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Review Article

A Narrative Review of the Individual Benefits of Maternal Exercise or PUFA Supplementation During Pregnancy: Are We Missing Something?

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Abstract

Evidence indicates that poor nutrition and physical inactivity during pregnancy are associated with increased risk of the child developing obesity, type 2 diabetes, and/or heart disease later in life. Current research demonstrates that maternal aerobic exercise and supplementation of Docosahexaenoic acid (DHA) and Eicosapentaenoic acid (EPA) during pregnancy are associated with improved maternal lipid profiles and infant outcomes, such as a decreased risk of childhood obesity and improved infant cardiac autonomic function (i.e., lower heart rate (HR), increased heart rate variability (HRV)). Currently, the relationships between maternal DHA and EPA with maternal exercise on maternal lipids, infant body composition, and infant cardiac autonomic development are not known. The purpose of this literature review is to synthesize the current state of scientific evidence regarding the effects of prenatal aerobic exercise and maternal DHA and EPA concentrations on maternal lipids as well as infant body composition and cardiac autonomic health. In this review, we examine the individual influence of maternal exercise or DHA and EPA supplementation on maternal lipid profiles, infant body composition, and infant heart outcomes.

Keywords: Polyunsaturated Fatty Acids (PUFA); Docosahexaenoic Acid (DHA); Eicosapentaenoic Acid (EPA); Pregnancy; Infant

Introduction

Over the last 40 years, the prevalence of modifiable risk factors (e.g. physical inactivity) of heart disease and obesity has increased in children as young as 2.5-3 years old [1]. In 2015, 14% of all 2-5 year old children in the United States were classified as obese and already had signs of heart disease [1]. Therefore, It is likely that the modifiable risk factors were present prior to this age. Starting in the late 80s, researchers began to explore correlations between birth or early postnatal measures and mortality and morbidity [2,3]. For instance, increased coronary heart disease mortality, hypertension, glucose intolerance, total cholesterol, and LDL were found to be associated with low infant birth weight, low infant abdominal circumference, and high placental weight [2,3]. Numerous studies have correlated maternal behaviors (e.g., smoking, diabetes, obesity) with the *in-utero* environment and thus the health outcomes of the infant after birth and into adulthood [2-10]. The amniotic sac *in-utero* is the environment to which every individual is first exposed during their life cycle. Maternal behaviors provide positive or negative effects on the *in-utero* environment and thus on the developing organs of the fetus; therefore, the *in-utero* environment can program fetal organs towards health or a disease. Prevention of the possible onset of obesity, diabetes, or heart disease later in life can be achieved through the intervention of positive maternal behaviors during pregnancy.

The current narrative review describes the current evidence from observational studies, clinical trials, and systematic reviews on polyunsaturated fatty acids (PUFAs) and pregnancy. Similarly, this review gives a brief overview of exercise during pregnancy. Next, the review focuses on maternal lipids, with sections that then discuss the individual influence of PUFA and gestational exercise on maternal lipids. Similarly, this review explains current evidence related to infant body composition, with sections that describe our current state of knowledge on the influence of PUFA and prenatal exercise individually on infant body composition. Lastly, an overview of infant heart rate (HR) and heart rate variability (HRV) is provided. Following the same pattern, the effect of PUFA and exercise during pregnancy on infant HR and HRV will be discussed separately. These topics will then be summarized with potential next steps needed in the field.

Polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs) are fatty acids that contain multiple double bonds and include omega-3 fatty acids, such as Docosahexaenoic acid (DHA, cis22:6n-3) and Eicosapentaenoic acid (EPA, C20:5n-3), and omega-6 fatty acids such as arachidonic acid (AA, C20:4n-6). Both omega-3s and omega-6s are important for proper brain development, fatty acid composition, eicosanoids precursors, and as structural components of cells [11-13]. Specifically, DHA (n-3 PUFA) and AA (n-6 PUFA) are the two most relevant PUFAs to brain development during pregnancy and during the first year of life [14]. Most omega-3s and omega-6s are conditionally essential fatty acids; conditionally essential means the human body cannot produce them endogenously without their essential fatty acid precursors; α-linolenic acid (ALA, C18:3n-3) and linoleic acid (LA, C18:2n-6) in Figure 1. ALA is an omega-3 and therefore is the essential fatty acid precursor for DHA and EPA, while LA is an omega-6 that is the essential fatty acid precursor to AA [11,13].

Dietary ALA and LA share the elongation and desaturation pathway to produce their respective products; although ALA and LA compete for the desaturation enzymes, omega-3s are preferred by the enzymes [13]. However, diets high in LA or trans fatty acids can disrupt this pathway and show a higher affinity towards omega-6 biosynthesis [13].

The body also acquires omega-3s (DHA and EPA) and omega-6s (AA) by ingestion through our diet [11-13]. Omega-3s are found mainly in coldwater fish and algae, while omega-6s are generally found in red meats, chicken, and corn oil [11,12]. The suggested ratio of omega-6s to omega-3s for both biosynthesis and bioavailability is between 4:1 and 1:1 [15,16]. Omega-3s and omega-6s share similar pathways, but they have very distinct opposing physiological functions, such as the eicosanoid pathways [11-13]. DHA and EPA, for instance, compete with AA for the enzymes cyclooxygenase and 5-lipoxygenase in order to produce less inflammatory eicosanoids, such as prostaglandin I_3, thromboxane A_3, and leukotriene B_5 [11-13]. Furthermore, most western diets have an omega-6s to omega-3s ratio of 15:1 [15,16]; this increased proportion of omega-6s relative to omega-3s leads to an increased rate of more inflammatory derived eicosanoids; prostaglandin A_2, thromboxane A_2, and leukotriene B_4 [11-13]. This is especially important during fetal development.

DHA and EPA are structurally and functionally important in all cell membranes. DHA is essential for fetal neuronal development. Thus, DHA and EPA are critical in the development of the nervous

system and retina [14]. DHA accumulates in the fetal brain; its concentration is dependent upon maternal dietary intake since infants lack the proper desaturation enzymes to supply omega-3s until after birth [14]. If the maternal environment lacks EPA, then she will be unable to produce the appropriate balance of pro-inflammatory and anti-inflammatory eicosanoids, which limits the transport and uptake of DHA into fetal cells [6,12,17]. Therefore, the American Heart Association advocates the consumption of at least two servings of fish during pregnancy, which are high in omega-3s per week to achieve the recommended amount of EPA and DHA through the diet [18].

Researchers have also examined other possible benefits of omega-3s, particularly with supplementation. A meta-analysis by Mozaffarian and Wu (2012) evaluated cardiovascular benefits of DHA and EPA supplementation in the general population; DHA and EPA supplementation decreased triglycerides (TG), inflammation, and oxidative stress with concomitant increases in low-density lipoprotein (LDL) and high-density lipoprotein (HDL), thus leading to lower risk of cardiovascular events [19]. Similarly, evidence has also shown the potential for DHA and EPA supplementation to protect against obesity by reducing inflammation and adipocyte formation, coupled with changes in lipid profiles (e.g. decreased TG, increased LDL, and HDL) [20]. Researchers have started to investigate the potential for similar benefits of maternal supplementation with DHA and EPA on maternal and infant health. Research has shown potential benefits of maternal DHA and EPA supplementation to mitigate the rise in maternal lipids during gestation [21], improve infant body composition (decrease fat mass, increased lean mass) [22-24], and improve infant cardiac autonomic development (i.e. lower HR, increased HRV) [6,17].

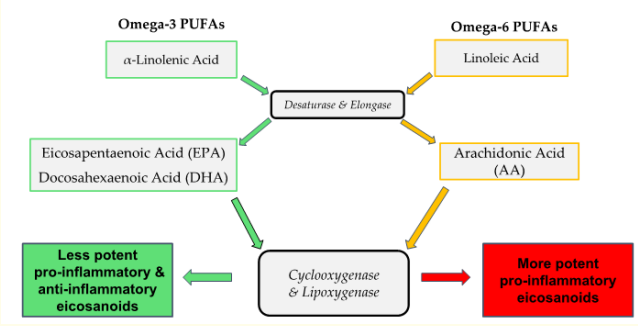

Figure 1: Overview of metabolic pathway for omega-3 and omega-6 fatty acids.

Exercise during pregnancy (Figure 2)

Exercise has been shown, through a plethora of research, to be beneficial to both general and special populations. Since the benefits of exercise are so vast, the American College of Sports Medicine (ACSM) and the American Medical Association initiated the "Exercise Is Medicine" initiative [25]. Previously, physical activity during pregnancy was met with skepticism and concern. In the late 19th to early 20th century, physical activity more than housework was thought to be detrimental to the infant leading to lower birth weights, while bed rest were contributed to healthier and higher birth weights [26]. Clinicians hypothesized physical activity during pregnancy would have adverse effects on the fetus. For example, it was thought that the maternal and fetal competition for oxygen and substrates during maternal exercise would lead to fetal hypoxia, attenuated fetal growth, potential miscarriage, and preterm delivery [7,27,28]. However, these outcomes do not occur during maternal exercise [28].

Pregnancy causes great physiological and psychological changes that can lead to decreases in motivation toward physical activity [26]; for instance, between 1994 and 2000, only 10% of pregnant women in the United States met the recommended physical activity guidelines [27]. The American College of Obstetricians and Gynecologists (ACOG) recommends that pregnant women, without contraindications to exercise, should either begin or maintain their physical activity and achieve 150 minutes of moderate intensity exercise throughout pregnancy [28]. Physical activity throughout pregnancy can lead to positive maternal and infant outcomes, such as lower incidences of gestation weight gain (GWG), gestational diabetes (GDM), cesarean birth, preterm birth, and normal infant birth weight [29]. Researchers have studied other potential maternal benefits of exercise that could translate to improved infant outcomes. For instance, pregnant women with high cholesterol and TG have an increased likelihood of poor maternal outcomes, such as pregnancy-induced hypertension, preeclampsia, and GDM [30,31], which can lead to poor infant outcomes, such as large for gestational age (LGA), increased infant adiposity, and fatty aortic streaks of the heart [32,33]. Recent studies have shown maternal exercise to mitigate the rise in maternal lipids [34-36], decrease infant adiposity [8,37,38], and improve infant heart outcomes [4,5].

Maternal lipids during pregnancy (Figure 2)

The particular food substrates utilized, and the stage of development are important for maternal health and fetal

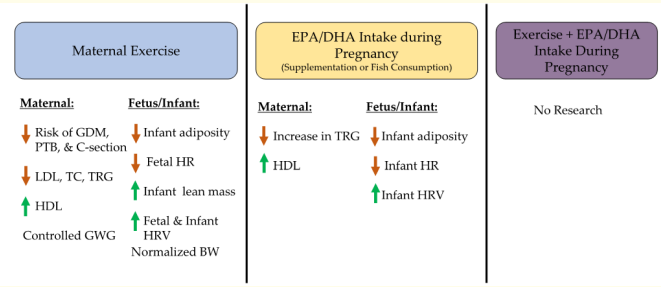

Figure 2: Summary of material and infant outcomes with maternal exercise, material supplementation of EPA/DHA n-3 PUFA supplementation, and combination of maternal exercise and supplementation.

development. More importantly, cholesterols and triglycerides (TG) have critical roles in fetal development. Cholesterol provides structure and integrity to cell membranes, is a precursor to steroid hormones, and plays an essential role in the development of the central nervous system [39]. Throughout gestation, TG provide an additional fuel source for pregnant women and fetal development [32,40]. It is estimated that 80% of fetal energy comes from glucose, leaving an additional 20% from other sources [32]. TG can provide both free fatty acids and ketones which can cross the placental barrier to be used as a fuel source by the fetus [40,41]. Studies have shown significant increases in maternal TC, LDL, HDL, and TG in the 2nd and 3rd trimesters, [31,41,42]. Although there is an expected increase in cholesterols and TG with pregnancy, excessive increases can cause maternal and infant complications. Elevated TC and/or TG are associated with increased incidences of preterm birth, preeclampsia, large for gestational age (LGA) [30,31], and increased infant birth weight [30,31]. As most of the fetal fat accumulation occurs during the 3rd trimester and comes from the transfer of placental fatty acids, it is believed that elevated TC, LDL, and TG leads to augmented infant adiposity via adipocyte, or fat cell, hyperplasia [43]. Therefore, maternal cholesterol and triglycerides need to be within the normal healthy range to ensure healthy maternal and infant outcomes.

Maternal TC and TG are important for the development of the fetus and placenta [33,39]. As pregnancy progresses, the steady increase in maternal estrogen causes a switch in maternal fat deposits from anabolic to catabolic states [39]. The augmented breakdown of fat stores increases the amount of TC and TG available for maternal and fetal utilization. Low levels of total cholesterol (TC) and triglycerides (TG) have been associated with intrauterine growth restrictions and pre-term birth [44,45]. Conversely, elevated levels of TC, LDL, and TG have been associated with risks of gestational diabetes, preeclampsia, fetal macrosomia, and cardiovascular disease [30-32,42]. Increased HDL has also been shown to be negatively correlated to birth weight. Therefore, pregnant women need to have a normalized maternal lipid profile to ensure healthy pregnancy outcomes and fetal development.

Maternal lipids and maternal DHA and EPA levels (Figure 2)

Numerous double-blind, placebo controlled trials in adults have shown DHA and EPA supplementation reduces TC, LDL, and TG, as well as increases HDL [46,47]. Most studies observed more than a 20% decrease in TG after 4 weeks of supplementation. Additionally, increased intake of DHA and EPA, either through fish consumption or supplementation, leads to reductions in adipocyte inflammation, oxidative stress, and free radical accumulation, which in turn, leads to lower TC, LDL, and TG with increased HDL [48,49]. Researchers have studied the effects of DHA and EPA intake during pregnancy, via supplementation or fish consumption, on maternal lipids [21,50]. In a randomized, double-blind study of 341 pregnant women, Helland., *et al*. (2006) observed the effects of PUFA intake on maternal lipids at 17 and 35 weeks of gestation [21]; this study had two groups: 1) supplement of 10 mL/day of cod liver oil containing DHA (1183 mg) and EPA (803 mg) or 2) supplement of 10 mL/day of corn oil containing LA (4744 mg) and ALA (92 mg). The authors observed a smaller increase in TG, with an increase in HDL, in the DHA/EPA supplement group compared to the LA/ALA group [21]. However, this study did not disclose if the pregnant women were in the fasted state for the blood collection. Also, omega-6 was not considered; therefore, these findings may be due to the effects of high omega-6 intake rather than benefits of omega-3 intake. Williams., *et al*. (2006) investigated self-reported fish consumption and measured maternal RBC concentrations of DHA, EPA, and lipids before 20 weeks of gestation [50]. These investigators reported significantly lower TG and higher HDL in women that reported having fish twice per week compared to women who reported consuming fish less than once per week [50]. However, this study only observed maternal lipids at early term pregnancy (average 13 weeks of gestation) which is prior to the natural pregnancy-related increases in maternal lipids [30,32,42]. The samples were also non-fasted. Therefore, a gap still exists on

the effect of maternal DHA and EPA concentrations on mitigating the rise in TC, LDL, and TG, as well as increasing HDL from early to late pregnancy.

Maternal lipids and maternal exercise (Figure 2)

Exercise is known to reduce TC, LDL, and TG while increasing HDL in non-gravid women and the general population; a few studies have seen similar results on the effects of exercise and lipid levels in the pregnant population [34-36]. One randomized control trials (RCT) recruited sedentary pregnant women in their 1st trimester, implemented a 12 week exercise intervention, and examined cholesterol and TG before and after the intervention [35]. Beginning about 16-20 weeks of gestation, pregnant participants engaged 50 minutes of exercise (10 minute walking warm-up, 30 minutes of aerobic exercise, 10 minutes of resistance exercise) 3 days per week, for 12 weeks. Between 28-32 weeks of gestation, pregnant women in the exercise group had significantly less increase in TG compared to their non-exercising counterparts. Pregnant exercisers had an overall decrease in LDL, while non-exercising controls had increased LDL [35]. However, it is unclear if the investigators controlled for timing and fasted state of the blood measures. Loprinzi., *et al*. (2013) also examined maternal physical activity and lipids. The authors recruited all pregnant individuals, regardless of gestational age, that could walk and wear an accelerometer. The accelerometer was worn for 7 days to assess maternal physical activity levels. Pregnant women who engaged in moderate to vigorous activity exhibited higher HDL and those that were sedentary exhibited higher LDL [34]. However, this study was cross-sectional and did not control for week of gestation or address individual changes in lipids due to physical activity or week of gestation, since only one blood sample was collected. Butler., *et al*. (2004) examined maternal physical activity and lipids in early pregnancy. The authors observed lower TC and TG in pregnant women who participated in physical activity compared to those that were inactive. However, this study was cross-sectional, utilized self-reported questionnaires, and did not use fasted samples. One RCT by Strom., *et al*. (2022) examined the effects of maternal aerobic exercise, polyunsaturated fatty acids, and maternal lipid levels at 16 and 36 weeks of gestation [51]. Pregnant women were recruited in their 1st trimester and engaged in aerobic exercise of 50 minutes of exercise 3 or more days a week for the remainder of their pregnancy (~24 weeks).These investigators observed that women in the aerobic exercise group exhibited significantly lower TG compared to the non-exercising controls [51]. This study was a longitudinal study that utilized fasting blood samples, however, they only utilized aerobic exercise and blood samples were only taken at 16 and 36 weeks of gestation. Therefore, a gap still exists regarding the influence of exercise and exercise type throughout multiple time points in pregnancy on maternal lipids.

Infant body composition and pregnancy outcomes (Figure 2)

Obesity during pregnancy is a major risk factor for the mother and the fetus. Cnattingius., *et al*. (2012) accessed birth records of approximately 163,000 nulliparous women [52]. The authors found a positive correlation between maternal birth weight with her risk of adult obesity, as well as maternal birth weight with the incidence of her child being large for gestational age (LGA). Infants that were born to women who were born LGA and obese as an adult had the highest risk of being born LGA compared to infants born to women with lower birth weight and obese as adults or compared to infants of women who were born LGA and had a normal BMI into adulthood [52]. Their findings highlighted that women who were obese in pregnancy had the highest risk of having infants with high birth weights [52]. Maternal obesity is only one risk factor for poor infant body composition outcomes. A study by Vrijkotte., *et al*. (2012) evaluated non-fasting total cholesterol and triglyceride levels at early gestation and infant outcomes of preterm birth, small for gestational age (SGA), LGA, and fetal/infant death [30]. In 2,037 pregnant women, elevated triglycerides were linearly associated with LGA and preterm delivery [30]. Infants born LGA or preterm had an increased likelihood of developing obesity and diabetes [52]. Additionally, infants born SGA are also at risk of adverse health outcomes. Wei., *et al*. (2003) screened all 6-18 year old children in Taiwan for diabetes [53]. The authors collected fasting blood glucose tests for students that tested positive for glucosuria twice in 2 weeks [53]. They found that a U-shaped relationship existed between birth weight and risk of type 2 diabetes, thus showing that metabolic diseases are more likely to occur to infants that are born with higher and lower birth weights outside of the normal range. Therefore, it is important to create a positive in utero environment to help normalize birth weight and prevent either SGA or LGA.

Maternal DHA and EPA concentrations and infant body composition (Figure 2)

As previously stated, supplementation of DHA and EPA in the general population protects against obesity by reducing

inflammation and adipocyte formation and is coupled with changes in lipid profiles (e.g. decreased TC, TG, increased LDL, HDL) [20]. Researchers have started to investigate the effects of maternal DHA or EPA supplementation on infant body composition. Carlson., *et al*. (2013) implemented a double-blind, randomized controlled trial with 350 women from 20 weeks of gestation until delivery [54]. The treatment group received 600 mg/d of DHA and the control received a placebo. RBC concentrations of DHA were analyzed from pregnant women at 20 weeks of gestation and birth, as well as from cord blood; it was not stated if the samples were taken in the fasted or non-fasted state. The authors observed longer gestation, increased birth weight, length, and head circumference in the supplemental group compared to the control [54]. Much., *et al*. (2013) recruited 208 pregnant women in an open-label randomized controlled trial to observe the effects of high dose omega-3 supplementation with diet counseling on infant body composition at birth, 6 weeks, 4 months, and 12 months after delivery [55]. Pregnant women received 1200 mg of omega-3s from 15 weeks of gestation until 4 months after delivery [55]. Maternal fasting blood samples were collected at 15 and 32 weeks of gestation as well as 6 weeks and 4 months postpartum [55]. Maternal DHA, EPA, total omega-3s, AA, and total omega-6s at 32 weeks of gestation were all positively correlated to infant weight, length, and lean body mass at birth similar to Carlson., *et al*. (2013) [54,55]. Maternal DHA and EPA supplementation was also negatively correlated with infant fat mass at birth and 6 weeks of age [55]. The observed effect of maternal DHA and EPA supplementation was no longer detected at one year of age, in which they suggested that DHA and EPA growth patterns were prenatal rather than postnatal. However, supplementation was stopped 4 months postnatal and observed effects may not have persisted up to 1 year of age from the lack of supplementation, which suggests continual supplementation may enable enhanced postnatal growth patterns to persist.

Donahue., *et al*. (2011), however, did see an effect of maternal DHA and EPA concentrations in infants after 1 year of age [22]. Researchers compared the DHA and EPA concentrations, in non-fasted blood samples at 29 weeks of gestation as well as in umbilical cord blood at delivery, with child body composition at a 3 year follow-up [22]. The authors observed that women with higher DHA and EPA concentrations at 29 weeks of gestation and higher DHA and EPA concentrations in cord blood at delivery had children with significantly less adiposity [22]. Three-year old children who were born to women with a higher omega-6 to omega-3 ratio had higher adiposity [22]. Although the blood samples were non-fasted, PUFA concentrations in maternal blood correlate with the self-reported levels from a food frequency questionnaire. Other studies by Hidaka., *et al*. (2018) and Vidakovic., *et al*. (2016) observed similar findings up to 5 and 6 years after delivery [23,24]. In a randomized trial, Hidaka., *et al*. (2018) observed increased maternal RBC DHA concentrations in the group receiving 600 mg of DHA compared to the placebo group. They also observed a positive correlation between change in maternal RBC DHA concentrations and higher offspring fat-free mass at 5 years of age [24]. Vidakovic., *et al*. (2016) observed that lower omega-3s and higher omega-6s in the second trimester of pregnancy (~20 weeks gestation) correlated to higher body fat and abdominal fat at 6 years of age [23]. Neither study disclosed if the blood samples were taken in a fasted state. Altogether, current evidence suggests that omega-3s, such as DHA, have positive impacts on infant body composition from birth and up to 6 years of age. However, a gap still exists between late pregnancy (36-40 weeks of gestation), maternal fasted PUFA concentrations, with specific infant body composition and morphometric measures. Particularly, studies need to observe a "baseline" infant measure that is close to delivery but provides for a "wash out" period from pregnancy, just as 4 weeks postnatal.

Maternal exercise and infant body composition (Figure 2)

Maternal exercise during pregnancy improves infant body composition by reducing fat mass and increasing lean mass [8,37,38]. Clapp., *et al*. completed three different studies between 1996-2002 [8-10]. In 1996, Clapp., *et al*. recruited 40 pregnant women (matched for socioeconomic status, education, parental morphometry, maternal employment, preconception fitness, maternal weight change, infant sex, gestational age) to either continue their moderate intensity physical activity level or to decrease to light intensity walking [10]. The authors observed infants of pregnant women that maintained moderate intensity exercise during pregnancy exhibited lower birth weight and body fat percent (BF%) relative to infants of pregnant women that decreased to light intensity exercise during pregnancy; interestingly, parallel results were observed in decreased body weight and sum of skinfolds in the children at the five-year follow-up [10]. In a different population of 104 women [9], Clapp., *et al*. (1998) observed a similar decrease in birth weight and BF% in

response to moderate intensity exercise during pregnancy, however, did not see the same effects in the children at the 1 year follow up [9]. In a prospective randomized 3 group study, Clapp., *et al*. (2002) observed the effects of different exercise doses with standard intensity (oxygen consumption, 55%-60% of pre-pregnancy VO_{2max}) throughout pregnancy on infant weight and BF% at 5 days after birth [8]. The authors recruited 80 women to participate in one of the 3 groups: 1) Lo-Hi group exercised 20 minutes a day, 5 days up to week 24 then exercised 60 minutes a day, 5 days a week to delivery; 2) Mod-Mod group exercised 40 minutes a day, 5 days a week throughout pregnancy; and 3) Hi-Lo group exercised 60 minutes a day, 5 days a week up to week 24 then exercised 20 minutes a day, 5 days a week until delivery. They observed that the moderate exercise dose throughout pregnancy (Mod-Mod) had lower BF% in five-day old infants compared to same age infants of women in the other two groups [8]. Measures at birth or five days after birth is essentially an extension, final timepoint, of the exposure during pregnancy; however, months after delivery may have numerous extraneous environmental (e.g. daycare, solid food, etc.) differences between groups. Therefore, it is important to assess infants around 4 weeks of age, which allows for a potential de-training from the in-utero environment, to determine if changes persist after birth. Overall, there are gaps particularly using current recommended guidelines of exercise and measuring infant body composition at 1 month of age.

Infant heart rate (HR) and heart rate variability (HRV) (Figure 2)

In the United States, cardiovascular disease is the leading cause of death [56]. Lower HR and increased HRV are associated with decreased risk of cardiovascular disease [57-59]. Findings from a 2013 study indicated higher resting HR is associated with an increased risk of cardiovascular death by 34% [57]. Decreased HRV is associated with many cardiovascular disease risk factors such as obesity, diabetes, high cholesterol, hypertension, as well as modifiable lifestyle risk factors such as smoking and physical inactivity [58]. HR and HRV are also used to determine appropriate fetal and infant cardiac autonomic maturation. The parasympathetic nervous system, specifically the portion that regulates HR, experiences the most significant development and myelination during the last trimester of pregnancy [60]. The fetal HRV pattern observed *in-utero* persists into adulthood [59]. Thus, improving fetal cardiac autonomic control, as measured by HRV, may lead to decreased risk of cardiovascular disease after birth. More importantly, HRV can be used to assess autonomic imbalance and is an indicator of appropriate cardiac autonomic development in infants, as it directly relates to vagal nerve myelination *in-utero* [58,60].

Maternal DHA and EPA concentrations and infant HR and HRV (Figure 2)

Previous research has shown a positive effect of maternal PUFA intake, particularly DHA and EPA, on fetal and infant HR and HRV [6,17]. Gustafson., *et al*. (2013) observed the effect of maternal DHA supplementation on fetal autonomic control through a randomized, double-blind, trial that recruited and retained 46 women in their 1st trimester and followed them until delivery [6]. The authors observed fetal HR and HRV at 24 weeks, 32 weeks, and 36 weeks of gestation [6]. The treatment group received 600 mg/day of DHA and the other received a placebo [6]. They also collected maternal blood samples (enrollment, after delivery), and cord blood [6]. They observed significantly increased fetal HRV measures, such as standard deviation of normal to normal R peaks (SDNN), very low frequency (VLF), and low frequency (LF) from the DHA supplementation group relative to fetuses of women in the placebo group [6]. Although they did not disclose if their blood samples were fasted, they observed a significant increase in maternal RBC DHA concentrations in their supplemental group [6]. Drewery., *et al*. (2017) recruited 11 pregnant women [17]. The authors analyzed maternal DHA and EPA concentrations in RBCs obtained at 20, 24, 32, and 36 weeks of gestation. The maternal RBC DHA and EPA concentrations were correlate with infant HR and HRV measures recorded at 2 weeks, 4 months, and 6 months [17]. They observed decreased 4 and 6 months old infant HR and increased HRV with higher maternal omega-3 concentrations [17]. Another important finding from this study was an association observed with omega-6s, in which high concentrations of maternal omega-6s at 20, 24, 32, and 36 wks in pregnancy was associated with higher HR and lower HRV in infants at 2 weeks, 4 months, and 6 months [17]. The study had a small sample size but suggests a potential association between maternal DHA/EPA level and infant cardiac autonomic control.

Maternal exercise on infant HR and HRV (Figure 2)

A few studies that have examined the effects of maternal exercise and fetal and infant HR and HRV [4,5]. May., *et al*. (2010)

recruited 26 physically active pregnant women and 35 non-exercising women that self-reported their physical activity and recorded fetal magnetocardiograms (MCGs), recordings similar to electrocardiograms, at 28, 32, and 36 weeks of gestation [4]. The authors found the fetuses of women that exercised exhibited significantly lower HR and increased measures of HRV at 36 weeks of gestation compared to the fetuses of non-exercising women [4]. In a follow-up study, May., *et al*. (2014) observed increased infant HRV in one-month old infants born to exercise trained women compared to infants of non-exercisers [5]. These studies suggest potential long-term benefits of maternal exercise on infant cardiac autonomic control.

Summary and Statement of Problem

These studies suggest that fetal development may be programmed by maternal *in utero* environment, specifically exercise or PUFA supplementation, to have a positive impact on infant health measures [2,3]. Although, the evidence demonstrates similar positive infant outcomes for the exercise or PUFA supplementation during pregnancy, there has been no studies to date on the interaction of maternal exercise and PUFA concentration related to offspring risk of heart disease, obesity, and diabetes. Current research indicates that maternal aerobic exercise or adequate PUFA individually intake are associated with improved maternal lipid profiles and decreased infant obesity [35,50,51]. Furthermore, our research and that of others have demonstrated aerobic exercise during pregnancy is associated with decreased infant adiposity [10] and decreased markers of heart disease risk (lower HR and increased HRV, markers of autonomic control) [5,10]. Interestingly, similar improvements in infant body composition, HR and HRV are also evident with maternal supplementation of polyunsaturated fatty acids (PUFAs), such as DHA and EPA, during pregnancy [6,17]. Since aerobic exercise or polyunsaturated fatty acid (PUFA) supplementation during pregnancy individually are both associated with improved health, maternal lipids, decreased infant adiposity, increased infant HRV [5,6,10,17], the potential interaction of maternal exercise and PUFA concentrations on maternal and infant health outcomes warrants investigation. Therefore, future research should focus on the potential interaction of maternal exercise and PUFA levels to influence maternal lipids, infant body composition, and infant health outcomes.

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