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Adipose tissue dysregulation and metabolic consequences in childhood and adolescent obesity: potential impact of dietary fat quality

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Evidence suggests that at a population level, childhood and adolescent obesity increase the long-term risk of chronic diseases such as type 2 diabetes and CVD. At an individual level, however, the metabolic consequences of obesity in youth vary immensely. Despite comparable BMI, some adolescents develop impaired glucose tolerance while others maintain normal glucose homeostasis. It has been proposed that the variation in the capacity to store lipid in the subcutaneous adipose tissue (SAT) may partially discriminate metabolically healthy from unhealthy obesity. In positive energy balance, a decreased capacity to expand SAT may drive lipid accumulation to visceral adipose tissue, liver and skeletal muscle. This state of lipotoxicity is associated with chronic low-grade inflammation, insulin resistance and dyslipidaemia. The present review examines the differential adipose tissue development and function in children and adolescents who exhibit metabolic dysregulation compared with those who are protected. Additionally, the role of manipulating dietary fat quality to potentially prevent and treat metabolic dysfunction in obesity will be discussed. The findings of the present review highlight the need for further randomised controlled trials to establish the effect of dietary *n*-3 PUFA on the metabolic phenotype of obese children and adolescents. Furthermore, using a personalised nutrition approach to target interventions to those at risk of, or those with established metabolic dysregulation may optimise the efficacy of modifying dietary fat quality.

Childhood obesity: Adipose tissue: Adipogenesis: Metabolic health: Fatty acids

Childhood and adolescence represent dynamic periods of rapid growth and weight gain[1]. Chronic intake of excess energy and sedentary behaviours however promote a state of positive energy balance and expansion of adipose tissue (AT) mass beyond that which is expected during normal maturation[2,3]. The short- and long-term health consequences of elevated BMI in childhood and adolescence remain unclear. While some prospective studies suggest that excess weight gain during these developing years is directly associated with adverse future health outcomes, including incidence of type 2 diabetes (T2D)[4,5], CVD[6,7] and some cancers[8,9], others disagree[10–12]. Studies that fail to show a relationship between childhood weight and disease outcome in adulthood have suggested that significant relationships dissipate when adjusted for adult BMI[12].

Abbreviations: AGA, appropriate weight for gestational age; AR, adiposity rebound; AT, adipose tissue; BAT, brown adipose tissue; ECM, extracellular matrix; HFD, high-fat diet; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; IR, insulin resistance; IRS, insulin receptor substrate; LC, long-chain; LGA, large for gestational age; MHO, metabolically healthy obese; MMP, matrix metalloproteinase; MUO, metabolically unhealthy obese; NGT, normal glucose tolerance; PL, phospholipid; RCT, randomised controlled trials; SAT, subcutaneous adipose tissue; SREBP-1, sterol regulatory element-binding protein-1; T2D, type 2 diabetes; UCP-1, uncoupling protein 1; VAT, visceral adipose tissue; WAT, white adipose tissue.

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Furthermore, healthy weight adults who were obese during childhood have similar risk for T2D and heart disease as individuals who have maintained a healthy weight throughout life[13]. These data suggest that direct associations between childhood BMI and later metabolic disease risk may reflect tracking of weight status and persistent obesity rather than an independent effect. The more immediate metabolic consequences of overweight and obesity in children and adolescents are considerably variable. Despite marked obesity, up to 95 % of children and adolescents maintain normal glucose tolerance (NGT)[14,15]. Although it is established that adiposity significantly correlates with insulin resistance (IR) in obese children and adolescents[16–18], the relatively moderate nature of this association (R^2 0·05–0·40)[16–18] strongly suggests a more complex relationship which is likely to involve an interplay between genetic and environmental factors.

Despite varying inter-individual obese phenotypes, successful weight management interventions consistently demonstrate improvements in LDL cholesterol, TAG and fasting insulin in this cohort[19]. However, achieving a significant reduction in BMI is difficult for this age-group[20]. Also, long-term studies have shown that weight regain frequently occurs[21,22]. Therefore there is growing interest in the investigation of dietary approaches that may improve metabolic outcome in the absence of weight loss. In this regard, cross-sectional and observational studies have suggested a relationship between dietary fat quality and metabolic phenotype, wherein SFA are inversely associated with insulin sensitivity, whereas MUFA and PUFA are positively associated with a favourable metabolic phenotype[23–27]. Additionally, animal studies have demonstrated that the replacement of SFA with MUFA or PUFA attenuates IR and dyslipidaemia, despite positive energy balance[28–37]. However, results from randomised controlled trials (RCT) are less consistent[38–48], suggesting that energy balance may be the most critical factor regulating metabolic risk. However, there is increasing evidence that responsiveness to dietary interventions may vary depending on the phenotypic characteristics[49]; thus personalised nutrition approaches may optimise efficacy of future dietary interventions within a background of weight stability. In order to design effective personalised interventions, it is important to firstly elucidate the determinants and consequences of distinct phenotypes within childhood and adolescent obesity.

Adipose tissue expandability: a determinant of the metabolic phenotype in paediatric obesity?

Intrauterine exposures, postnatal growth and family history of T2D may all play a role in discriminating metabolically healthy (MHO) from unhealthy (MUO) obese phenotypes in childhood, perhaps by modulating expandability of subcutaneous adipose tissue (SAT)[50]. In a state of positive energy balance, expansion of AT mass results from an increase in adipocyte cell size (hypertrophy), cell number (hyperplasia) or both[51]. Cell number is now considered a key regulator of metabolic function[52]. Hypertrophy is associated with a low generation rate of new adipocytes, whereas the more benign hyperplasia is associated with high adipocyte generation rates from adipogenic precursor cells (adipogenesis) and is linked to a more favourable phenotype[52]. The SAT expandability hypothesis, as presented in Fig. 1, proposes that SAT has a defined restricted capacity to increase its mass safely for any given individual[53]. With persistent energy overload, reduced SAT expansion capacity promotes lipotoxicity[54]. This is characterised by lipid deposition in visceral adipose tissue (VAT), myocytes, hepatocytes and pancreatic β-cells, accompanied by impaired insulin sensitivity, elevated NEFA and TAG and a pro-inflammatory profile; important drivers of MUO[53,55,56]. Thus, metabolic dysregulation within the context of obesity may occur upon exhaustion of an individual's SAT expansion capacity rather than at an absolute AT mass[57]. Consistent with this hypothesis, obese adolescents with impaired glucose tolerance (IGT) were shown to have decreased SAT, increased VAT, raised intramyocellular lipid content and impaired non-oxidative glucose disposal compared with NGT controls, despite similar weight, BMI and body fat percentage[58]. Likewise, when obese adolescents were stratified by proportion of VAT (VAT (cm^2)/VAT+SAT (cm^2)), those in the highest tertile had significantly increased 2-h glucose, insulin, c-peptide and TAG concentrations[59]. Most interestingly, these high-risk subjects had a lower BMI and total body fat percentage than their metabolically healthier counterparts[59]. A recent study of adult weight-discordant monozygotic twins demonstrated SAT hypertrophy, low adipocyte number and down-regulation of the adipocyte differentiation pathway in co-twins with MUO[56]. Interestingly, MUO but not MHO was accompanied by low mitochondrial and high inflammatory transcript activity[56]. Down-regulation of mitochondrial metabolism reduces the availability of acetyl-CoA and ATP, key substrates necessary to support *de novo* lipogenesis in adipocytes. Consistently, gene expression analysis in SAT of adolescents with MUO demonstrated down-regulation of key components of the lipogenesis pathway, including sterol regulatory element-binding protein-1 (SREBP-1), acetyl-CoA carboxylase alpha, fatty acid synthase, lipoprotein lipase and PPARγ[60]. Moreover, results from a second study by the same group revealed that in contrast to SAT, there was increased expression of lipogenic genes such as carbohydrate-responsive element-binding protein, SREBP-1c, patatin-like phospholipase domain-containing protein 3, fatty acid synthase and acetyl-CoA carboxylase in the liver of obese adolescents with IGT/T2D compared with equally obese NGT controls[61]. These results highlight the tissue-specific differential implications of lipogenesis and adipogenesis on metabolic health.

Adipose tissue expandability: mechanisms of action

AT expansion is dependent upon two mechanisms: adipogenesis and lipogenesis. Adipogenesis is the process

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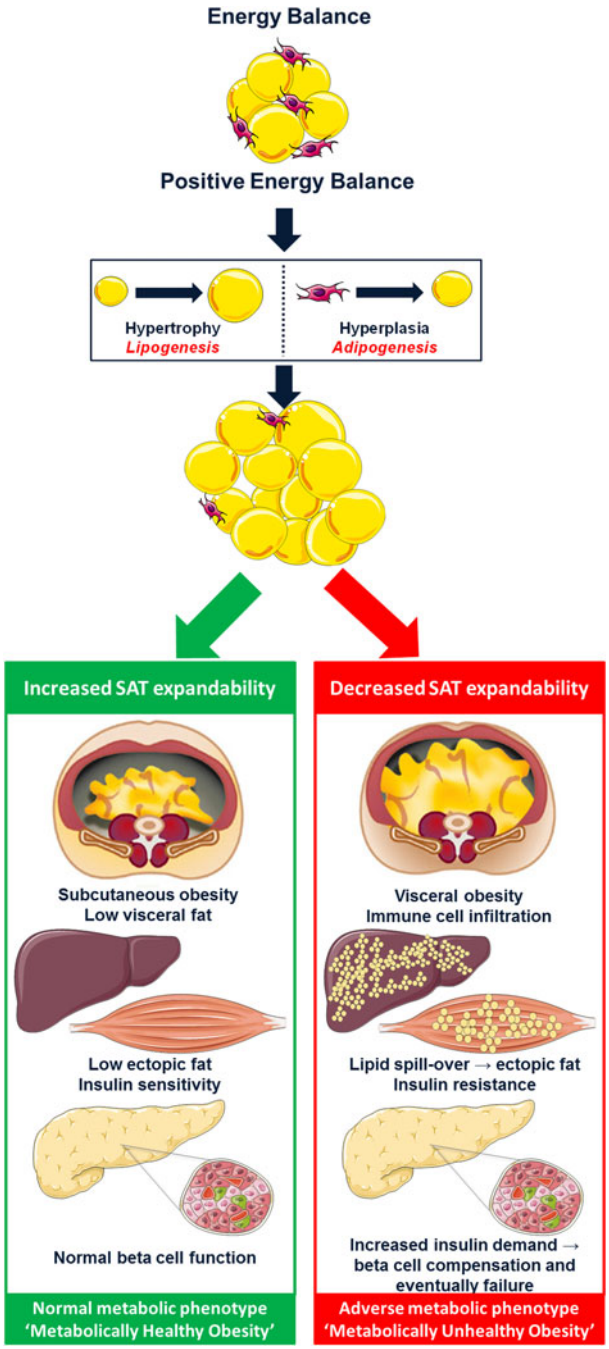

Fig. 1. (colour online) The subcutaneous adipose tissue expandability hypothesis[53]. The hypothesis proposes that in positive energy balance, subcutaneous adipose tissue (SAT) has a limited capacity to increase its mass. Exceeding this threshold promotes lipotoxicity. Excess lipid accumulates within visceral adipose tissue, liver and skeletal muscle rendering these tissues insulin resistant. In an effort to compensate for reduced insulin sensitivity, hyperinsulinaemia ensues eventually leading to pancreatic β-cell failure and type 2 diabetes (metabolically unhealthy obesity). However, increased capacity to expand SAT protects against lipotoxicity and maintains metabolic homeostasis despite obesity (metabolically healthy obesity). Adapted from Després and Lemieux[62].

wherein new mature adipocytes are generated from adipogenic precursor cells termed preadipocytes[63]. This process involves two major phases; firstly preadipocytes are recruited and proliferated (phase one) after which these precursor cells are differentiated into mature fat cells (phase two)[64]. The differentiation step ultimately increases the lipogenic potential of adipocytes, or in other words the capacity of the adipocyte to store lipid as TAG. Adipogenesis involves a cascade of events involving two transcription factor families; PPARγ and CCAAT/enhancer-binding proteins α, β and δ. Lipid accumulation within mature adipocytes is determined by the balance between lipogenesis and lipolysis. Lipogenesis encompasses the synthesis of fatty acids and subsequently TAG from acetyl-CoA, an intermediate of glucose metabolism. Lipogenesis is largely under the control of the insulin-sensitive transcription factor SREBP-1 and Insig1, an endoplasmic reticulum membrane protein[65]. Lipolysis involves the release of NEFA from AT TAG[66]. TNFα, a pro-inflammatory cytokine that is often elevated in MUO is an inducer of lipolysis[67]. Furthermore, lipolysis is increased in T2D, as insulin fails to appropriately suppress lipolysis promoting ectopic lipid accumulation in peripheral tissues such as liver and skeletal muscle[54].

Adipogenesis

Animal studies that utilised a high-fat diet (HFD) to mimic an obesogenic environment have confirmed the importance of adipogenesis in the determination of the metabolic phenotype. It has been demonstrated that knockdown of a key adipogenic gene, PPARγ-2 in the *ob*/*ob* mouse model promoted decreased fat mass accompanied by severe IR, β-cell failure and dyslipidaemia compared with control mice[68]. Consistently, *ob*/*ob* mice overexpressing adiponectin, i.e. adiponectin transgenic mice, were shown to have a near limitless capacity to expand SAT and importantly did not develop components of the metabolic syndrome; demonstrating normal glucose and insulin levels compared with controls[69]. Additionally, macrophage infiltration into AT was reduced and PPARγ targets were increased in these adiponectin transgenic mice compared with control *ob*/*ob* mice[69]. Adiponectin was proposed to signal storage of TAG specifically in AT, while reducing TAG levels in liver and muscle, where ectopic lipid accumulation can impair insulin signalling[69]. A dominant negative mutation in PPARγ in human subjects results in lipodystrophy, characterised by significant loss of SAT from the extremities, and severe IR[70]. Interestingly, in an animal model, the same phenotype was only observed when these mice were challenged with excess energy availability (*ob*/*ob* background)[71]. The presence of this PPARγ mutation prevented adipocyte recruitment as well as adipocyte hypertrophy[57]. Importantly the present study showed that when AT expandability was limited there was a worsened IR state compared with control *ob*/*ob* mice[57]. In addition, components of the TNFα and IL-1-β-signalling pathways prevent PPARγ binding to DNA by associating with NF-κB[72]. This

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suppresses PPARγ function, which is important for determining stem cells to the adipocyte lineage and therefore prevents hypertrophy[72].

Extracellular matrix flexibility

Another important aspect for AT expandability is maintenance of flexibility within the extracellular matrix (ECM). This allows the AT to expand in a healthy manner without any adverse effects. However, with increased obesity, interstitial fibrosis in white adipose tissue (WAT) may decrease ECM flexibility, which eventually leads to adipocyte dysfunction[73]. The ECM and its primary protein collagens are vital for maintaining the structural integrity of adipocytes and are important regulators of adipogenesis and AT formation[73]. During adipocyte differentiation, ECM components are present at variable time-points where initially fibronectin is increased, followed by collagens III, V, VI and I[74,75]. Several studies have highlighted significant correlations between collagen VIα3 and chronic immune cell infiltration, based on increased M1 macrophages[76]. Collagen VI is primarily involved in maintaining ECM structure and is composed of three subunits in its mature form: α1; α2; α3[77]. All three of these isoforms are responsible for formation of a stable protein structure[77]. Mice lacking collagen VI challenged with either HFD or genetically induced obesity demonstrated increased ECM flexibility and decreased AT fibrosis[78]. There was evidence of unlimited adipocyte expansion and, as a result, there were whole body improvements in energy homeostasis[78]. During normal development of the AT, the ECM is highly dynamic[79]. However, ECM processes become dysregulated in obesity and coupled with immune cell accumulation in the AT, impair metabolic function and suppress capacity for AT expansion[80]. Abnormal collagen deposition has been shown to be a hallmark of fibrosis development in AT and is tightly associated with tissue inflammation characterised by the influx of macrophages[73]. In contrast, a study that examined ECM remodelling in developing AT in healthy weight and obese children illustrated characteristics of collagen deposition that differed in normal weight and obese subjects[79]. Moreover, these features observed in AT of children were distinct from adults with established obesity or animal models of diet-induced obesity such as immune cell infiltration and fibrosis[79]. Findings from the present study showed that in normal-weight children there was greater collagen deposition in AT, which may restrict growth[79]. Conversely lower collagen in AT of overweight children was observed, but increased with age and fat cell size allowing for the expansion of fat cell size and thus tissue growth[79]. These findings may reflect an overall situation of dynamic tissue remodelling reflecting normal physiological growth processes involving increases in fat cell size[79]. It would be expected that normal growth and expansion of fat cell size would have no adverse effects if ECM remains flexible and there are proportional increases in blood flow and oxygenation[79]. However, if collagen deposition occurs along with recruitment of M2 macrophages in children, this may inhibit AT expansion[79].

Matrix metalloproteinases

Collagenases are involved in the breakdown of excessive accumulation of ECM. A family of endopeptidases, matrix metalloproteinases (MMP), are involved in cleaving collagenous proteins enabling the remodelling of the ECM[73]. The use of a broad MMP inhibitor in a mouse model demonstrated the important role MMP plays in remodelling during obesity[81]. Administration of this MMP inhibitor reduced collagen degradation, which resulted in the formation of a collagen-rich matrix that impeded AT growth[81]. Other MMP, such as 2 and 9, are elevated in obesity and increased during adipocyte differentiation[82]. One particular MMP, MT1-MMP plays a role in AT ECM remodelling and is required for the modulation of tight pericellular collagens to allow preadipocytes to grow out of the stroma[83]. In mice, the absence of MT1-MMP impedes AT development, causing a lipodystrophic phenotype in these mice[83].

Hypoxia

Rapid expansion of AT results in a hypoxic state as the adipocytes reach their diffusion of oxygen limit quickly due to the lack of neovasculature establishment for the expanding AT[73]. Therefore this hypoxic state is one of the early determinants of AT dysfunction[66]. Hypoxia inducible factor-1, which is a transcription factor induced by a hypoxic state can initiate in turn a profibrotic transcriptional programme[73]. With persistent positive energy balance, a point will eventually be reached at which SAT can no longer store excess lipid. When subcutaneous adipocytes overfill, hypoxia inducible factor-1α suppresses β-oxidation via transcriptional repression of sirtuin-1, which deacetylases and thus activates PPARγ coactivator1α[84]. A lipotoxic state emerges, with net lipid flux to non-adipose organs and ectopic lipid deposition[84]. HFD induces doubling of the fat cell area and can create a local hypoxia state resulting in increased hypoxia inducible factor-1α[73]. Hypoxia inducible factor-1α is not proangiogenic in AT, but it induces synthesis of ECM components leading eventually to the development of AT fibrosis[73].

Characteristics of metabolically unhealthy obesity in children and adolescents

Altered lipid partitioning as commonly exhibited by MUO youths may increase risk of IR through a number of potential mechanisms.

Adipose tissue dysfunction

Firstly, VAT to a greater extent than SAT secretes several pro-inflammatory insulin-desensitising cytokines, including TNFα and IL-6[85,86]. As a result, macrophages, T-cells and dendritic cells are recruited to VAT via various signals, including chemokines synthesised by

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adipocytes[87–89]. This favours a pro-inflammatory insulin-desensitising milieu, contributing to local and systemic IR[90]. Importantly, many of these pro-inflammatory mediators initially identified in adults have also been confirmed in the circulation of obese children, including elevated leptin, IL-6, C-reactive protein, TNFα, fibrinogen and vascular adhesion molecules[91–94]. Furthermore, in children and adolescents the anti-inflammatory adipocytokine adiponectin has been shown to correlate negatively with BMI and well as plasma levels of TAG and NEFA, and positively with peripheral insulin sensitivity. These findings confirm that obesity dysregulates inflammation, even in childhood.

Pro-inflammatory cytokines mediate their insulin desensitising effect via serine phosphorylation of insulin receptor substrates (IRS). In insulin sensitivity, a number of complex signalling cascades are induced when insulin binds to its receptor[87]. Tyrosine phosphorylation of IRS-1 leads to activation of (1) the phosphatidylinositol 3-kinase–protein kinase B pathway, which is responsible for insulin induced glucose uptake and gluconeogenesis suppression; (2) the mitogen-activated protein kinase pathway, which regulates gene expression[95]. In the hypertrophic obesity state, pro-inflammatory cytokines activate several serine kinases, including IκB kinase, cJun NH_2-terminal kinase, mammalian target of rapamycin and protein kinase C-θ[95]. These kinases inhibit insulin action by causing phosphorylation of serine residues on IRS-1. Serine phosphorylation of IRS-1 disrupts insulin-receptor signalling thereby impairing downstream propagation of insulin signalling[96]. Serine kinases also exert powerful effects on gene expression, including promoting further inflammatory gene expression through activation of activator protein-1 and NF-κB[96].

Hepatic lipid deposition

Lipid deposition in the liver has been proposed as the most critical marker of IR and glucose dysregulation in obese youth; prevalence in this cohort can range from 10 to 77 %[97,98]. Hepatic steatosis in obese children and adolescents is accompanied by inflammation and dyslipidaemia; specifically high levels of large VLDL and small dense LDL as well as decreased large HDL and low adiponectin concentrations[99]. The amount of lipid in hepatocytes is determined by a combination of events: (1) hepatic fatty acid uptake derived from AT lipolysis and hydrolysis of circulating TAG; (2) *de novo* fatty acid synthesis; (3) fatty acid oxidation; (4) fatty acid export from VLDL particles[100]. Evidence indicates that insulin is fundamental to the regulation of transcription factors such as SREBP-1c, which are abundantly expressed in the liver. SREBP-1c is a key regulator of hepatic lipogenesis and is increased in response to hyperinsulinaemia in the liver of *ob/ob* mice[101]. Additionally, inflammatory cytokines released by VAT or by the hepatic Kupffer cells may contribute to altered hepatic lipid metabolism; inflammation and increased oxidative stress factors are implicated in the pathogenesis of hepatic steatosis[102]. Although it is well established that IR and hepatic steatosis are closely associated, it is not known whether hepatic steatosis is a consequence or a cause of impaired insulin sensitivity[103]. Nevertheless, the presence of steatosis is an important marker of multi-organ IR, glucose intolerance and dyslipidaemia in obese children and adolescents[104].

Raised intramyocellular lipid content in skeletal muscle

Obese insulin resistant children have also been shown to have higher levels of intramyocellular lipid when compared with obese insulin sensitive children[105]. Furthermore, intramyocellular lipid content in these youths is inversely correlated with non-oxidative glucose disposal[106]. The effects of intramyocellular lipid deposition on insulin sensitivity are induced by fatty acid derivatives such as diacylglycerol and ceramides, which have also been demonstrated to alter the insulin signalling transduction pathway, leading to reduced glucose uptake and subsequent glycogen synthesis[107].

Pancreatic β-cell dysfunction

Pancreatic β-cell dysfunction has been proposed as the ultimate determinant of IGT/T2D onset in obese youth, and is the result of either a progressive decline in β-cell mass, or a functional defect of the β-cell that inhibits sufficient insulin secretion to offset systemic glucose load[108]. Obese adolescents with IGT and T2D have demonstrated significant decreases in first phase insulin secretion, that is the initial brief spike in insulin, when compared with NGT adolescents with a similar BMI[109]. In contrast, second-phase insulin secretion was preserved in NGT and IGT but not in T2D youths[109]. It has been suggested that increased β-cell apoptosis leads to the progressive loss of β-cells[110]. Apoptosis is likely to be induced by a number of local factors, including 1L-1β production, reactive oxygen species, endoplasmic reticulum stress and glucose toxicity within β-cells[110–112].

Critical periods of adipose tissue development: potential dietary approaches to improve metabolic outcome

Maintenance of a healthy weight through balanced energy intake and expenditure is considered the first-line strategy for the prevention and treatment of metabolic complications in childhood and adolescent obesity[113]. However, it is clear from the aforementioned evidence that BMI is not the sole predictor of metabolic status in young people. Additionally, a meta-analysis of lifestyle interventions highlighted that weight loss is difficult to achieve in this age group[20]. To this end, manipulation of dietary fat quality in the absence of energy restriction is a tempting alternative approach. Evidence indicates that the effect of fatty acids on AT function varies according to the degree of fatty acid saturation[114]. While SFA has been identified as a potent stimulator of AT macrophage infiltration as well as pro-inflammatory, insulin de-sensitising cascades[115], PUFA has demonstrated the potential to partially attenuate the metabolic stress conferred by chronic nutrient overload[116].

Perreault *et al.* illustrated a more favourable plasma fatty acid profile in individuals with MHO, compared

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with MUO controls[23]. Specifically, phospholipid (PL) and TAG fatty acid composition comprised lower SFA and higher PUFA in MHO subjects. In fact, fatty acid composition of the plasma PL and TAG fractions explained 58 % of the variability in metabolic status across groups[23]. It has been proposed that the protective effect of PUFA may be partially mediated via lipidome remodelling in the PL membrane of AT, given that increased PL PUFA incorporation is known to improve membrane fluidity[24]. Indeed, the examination of SAT PL membranes in monozygotic weight-discordant twins revealed that adipocyte expansion in the obese co-twins was accompanied by a proportional increase in PUFA-containing ether lipids and a concurrent reduction in saturated and shorter-chain ester-bound lipids[24]. Moreover, there is evidence to suggest that *n*-3 and *n*-6 PUFA differentially modulate AT function upon incorporation into the PL membrane. *In vitro* and animal studies suggest that *n*-6 PUFA promotes hypertrophy, while *n*-3 PUFA is associated with the more benign hyperplastic obesity[30,117]. Interestingly, inhibition of lipogenesis by *n*-3 PUFA appears to be site-specific, at least in animal models. Studies that utilised rat WAT have demonstrated that *n*-3 PUFA limits hypertrophy in the intra-abdominal depots only[33,34,118] and this translates to an improved phenotype[34]. Okuno *et al.* reported that reduced VAT hypertrophy was accompanied by suppression of key regulators of late phase adipocyte differentiation; CCAAT/enhancer-binding protein α, adipsin, adipocyte protein 2 and PPARα in response to *n*-3 PUFA feeding[34]. Additionally, 3 weeks long-chain (LC) *n*-3 PUFA DHA administration in mice up-regulated PPARγ in SAT but concurrently down-regulated PPARγ expression in liver[36]. Site-specific effects suggest that the promoter regions of adipogenic and lipogenic genes may differ between tissues[119]. In contrast to *n*-3 PUFA, *in vitro* and animal studies have demonstrated that an HFD rich in *n*-6 PUFA promotes activation of cyclic AMP-dependent signalling pathways in preadipocytes, a process which is known to favour adipocyte hypertrophy[37]. Conversely, mice fed a mixture of *n*-3 and *n*-6 fats, thus lowering the *n*-6:*n*-3 ratio may favour hyperplasia to accommodate excess energy[37]. It has been proposed that the shorter chain *n*-3 PUFA α-linolenic acid and its metabolites suppress Δ6 desaturase activity, thus reducing generation of the *n*-6 PUFA arachidonic acid and subsequent cyclic AMP production[120].

There is growing evidence that gestation, infancy, age of adiposity rebound (AR) and adolescence represent critical periods in the course of AT development during which nutritional and environmental exposures determine future metabolic risk[121]. Thus, manipulation of (i) energy balance or (ii) dietary fat quality intake during these unique windows of opportunity may improve metabolic outcome.

Gestation

In the growing fetus, AT formation occurs between 5 and 29 weeks gestation[122]. Early in this process, mesenchymal precursor cells differentiate into preadipocytes[123] after which intense preadipocyte proliferation continues until approximately 23 weeks gestation[122]. By week 28, WAT is present in the principal fat depots throughout the body[123], while brown adipose tissue (BAT) can be identified earlier in development[124]. At full term, AT accounts for approximately 20 % of body mass in infants born an appropriate weight for gestational age (AGA); 80–90 % of which is stored subcutaneously[125–128].

Energy balance. Expansion of fetal AT is largely determined by maternal substrate availability[129]. Not surprisingly, maternal obesity as well as under- and overnutrition *in utero* have shown potential to instil long-lasting metabolic consequences, possibly via epigenetic modifications[130,131]. AT growth is significantly impaired during fetal growth restriction[128,132].The relatively high-energy cost of AT accretion means that during periods of suboptimal fetal energy supply, AT expansion is sacrificed in favour of other essential organs[133]. This raises the possibility of reduced capacity to expand SAT in the postnatal environment owing to reduced preadipocyte generation[134–136]. In parallel, it has been proposed that *in utero* overnutrition may increase the subcutaneous adipogenic and lipogenic capacity[136]. In keeping with this hypothesis Bouhours-Nouet *et al.* showed that despite similar percentages of body fat mass, obese children and adolescents born after accelerated fetal growth, but in the absence of gestational diabetes, exhibited lower central and higher peripheral fat distribution than those born with an AGA[137]. Whole-body and hepatic insulin sensitivities as well as adiponectin concentrations were significantly higher in high birth-weight subjects[137]. However, not all studies have associated MHO with prenatal overnutrition. In fact, several[138] although not all[139] observational studies have suggested an association between high birth-weight and T2D risk in adulthood, highlighting that the possible protection associated with accelerated early growth may be somewhat transient. Even within the context of higher adipogenic and lipogenic potential in SAT, buffering capacity can be exceeded by chronic overnutrition, resulting in MUO development[140].

Intervention studies that have attempted to optimise the *in utero* nutritional environment and subsequent offspring outcome have shown mixed success. Examination of cardiometabolic risk factors in 2–24-year-old offspring who were conceived after maternal gastrointestinal bypass surgery compared with their siblings born prior to surgery showed that improved maternal pre-pregnancy BMI reduced offspring waist circumference[141,142], body fat percentage[141], fasting insulin[141,142], homeostasis model assessment (HOMA)-IR[141,142], blood pressure[141] and LDL-cholesterol[142]. Guénard *et al.* proposed that these improvements were somewhat mediated via epigenetic mechanisms, demonstrating almost 6000 differentially methylated genes between siblings; significantly affected genes primarily related to glucose homeostasis, inflammation and vascular disease[141]. Conversely, a meta-analysis of 537 mother–neonate pairs

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revealed that although dietary interventions successfully reduced gestational weight gain by 6·5 kg in obese pregnant women, newborn birth-weight was unaffected[143]. These results indicate that maternal obesity, irrespective of gestational weight gain confers independent risk on fetal growth. The long-term effects of reduced gestational weight gain on metabolic outcome in the offspring of obese mothers have not yet been described in human studies. However, in animals it has been demonstrated that when HFD-induced obese mice were switched to a low-fat diet during pregnancy their female offspring maintained normal insulin sensitivity even when challenged with an HFD for 20 weeks[144].

Dietary fat manipulation. Epidemiological examination of the relationship between maternal fatty acid profile in pregnancy and offspring AT function yields mixed results. A recent systematic review revealed that equal numbers of studies have illustrated direct, inverse and no associations between maternal *n*-3 PUFA intake during pregnancy and offspring adiposity[145]. Equally, little is currently known about the long-term metabolic implications of fatty acid intake or status during pregnancy. Somewhat counterintuitively given the *in vitro* and animal data discussed previously, a study of over 250 children revealed an inverse relationship between the umbilical cord concentration of *n*-6 PUFA γ-linolenic acid and insulin, leptin and HOMA-IR at age 7 years but no associations were detected with umbilical cord *n*-3 PUFA[27]. Likewise, a second study examined the association between *n*-3 PUFA intake during the second trimester of pregnancy and cardiometabolic risk in 20-year-old offspring, and found no significant relationships[41].

RCT of dietary fat manipulation in pregnancy are sparse and those conducted to date do not provide evidence of long-term benefits to AT or metabolic function in 1-year[146] or 19-year-old[42,43,147] offspring (Table 1). However, in the shorter term, a meta-analysis of 921 women illustrated that risk of pre-term birth, a known risk factor for future visceral adiposity and metabolic dysfunction, was successfully reduced by *n*-3 PUFA supplementation[148], although the mechanisms are not yet established. Data emerging from RCT are somewhat in conflict with animal studies. In pregnant rats, consumption of a diet rich in *n*-3 PUFA results in reduced AT mass[28], smaller adipocyte size[28], lower serum leptin levels[28], improved glucose homeostasis[29] and increased pancreatic islet numbers[29] in offspring. Inconsistency in results may be due to lower fatty acid dose in human studies, genetic background, duration of intervention[149], as well as the stage of gestation during which the intervention commences[150]. Additionally, it should be noted that the effect of dietary fat manipulation within the context of maternal obesity or *in utero* overnutrition is yet to be described in human studies. The lipid content of AT in large for gestational age (LGA) infants weighs 250–500 g more than AGA infants[151]. Importantly, increased maternal-to-fetal transport of LC PUFA is required to facilitate cell membrane demand during SAT hypertrophy and hyperplasia[151].

Postnatal and infant (<2 years) growth

With the exception of the first 5–12 d after birth, the rate of AT expansion rises rapidly in response to increased nutrient availability in the postnatal environment[152]. During this period, precursor cells undergo morphological and functional transformation into mature lipid-laden adipocytes[152]. Adipocyte numbers continue to rise throughout infancy and childhood, eventually reaching a maximum in late adolescence[153,154]. After this time, adipocyte number remains relatively constant[52] and is therefore determined from early life[154].

Energy balance. Using data from over 8000 subjects, Druet *et al.* demonstrated that each +1 unit increase in weight SD score between 0 and 1 year doubles risk of childhood obesity (OR = 1·97), and increases risk of adult obesity by 23 % (OR = 1·23)[155]. Furthermore, cardiometabolic risk at age 17 was predicted by weight gain from 0 to 6 months[156]. However, birth-weight amongst other factors, may modulate the metabolic response to early weight gain. Intrauterine growth restriction predisposes individuals to visceral adiposity and IR in later life[157]. In a rodent model of intrauterine growth restriction, nutritionally induced catch-up growth led to AT hypertrophy as well as significant reductions in AT protein expression of IRS-1, phosphatidylinositol 3-kinase, protein kinase B-2 and phosphorylated protein kinase B[158]. Of note, many of the signalling impairments were apparent at 3 weeks in the absence of altered glucose and insulin concentrations, indicating that metabolic adaptations may occur early in the postnatal period[158]. Human studies indicate that in infants born small for gestational age, early infant weight gain (0–3 months) is positively correlated with fasting insulin concentration, HOMA-IR, lipid profile and systolic blood pressure in adolescence[159]. Conversely, no adverse relationships were detected between early weight gain and later metabolic risk in AGA infants[159]. Similarly, accelerated postnatal growth may not be detrimental to LGA infants, at least in the short term[137]. As discussed previously, LGA infants who later become obese demonstrated protection against metabolic dysfunction compared with their AGA counterparts[137]. When postnatal growth velocity was examined within this obese cohort, higher gains in BMI up to age 2 years conferred additional protection[137]. Thus, the children who were born LGA and demonstrated the greatest weight gain up to 2 years, were the most insulin sensitive at 10 years[137]. Interestingly, in a study of lean men and women, those who developed metabolic syndrome as adults despite healthy weight, exhibited slower gains in BMI during the first 2 years of life[10]. Together, these findings highlight a specific window encompassing early postnatal life during which fat accumulation may programme AT function and insulin homeostasis in later life. Additionally, accelerated early weight gain may have opposing effects on short-term cardiometabolic risk depending on birth-weight.

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Table 1. Randomised controlled trials which investigated the effect of dietary fat manipulation on adipose tissue distribution and metabolic phenotype during critical periods of adipose tissue development

Dietary intervention	Population (*n*)	Effect of intervention on body composition and fat distribution	Effect of intervention on metabolic phenotype
Gestation			
LC *n*-3 PUFA[41–43]	Off-spring of supplemented mothers, 19 years, male and female; *n* 243	BMI ↔; WC ↔	Insulin ↔; glucose ↔, HbA1c ↔; HOMA-IR ↔; leptin ↔; adiponectin ↔; IGF-1 ↔; hs-CRP ↔
Postnatal			
DHA-enriched preterm formula[44]	24-month-old infants born preterm, birth-weight <1500 g or gestational age <32 weeks, male and female; *n* 182	Total fat mass ↓; trunk fat ↓	Insulin ↓
n-3 and *n*-6 PUFA-enriched preterm formula[45]	9–11-year-old children, born preterm, birth-weight <1500 g and gestational age <35 weeks, male and female; *n* 107	BMI ↔; WC ↔; fat mass ↔; fat free mass ↔	SBP ↔; DBP ↔
Adolescence			
LC *n*-3 PUFA[39,40]	Overweight, healthy, 14–17 years, male and female; *n* 25	BMI ↔; WC ↔	Fasting: Glucose↔; insulin↔; NEFA↓; TNFα↓; IL-1β↓; IL-6↓; hs-CRP ↔ IVGTT: Glucose↓ girls only; insulin↓ girls only; Euglycaemic-hyperinsulinaemic clamp: ISI↑ girls only; glucose disposal rate↔
LC *n*-3 PUFA[46]	Overweight with fasting insulin >15 μU/ml, 9–18 years, male and female; *n* 76	BMI ↔; total fat mass ↔	Glucose↓; insulin↓; HOMA-IR ↓; TNFα↓; IL-6 ↔; leptin↓; adiponectin ↑
LC *n*-3 PUFA[47]	Overweight, healthy, 13–15 years, male only; *n* 78	BMI ↔; WC ↔; body fat % ↔; total fat mass ↔; trunk fat ↔	Leptin ↔; adiponectin ↔
LC *n*-3 PUFA[38]	Overweight with non-alcoholic fatty liver disease, mean age = 12 years, male and female; *n* 60	BMI ↔	Severe liver steatosis odds ratio ↓; HOMA-IR ↓; TAG ↓ in 250 mg/d DHA and 500 mg/d DHA
Mediterranean Style Diet[48]	Obese with at least 1 MetS component according to modified IDF criteria, mean age = 11 years, male and female; *n* 49	BMI ↓; fat mass ↓; lean mass ↑	Glucose ↓; TAG ↓; total cholesterol ↓; HDL-cholesterol ↑; LDL-cholesterol ↓

↔, no effect; ↓, decrease; ↑, increase; LC *n*-3 PUFA, long chain *n*-3 PUFA; WC, waist circumference; HbA1c, glycated haemoglobin; HOMA-IR, homeostasis model assessment–insulin resistance; MetS, metabolic syndrome; IDF, International Diabetes Foundation; IGF-1, insulin-like growth factor 1; hs-CRP, high-sensitivity C-reactive protein; IVGTT, intravenous glucose tolerance test; ISI, insulin sensitivity index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Data from the EU childhood obesity programme revealed that an increased weight gain velocity during the first months of life is induced by high protein intake[160]. In a controlled trial of small for gestational age infants, de Zegher *et al.* demonstrated that feeding practices differentially affected weight partitioning and metabolism during the first year of life[161,162]. For a minimum of 5 months, small for gestational age infants were fed exclusively on either breast milk or an iso-energetic, higher protein infant formula. By 12 months, breast milk infants had normalised lean mass and bone mass but low fat mass persisted[161,162]. This hypo-adipose state was associated with increased insulin sensitivity as well as normal insulin-like growth factor-1 and high-molecular-weight adiponectin concentrations[161,162]. In contrast, iso-energetic, higher protein infant formula infants managed to normalise fat mass by 12 months, but interestingly this was associated with high insulin-like growth factor-1 and low high-molecular-weight adiponectin concentrations[161,162]. The authors concluded that in fact neither of the nutrition options was able to normalise both body composition and metabolic status, possibly due to an irreversible reduction in prenatal adipogenesis[161,162]. This further suggests that children and adolescents born small for gestational age may experience metabolic dysfunction at a lower BMI and fat mass compared with their AGA and LGA peers.

Dietary fat manipulation. Animal studies have demonstrated that postnatal fatty acid exposure influences later body composition and metabolic regulation. Oosting *et al.* illustrated that mice fed a diet rich in *n*-3 PUFA from postnatal day 2 who were later challenged with high SFA/Western Style diet were protected against metabolic aberrations[30]. Results showed that mice fed a diet rich in *n*-3 PUFA exhibited 30 % less AT gain and maintained better glucose homeostasis compared with control mice[30]. Additionally, examination of AT cellularity revealed significantly less AT hypertrophy and a larger number of small adipocytes in the mice fed the *n*-3 PUFA-enriched diet[30]. Monounsaturated fat has also shown potential to modulate postnatal growth[31]. Offspring of rats

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supplemented with MUFA-rich olive oil from gestational day 14 and throughout lactation showed lower postnatal body weight gain[31]. Additionally, these rats expressed higher levels of uncoupling protein 1 (UCP-1) in BAT, demonstrating increased thermogenic capacity induced by maternal MUFA-rich diet[31].

From a translational perspective, feeding an LC *n*-3 PUFA enriched formula to preterm infants until 1 year gestation-corrected age resulted in lower trunk fat and reduced fasting insulin concentrations compared with those fed a matching unsupplemented formula[44], as detailed in Table 1. Despite the favourable impact of *n*-3 PUFA supplementation in the relatively short term, when Kennedy *et al.* examined 10-year-old children who had received LC PUFA supplemented formula after pre-term birth, they found no long-lasting effect on body composition or blood pressure[45]. However, no circulating markers of metabolic health were assessed. There is a clear need for further RCT to determine the long-term implications of these findings at birth. It is also interesting to note that in a rodent model, Gorski *et al.* demonstrated that postnatal nutrition can override prenatal programming of offspring obesity and IR[163].

Adiposity rebound

BMI reflects both body mass and length/height[164]. During the first year of life, BMI rises rapidly reaching a peak at approximately age 1 year[121]. After this time, BMI undergoes a gradual decline until it reaches a nadir at about age 6 years[165]. AR is defined as the second rise in BMI that usually occurs between age 5 and 7 years[166]. Using dual-X-ray absorptiometry, Taylor *et al.* confirmed that the increase in BMI during the AR period is driven specifically by changes in fat mass rather than in fat-free mass[167].

Energy balance. Longitudinal studies have demonstrated that timing of AR has the potential to modulate future metabolic risk[168,169]. Findings from the Helsinki Birth Cohort Study suggest that earlier AR (<5 years) was associated with a pronounced increased risk of T2D in later life[169]. Although some argue that age of AR bears no functional role and simply highlights children who are upward BMI centile crossing/gaining weight rapidly[170], others disagree[171]. Furthermore, it has been suggested that early AR-induced metabolic aberrations may manifest rather quickly; early AR was related to higher waist circumference, glucose, HOMA-IR, TAG, apol B, blood pressure and lower HDL-C levels in 7–12-year-old children[172,173]. These results suggest that AR timing may modulate AT growth and function. However, up to now no dietary intervention studies to examine the impact of energy/protein manipulation on timing of AR have been conducted.

Dietary fat manipulation. A prospective study of 222 children demonstrated that the *n*-3 PUFA DHA content of breast milk was positively associated with age of AR in girls[174]. Importantly, these results have been replicated in an RCT. Bergmann *et al.* studied the effect of 200 mg/d DHA supplementation from mid-pregnancy until 3 months postpartum and illustrated that age of AR was delayed in offspring of DHA supplemented mothers[175]. Further long-term follow-up studies are required in order to confirm the long-term metabolic implications of DHA-induced AR delay.

Adolescence

Adolescence is characterised by a multitude of body composition changes, including increases in annual height velocity, body weight, lean body mass and bone mineral content[176]. Girls undergo a significant fat mass gain, while adolescent boys decrease body fat and experience increased height velocity[176]. Interestingly, recent evidence points to a higher prevalence of metabolically active BAT in adolescent boys and girls. While 1 in 5 positron emission tomography–computerised tomography examinations in pre-pubertal children display metabolically active BAT, greater than 75 % of scans in pubertal teenagers confirm the presence of this tissue[177]. It has been proposed that BAT activity may be stimulated by sex steroids and growth hormone[178–180].

Energy balance. For overweight individuals, the adolescent years represent a high-risk period for the development of IR and T2D[181]. Pubertal increases in growth hormone, sex steroids and insulin-like growth factor-1 in boys and girls as well as increased fat mass in girls leads to a natural reduction in insulin sensitivity[181]. Puberty-related IR manifests early in adolescence, peaking mid-puberty, and is generally compensated by increased insulin secretion[182]. In healthy weight adolescents, this transient state of IR commonly resolves by the end of pubertal growth[181]. However, resolution does not always occur in obese adolescents indicating possible β-cell deterioration during this critical period of development[183]. These findings suggest that the metabolic risk of overweight adolescents is further exacerbated by a 'pubertal trigger'[183]. Despite convincing evidence that factors other than absolute AT excess determine metabolic phenotype in obese adolescents[58,59], successful weight management is accompanied by improved phenotype in this cohort. The most recent meta-analysis of lifestyle interventions (RCT) in paediatric obesity demonstrated reductions in fasting insulin and lipid profile in response to improved BMI in over 300 subjects[19]. This suggests that weight management in this age-group may optimise metabolic control, even within the context of a metabolically healthy phenotype, as has been demonstrated in MHO adults[184,185].

Dietary fat manipulation. Cross-sectional studies in overweight adolescents have shown that plasma SFA concentrations correlate positively with IL-6[25] and C-reactive protein[26]. Although no intervention studies have chronically increased SFA intake in overweight adolescents, healthy men showed higher concentrations of C-reactive protein, fibrinogen and IL-6 after 5 weeks consuming a diet enriched with the SFA stearic acid or

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a mix of SFA lauric, myristic and palmitic acid, when compared with a MUFA-rich high oleic acid control diet[186]. Additionally, much like in adults[23], overweight adolescents with the metabolic syndrome had a lower plasma PUFA:SFA ratio than overweight adolescents without metabolic syndrome[25]. The pro-inflammatory effects of SFA are thought to be largely mediated by their ability to serve as ligands for toll-like receptor-2 and 4. Binding of SFA to toll-like receptor-2 and/or toll-like receptor-4 in macrophages and adipocytes leads to activation of NF-κB, cJun NH_2-terminal kinase, and p38 mitogen-activated protein kinase inflammatory signalling cascades[115,187].

The effects of dietary fat manipulation on the metabolic phenotype of overweight adolescents show inconsistent results when examined by RCT, as presented in Table 1. Although some studies demonstrated improvements[38,46,48], others show no effect on fasting markers of metabolic function[39,47]. Remarkably, Dangardt *et al.* did not detect an intervention effect in the fasted state[39]; however, when subjects underwent a metabolic challenge significant improvements in glucose and insulin homeostasis were revealed[40], highlighting the potential limitations of assessing metabolic plasticity during fasting. It is also worth noting the differences between RCT with respect to the baseline phenotype of participants. Interestingly, the studies in which subjects were recruited based on a phenotype more indicative of MUO detected significant metabolic improvements post-intervention[38,46,48], whereas in the absence of marked metabolic dysfunction no significant changes occurred in fasting biomarkers[39,47]. This observation suggests that baseline phenotype may partially determine responsiveness to dietary fat manipulation.

Renewed interest in BAT as a possible therapeutic target in obesity has arisen from recent identification of this thermogenic tissue beyond infancy[188,189]. Interestingly, puberty has emerged as a potentially critical period with respect to BAT development[177], which raises the possibility of its involvement in the MHO phenotype. In contrast to lipid-rich white AT, BAT stores little fat and its primary function is to induce non-shivering thermogenesis; dissipating energy via the uncoupling of oxidative respiration from ATP production[190,191]. This process is regulated by UCP-1, a protein located in the inner mitochondrial membrane of BAT[190,191]. Lack of BAT or UCP-1 in mice induces obesity, IR and dyslipidaemia[192,193]. Interestingly, evidence from human studies indicates that the molecular pathways of BAT development are amenable to reactivation; preadipocytes isolated from supraclavicular fat in adults differentiated into brown adipocytes *in vitro*[194]. Importantly, there were no morphological differences in fully differentiated cells from subjects with or without metabolically active BAT[194]. Furthermore, exposure of WAT to chronic cold or PPARγ agonists can induce a distinct form of BAT termed 'brown-in-white' AT, which also expresses UCP-1[178]. In this regard, rodent studies have illustrated the potential for dietary fat manipulation to modulate BAT activity. *n*-3 PUFA[195], MUFA-rich extra virgin olive oil[196] and oleuropein, a phenolic compound in olive oil[197] have all demonstrated increased UCP-1 content and/or activity in rodent BAT. However, it should be acknowledged that the role of BAT in murine models differs very much to man. Furthermore, the potential of unsaturated fats to up-regulate UCP-1 mediated thermogenesis in man has yet to be investigated.

Personalised nutrition: potential to optimise efficacy of dietary fat manipulation?

It is clear that the effects of dietary fat manipulation on AT function and metabolic phenotype are heterogeneous and inconsistent. So too are the phenotypes associated with obesity in childhood and adolescence. Using personalised nutrition approaches to target interventions towards specific populations sharing a common set of characteristics may ultimately improve efficacy[198]. Therefore, categorisation of obese youth based on their metabolic phenotype may be important in determining their level of responsiveness, a concept that was elegantly demonstrated by Gilardini *et al.*[199]. The present study examined the impact of a 3-month lifestyle intervention on insulin sensitivity in 202 obese children[199]. At the end of the intervention, two very distinct groups emerged from the data; responders (55 %) and non-responders (45 %)[199]. Interestingly, the two groups were comparable in BMI, waist circumference and body composition; however, responders were characterised by higher fasting insulin, HOMA-IR, fasting glucose and 2 h glucose and had a lower matsuda index[199]. Remarkably, while responders exhibited improvements in glucose and TAG post-intervention, paradoxically insulin-sensitive non-responders demonstrated increases in insulin, leucocytes and TAG concentrations[199]. Furthermore, a second study of overweight and obese adolescents identified and validated significantly differentially methylated genes related to lipid metabolism and inflammation between individuals who had a high and low response to a multidisciplinary lifestyle intervention[200]. This further suggests that intervention responsiveness tends to vary according to baseline participant characteristics. Importantly, childhood and adolescence may present as a unique window during which MUO individuals exhibit a heightened level of responsiveness. A recent study of more than 2000 subjects indicated that MUO adults are no longer dietary responsive[201]. The authors suggested that the metabolic burden caused by the simultaneous dysfunction of the pathways involved in insulin signalling, inflammation, and glucose and lipid metabolism render MUO but not MHO unresponsive to intervention[201]. Although there is a vital need to replicate these findings in further RCT, emerging data thus far suggest that large inter-individual responses to dietary interventions may be somewhat accounted for by baseline phenotype. It is important to note that the human evidence in relation to dietary fat manipulation during critical periods of AT development has largely emerged from studies within the context of a healthy phenotype. For example, in the two large follow-up studies of LC PUFA supplementation during pregnancy[41] and in the

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postnatal period[45], offspring exhibited a mean follow-up BMI within the healthy range. Given that healthy subjects have an extraordinary capacity to maintain homeostasis[202], it is worth considering that the metabolic benefits of supplementation may go undetected without the challenge of chronic nutrient overload and subsequent obesity. Future studies should focus on targeted interventions to characterise the effect of dietary fat manipulation on the phenotype of children and adolescents with MUO or at risk of MUO later in youth.

Conclusion

Overall, data suggest that the short- and long-term metabolic consequences of obesity in childhood and adolescence are varied and may be modulated by a number of factors, including the *in utero* environment, postnatal growth and inherited risk. Although the majority of obese youth demonstrate maintenance of metabolic homeostasis, those individuals with established metabolic dysfunction may be characterised by increased central and decreased peripheral adiposity, perhaps triggered by decreased SAT expansion capacity. There is convincing evidence from *in vitro* and animal studies that AT function and subsequent metabolic outcome can be manipulated by dietary fat quality during critical periods of AT growth. However, translation of these results in human studies has shown mixed success in the short-term and little success in the long-term. Given the wide inter-individual variability that accompanies obesity in children and adolescents, it is not surprising that the varying characteristics may modulate responsiveness to dietary intervention. A limited number of studies have suggested that MUO youth may respond more favourably to intervention than their MHO counterparts. Thus, targeting dietary interventions towards established MUO or individuals at risk of MUO may optimise efficacy of dietary fat manipulation. Particularly high-risk populations may include obese pregnant women, offspring exposed to *in utero* under- or overnutrition, infants demonstrating slow or accelerated postnatal weight gain, children with early AR and adolescents with established metabolic dysfunction. Future long-term, well-designed RCT are required to determine whether dietary fat manipulation may be therapeutically beneficial for the treatment and prevention of MUO in children and adolescents.

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Conflicts of Interest

None.

Authorship

A. M. M. and R. M. C. completed the review. H. M. R. advised in relation to review content. H. M. R. and F. E. L. critically evaluated the manuscript. All authors approved the final review.

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