanced or faster growth and obesity later in life (Poston *et al.*, 2011; Symonds *et al.*, 2013). These effects may partly be related to the heightened risk of gestational diabetes (GDM). GDM is currently one of the most common medical complications in pregnancy affecting one in every seven births globally (Guariguata *et al.*, 2014). Both the mothers and their offspring are at increased risk of short and of longer-term complications like development of type 2 diabetes (Silverman *et al.*, 1998; Metzger *et al.*, 2008). Although the evidence

available currently favors actions directed at controlling pre-pregnancy weight and preventing obesity and GDM, adequate dietary guidance before and during pregnancy (Hanson *et al.*, 2015), especially in the case of GDM diagnosis (Yamamoto *et al.*, 2018), is crucial. Even more importantly, given the risk for accelerated adiposity development in the infants after birth (Logan *et al.*, 2016, 2017), further research to optimize dietary support to secure balanced growth and to improve later outcomes for GDM offspring as a specific risk population is key.

Although HM lipids have been investigated intensively (Zeisel *et al.*, 1986; Jensen, 1996; Mitoulas *et al.*, 2002; Yuhas *et al.*, 2006), many aspects have remained relatively unclear, such as the role of specific maternal factors and their interactions. Our preclinical results clearly indicate that maternal dietary PUFA content during lactation is readily translated to PUFA content in milk (Oosting *et al.*, 2015b). In lactating women, dietary PUFA have been retrieved from HM within 6 h after intake (Hachey *et al.*, 1987; Francois *et al.*, 1998). The global increased LA and decreased n-3 LC-PUFA intake is reflected in mature milk (Ailhaud *et al.*, 2006; Gibson *et al.*, 2011). Current recommendations regarding n-3 and n-6 EFA and LC-PUFAs are based on HM composition and infant FA status and safety rather than on (long-term) health outcomes, due to lack of scientific proof in healthy term infants. It is tempting to speculate that specific subpopulations of infants at risk for obesity and NCD due to an adverse fetal environment (Vohr and Boney, 2008; Nelson *et al.*, 2009) may benefit more clearly from increased n-3 LC-PUFA intake. Generally, however, rather than increasing n-3 LC-PUFA intake, reducing LA intake might ultimately prove to be more effective. In fact, Hibbeln and colleagues (Hibblen *et al.*, 2006) argue that n-3 LC-PUFA recommendations could even be reduced to a tenth of current recommendations by reducing n-6 PUFA intake effectively.

As stated previously, current recommendations for EFA and LC-PUFAs in IMF are based on content in HM of Caucasian women, data on infant PUFA status and data on functional outcome such as growth and visual acuity (Uauy and Dangour, 2009). With the concerns of scientists and health care professionals about the imbalance between dietary n-6 and n-3 intake, recommendations based on contemporary HM originating from Caucasian women on a typical Western diet merits re-evaluation. Kuipers and others suggest IMF recommendations should be based on HM FA composition originating from ancient paleolithic diets rather than from our contemporary western diets (Kuipers *et al.*, 2005). This ancient, paleolithic diet would entail a high n-3 PUFA (ALA), high n-3 LC-PUFA (DHA and EPA), high n-6 LC-PUFA (ARA) content and a low ARA/DHA ratio, but lower LA intake compared to our contemporary western diets. Such diets might protect against proinflammatory eicosanoid signaling, enhanced LDL oxidation, enhanced platelet aggregation and reduced incorporation of n-3-LC-PUFAs in membranes associated with high dietary n-6 PUFA intake and many chronic diseases (Simopoulos, 2006, 2008).

Yet, HM milk remains in many aspects superior to IMF due to reasons discussed in previous sections. It is now clear that dietary lipid structure can be added to the factors contributing to the potential long term health benefits of breastfeeding. It is impossible to exactly mimic all the characteristics of human milk in human milk substitutes, *i.e.* IMFs available if infants cannot be breastfed. However, our present studies suggest that we can further improve IMF lipid quality beyond FA composition by adjusting the lipid structure. This infant formula, containing large, PL-coated lipid droplets (Nuturis®, Gallier *et al.*, 2015) supports equivalent growth in term born infants (Breij *et al.*, 2019), and further clinical studies testing growth- and other developmental outcomes are ongoing.

10 Conclusion

Our experimental studies showed long term beneficial effects of FA composition and physical lipid structure in animal models. Future preclinical studies should at least investigate interaction between individual lipid aspects/compounds, because effects of individual compounds can be enhanced or abrogated when combined. As suggested for instance, high n-3 LC-PUFA supplementation may be more effective under a low LA background. The high n-6 PUFA recommendations may need to be addressed more specifically in future clinical studies given the proadipogenic properties as demonstrated in preclinical studies. Both the absolute amounts of dietary EFA and LC-PUFA as well as the ratio should be taken into account for a balanced n-6/n-3 status. Combining an optimized PUFA content and ratio with the altered lipid structure may be a promising strategy to further improve lipid quality of infant nutrition.

Randomized clinical trials are essential to generate solid data concerning safety and efficacy in infants and to test whether these promising results ultimately allow future implementation and improvement of IMF concepts that may improve long-term health. The changes in dietary lipids during infancy may especially benefit infants “at risk”, such as infants from women with GDM or obesity which are potentially exposed to fetal overnutrition, but also for small-for-gestational age infants that may have experienced fetal undernutrition and preterm infants which may have specific nutritional needs due to their immaturity at birth. Clinical studies in specific target populations will help to develop specific strategies to adapt infant nutrition based on the need with the aim to improve long term outcomes.

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