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# Pregnancy Determinants of Child Growth and Neurodevelopment:

## Adiposity, gestational diabetes mellitus, and diet

Lotta Saros

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*To my family*

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ABSTRACT

Maternal lifestyle and health during pregnancy may have far-reaching effects on the health of children. The aim in this thesis was to investigate the extent to which adiposity, gestational diabetes mellitus (GDM), and diet in pregnancy influence the growth and neurodevelopment of children up to 5–6 years of age. Also, the impact of maternal fish oil and/or probiotics intervention on a child's growth was studied.

The mothers, with overweight or obesity, were randomised into intervention groups (fish oil + placebo, probiotics + placebo, fish oil + probiotics, placebo + placebo) from early pregnancy onwards. The mothers were followed throughout pregnancy and their children for 5–6 years postpartum (n=159–373). The growth data (0–2 years) were collected from welfare clinic cards and body composition was measured by an air displacement plethysmography (2 years). Neurodevelopmental assessments were performed at 2 and 5–6 years of age. Diet (diet patterns from food diaries, Index of Dietary Quality) and body composition were evaluated in early and late pregnancy. GDM was diagnosed by an oral glucose tolerance test. The data were analysed using linear/logistic regression models and Pearson/Spearman correlations.

A good dietary quality in pregnancy associated with an increased height and head circumference standard deviation score (SDS) at 0–2 years, but a lower adiposity in children at 2 years. GDM led to a lower infantile head circumference SDS while a higher maternal body fat mass to an increased height and head circumference SDS at 0–12 months. Maternal consumption of probiotics was associated with lower weight and lower odds for overweight in children at 2 years. Considering neurodevelopment, a good dietary quality and a healthy dietary pattern in pregnancy associated with better expressive language and motor skills in children at 2 and 5–6 years. GDM associated with less favourable language skills in children while a higher maternal body fat percentage and fat mass associated with less favourable cognitive, language, and motor skills at 2 and 5–6 years.

A health-promoting diet as well as consumption of probiotics during pregnancy by mothers with overweight or obesity, which are risk groups for pregnancy-related complications such as GDM, likely support their children's growth and neurodevelopment.

KEYWORDS: adiposity, diet, children, gestational diabetes mellitus, growth, neurodevelopment

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Biolääketieteen laitos ja Ravitsemus- ja Ruokatutkimuskeskus
Ravitsemus, Ruoka ja Terveys
LOTTA SAROS: Raskausajan säätelijät lapsen kasvulle ja hermostolliselle kehitykselle: lihavuus, raskausdiabetes ja ravinto
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TIIVISTELMÄ

Raskausajan elintavat ja terveys saattavat vaikuttaa lapsen pitkäaikaisterveyteen. Tässä väitöskirjassa tavoitteena oli selvittää missä määrin raskausajan lihavuus, raskausdiabetes ja ravinto vaikuttavat lapsen kasvuun ja hermostolliseen kehitykseen 5–6-vuotiaaksi asti. Lisäksi tutkittiin äidin kalaöljy- ja/tai probiootti-intervention vaikutusta lapsen kasvuun.

Äidit, joilla oli ylipainoa tai lihavuutta, satunnaistettiin interventioryhmiin (kalaöljy + lume, probiootti + lume, kalaöljy + probiootti, lume + lume) alkuraskaudesta alkaen. Äitejä seurattiin raskausaika ja heidän lapsiaan 5–6 vuotta synnytyksestä (n=159–373). Kasvutiedot (0–2 vuotta) kerättiin neuvolakorteista ja kehonkoostumus mitattiin ilman syrjäyttämiseen perustuvalla pletysmografialla 2-vuotiaana. Lasten kehitystä selvitettiin 2- ja 5–6-vuotiaana. Äitien ravinnonsaanti (ruokavaliotyypit ruokapäiväkirjoista, ruokavalion ravitsemuslaatuindeksi) ja kehonkoostumus mitattiin alku- ja loppuraskaudessa. Raskausdiabetes todettiin sokerirasitustestillä. Aineisto analysoitiin lineaarisilla/logistisilla regressiomalleilla tai Pearsonin/Spearmanin korrelaatioilla.

Raskausajan hyvä ruokavalion ravitsemuslaatu oli yhteydessä lapsen suurempaan pituuden ja päänympäryksen keskihajontalukuun (SD-luku) 0–2 vuoden iässä, mutta pienempään rasvamassan määrään 2-vuotiaana. Raskasdiabetes liittyi lapsen pienempään päänympäryksen SD-lukuun ja äidin korkeampi rasvamassan määrä lapsen suurempaan pituuden ja päänympäryksen SD-lukuun 0–12 kuukauden iässä. Äidin probioottien käyttö oli yhteydessä lapsen pienempään painoon ja pienempään ylipainon riskiin 2-vuotiaana. Kun lasten kehitystä tarkasteltiin, havaittiin, että raskausajan hyvä ruokavalion ravitsemuslaatu ja terveellisempi ruokavaliotyyppi olivat yhteydessä parempaan kielelliseen ja motoriseen kehitykseen 2- ja 5–6-vuotiaana. Raskausdiabetes liittyi lapsen heikompiin kielellisiin taitoihin, kun taas äidin korkeampi rasvaprosentti ja rasvamassan määrä heikompiin kognitiivisiin, kielellisiin ja motorisiin taitoihin 2- ja 5–6-vuotiaana.

Terveyttä edistävän ruokavalion noudattaminen ja probioottien käyttö raskausaikana tukevat todennäköisesti niiden lasten kasvua ja kehitystä, joiden äideillä on jo ennen raskautta ylipainoa tai lihavuutta ja näin ollen kuuluvat raskauskomplikaatioiden, kuten raskausdiabeteksen riskiryhmään.

AVAINSANAT: kasvu, kehitys, lapset, lihavuus, raskausdiabetes, ravinto

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# Abbreviations

| | |
|---|---|
| Bayley-III | The Bayley Scales of Infant and Toddler Development – Third Edition |
| BMI | Body mass index |
| CI | Confidence interval |
| DHA | Docosahexaenoic acid |
| DII | Dietary Inflammatory Index |
| E-DII | Energy adjusted Dietary Inflammatory Index |
| EPA | Eicosapentaenoic acid |
| GDM | Gestational diabetes mellitus |
| GW | Gestational week |
| HINE | The Hammersmith Infant Neurological Examination |
| IDQ | The Index of Diet Quality |
| IQR | Interquartile range |
| IL | Interleukin |
| LGA | Large-for-gestational age |
| Movement ABC-2 | The Movement Assessment Battery for Children – Second Edition |
| MUFA | Monounsaturated fatty acid |
| OR | Odds ratio |
| PUFA | Polyunsaturated fatty acid |
| SD | Standard deviation |
| SD-score | Standard deviation score |
| SGA | Small-for-gestational age |
| SFA | Saturated fatty acid |
| TNF-α | Tumour necrosis factor α |

# List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Saros L, Vahlberg T, Koivuniemi E, Houttu N, Niinikoski H, Tertti K, Laitinen K. Fish Oil And/Or Probiotics Intervention in Overweight/Obese Pregnant Women and Overweight Risk in 24-Month-Old Children. *Journal of Pediatric Gastroenterology and Nutrition*, 2023; 2: 218–226.

II Saros L, Vahlberg T, Koivuniemi E, Houttu N, Tertti K, Nitin S, Hébert J R, Niinikoski H, Laitinen K. Maternal diet and gestational diabetes mellitus modestly influence children's growth during their first 24-months. *Journal of Pediatric Gastroenterology and Nutrition*, 2025; 2: 355–366.

III Saros L, Lind A, Setänen S, Tertti K, Koivuniemi E, Ahtola A, Haataja L, Shivappa N, Hébert J R, Vahlberg T, Laitinen K. Maternal obesity, gestational diabetes mellitus, and diet in association with neurodevelopment of 2-year-old children. *Pediatric Research*, 2023; 1: 280–289.

IV Saros L, Setänen S, Hieta J, Kataja E-L, Suorsa K, Vahlberg T, Tertti K, Niinikoski H, Stenholm S, Jartti T, Laitinen K. The effect of maternal risk factors during pregnancy on children's motor development at 5-6 years. *Clinical Nutrition ESPEN*, 2025; 66: 236–244.

# 1 Introduction

It is widely acknowledged that both the genetic and environmental factors during the foetal period may affect later health and development in children. This has been detected, for example, in the studies regarding the Dutch famine (Roseboom et al., 2006); the individuals whose mothers were exposed to famine in any stage of pregnancy suffered more often from glucose intolerance. In addition, an exposure to famine in early pregnancy was related with offspring's higher risk for obesity, coronary heart disease and breast cancer in adulthood while an exposure to famine in mid-pregnancy led more often, e.g., to obstructive airways disease in offspring's later life (Roseboom et al., 2006). The association between early nutrition and later health of an offspring was later publicized by Professor Barker and his colleagues (Barker, 2000; Barker et al., 2002). They found in large cohort studies that a low birth weight of a new-born, which was used as a measure for maternal nutritional status and a compromised foetal growth, associated with an increased risk for coronary heart disease in later life. At that time, foetal programming theory was introduced. Programming refers to a phenomenon when a stimulus induces changes, for example, in the foetal metabolic or endocrine systems during a critical period, and these putative permanent changes in the cells and organs have lifelong health effects (Calkins & Devaskar, 2011). Subsequent research has also indicated that foetal predisposition to other maternal stressors during pregnancy, such as overweight, obesity or gestational diabetes mellitus (GDM) is associated with an increased disease risk in later life (Eriksson et al., 2014; Kinnunen et al., 2023; Razaz et al., 2020). Besides that, predisposition to stress or stress hormones in early pregnancy has been linked to a decreased brain volume and maturation delay, which in turn, may result in impaired neurodevelopment (Buss et al., 2012; Davis & Sandman, 2010; Ellman et al., 2008).

Maternal adiposity, GDM and nutrition are closely interconnected as excess energy intake is a major contributor for weight gain and, eventually obesity, which in turn predisposes women to GDM. These maternal factors induce changes, for example, in the maternal glucose metabolism and influence the level of systemic low-grade inflammation. Thus, they may influence the programming of foetal growth and neurodevelopment especially during the critical periods, when the major developmental steps take place. There is a wide interest to find new means to modify maternal diet during pregnancy, and thus likely to optimize the environment for foetal growth and brain development. Along with traditional diet counselling, dietary supplements have intrigued especially fish oil and probiotics. Fish oil is rich in n-3 polyunsaturated fatty acids (n-3 PUFAs) that are vital for the foetal brain development (González & Báez, 2017) while probiotics, live micro-organisms with potential beneficial health effects, have favourable impacts on weight in adults with overweight or obesity (Michael et al., 2021; Sudha et al., 2019). Preliminary evidence also suggests that these supplements may have beneficial effects on glucose metabolism and they can decrease the level of systemic low-grade inflammation, linked to overweight and obesity, in the adult population (Haghiac et al., 2015; Laitinen et al., 2008; Lalia & Lanza, 2016; Pan et al., 2021; Zheng et al., 2019). Moreover, probiotics have various favourable effects on the gut microbiota (Ma et al., 2023). The potential co-effects of fish oil and probiotics are not well studied and especially the research focusing on the growth and neurodevelopment of children is yet limited.

In conclusion, early-life circumstances, including maternal diet and metabolic health, are crucial in the early programming of the foetus. Modification of these circumstances may provide an opportunity to support the later growth and neurodevelopment of children. Particularly in the population of women with overweight or obesity, representing a risk group for GDM, it is of importance to gain more knowledge on what kind of a diet during pregnancy may support the optimal growth and neurodevelopment of children.

In this thesis, an overall aim was to investigate the associations between maternal adiposity, GDM and diet during pregnancy, and the growth and neurodevelopment of children. In addition, the impacts of dietary intervention with fish oil and/or probiotics during pregnancy and six months postpartum were examined.

# 2 Review of the Literature

## 2.1 Growth and neurodevelopment of children

In Finland, children's growth and development are regularly and frequently followed in the local child welfare clinics up to six years of age. Every Finnish child visits the child welfare clinic at least 15 times by age six years, most frequently during the first year of life when growth velocity and weight gain are at their peak.

The growth of children is regulated by various factors, such as maternal lifestyle habits, e.g., smoking but also genetics (Jelenkovic et al., 2016; Karvonen et al., 2021). At each scheduled visit to the child welfare clinic, height, weight and head circumference are carefully measured and the values are compared against the Finnish growth charts, which are based on the growth data obtained from healthy children (Saari et al., 2011). Children's growth in height as well as head circumference are evaluated by an age- and sex-specific standard deviation scores (SD-score). A positive value indicates an average higher/faster growth while a negative value indicates an average lower/slower growth. In Finland, children's weight can be evaluated by relating it to their height (weight-for-height%) where a positive value stands for weight higher than the average weight of children of same height and sex and, vice versa, a negative value denotes weight lower than the average weight of children of the same height and sex. For children aged ≥ two years, an age- and sex-specific body mass index (BMI) SD-scores can be used or, even more accurately and specifically, weight status can be evaluated using ISO-BMI, which converts a child's BMI to an adult equivalent. The most common cause for overweight and obesity in children is excess energy intake relative to energy expenditure. (Karvonen et al., 2012; Saari, 2023; Saari et al., 2011) Proportion of overweight children of all ages has increased drastically over the last few decades and nowadays as many as 14% and 24% of Finnish girls and boys aged 2–6 years had overweight or obesity, when assessed by ISO-BMI ($\geq 25 kg/m^2$) (Official statistics of Finland: Child and adolescent overweight and obesity, 2023).

The neurodevelopment of children is affected by various neonatal and maternal factors, for example male sex, low birth weight and/or gestational age as well as low maternal socio-economic status, and smoking (Linsell et al., 2015; Wehby et al., 2011). During each scheduled visit to the child welfare clinic, for example children's language skills (expressive and receptive), motor skills (fine and gross), and cognitive skills are assessed. Language skills can be divided into expressive language skills that refer to the ability to use language to express thoughts and ideas, while receptive language skills refer to the ability to understand the spoken and written language. Motor skills include fine motor skills that refers to coordination of small muscles such as fingers with vision, while gross motor skills refer to coordination of large muscles to enable movements such as walking. (Sinkkonen & Korhonen, 2021) In case of concerns about delay in neurodevelopment by parents, caregivers and/or health care professionals, children are referred to more detailed neurodevelopmental assessments such as the Bayley Scales of Infant and Toddler Development (Bayley-III) (Bayley Salo, S., Munck, P., Uusitalo, N., & Korja, R., 2006) performed by psychologists. The Bayley-III assesses the cognitive, language and motor skills in children aged 1–42 months. The most commonly used and best validated norm-referenced assessment method for detecting motor impairment in children aged 3–16 years, is the Movement Assessment Battery for Children (Blank et al., 2019). The revised version (The Movement Assessment Battery for Children – Second Edition, The Movement ABC-2) (Henderson et al., 2007) and its structural validity (Schulz et al., 2011) have previously been published. The prevalence of impaired cognitive skills in children, including learning difficulties, have been estimated to vary between 5–10%. The corresponding number for impaired language skills has been suggested to be 1–7% while for the motor impairment 5–6%. (Sinkkonen J & Korhonen L, 2021)

## 2.2 Obesity and gestational diabetes mellitus in pregnancy

### 2.2.1 Overview of obesity and gestational diabetes mellitus

The prevalence of overweight and obesity (BMI ≥25kg/m$^2$ and ≥30kg/m$^2$) has remarkably increased in the last decades affecting already 27.7% and 19.5% pregnant women in Finland, respectively (Official statistics of Finland: Perinatal statistics - parturients, delivers and newborns, 2023). BMI is a commonly used measure when assessing overweight or obesity but it does not distinguish between different tissues, such as fat and muscle. Body composition measurement is more accurate way to determine the level of fat mass or fat free mass. However, it is not generally used in the public health care. Overweight and obesity predispose pregnant women to various comorbidities, such as GDM, hypertension, pre-eclampsia, and an increased risk of miscarriage.

GDM is defined as glucose intolerance first detected during pregnancy, and its prevalence in 2019 was reported to be 19.1% in Finland (Official statistics of

Finland: Perinatal statistics – parturients, delivers and newborns, 2019). GDM is diagnosed with a two-hour 75 g oral glucose tolerance test in mid-pregnancy or in some cases already in early pregnancy. The test is offered to all mothers in the maternal welfare clinics (Gestational diabetes: Current care guideline, 2024). GDM has many short- and long-term consequences to the mother and child. The risk for pre-term delivery, macrosomia, and caesarean section is elevated (Ye et al., 2022). Later on, the mothers have a higher risk for cardiovascular diseases, type 2 diabetes (Kramer et al., 2019; Rayanagoudar et al., 2016), and children are predisposed to obesity (Lowe et al., 2019).

### 2.2.2 Adaptations in pregnancy and pathophysiology of gestational diabetes mellitus

During pregnancy various unique changes occur in the maternal body to ensure the proper growth and development of a foetus but also to prepare for lactation (Parrettini et al., 2020). In early pregnancy these adjustments are considered to be anabolic as maternal energy-storages increase, while in later stage of pregnancy catabolic adjustments happen to ensure foetal growth (Parrettini et al., 2020).

In pregnancy maternal fasting glucose level decreases, which is at least partially due to an increased blood volume as well as transport of glucose to the foetus throughout the pregnancy. This leads to mild insulin resistance that is considered to be vital for an adequate supply of glucose from mother to foetus (Angueira et al., 2015). However, in women with overweight or obesity insulin resistance is even greater, which is likely due to a higher amount of adipose tissue (Kampmann et al., 2019). Various hormones promote insulin resistance, including oestrogen, progesterone, leptin and placental hormones (Plows et al., 2018). In addition, cytokines such as tumour necrosis factor-α (TNF-α) are involved in the development of insulin resistance in obesity complicated pregnancies (Catalano, 2010). The increased need of glucose is compensated by enhanced gluconeogenesis and lipolysis, which results in higher blood glucose and triglycerides levels (Angueira et al., 2015).

Immunological adaptations happen in the maternal body as well. Early pregnancy is characterised as a pro-inflammatory phase that is needed in the implantation, followed by an anti-inflammatory phase in mid-pregnancy that is necessary for foetal growth. Finally, in late pregnancy a switch to pro-inflammatory phase occurs to induce labour (Mor et al., 2017). These processes are strictly regulated in normoglycemic pregnancies (Pantham et al., 2015). In pregnancies complicated by obesity or GDM the level of systemic low-grade inflammation is higher, which is manifested by elevated levels of pro-inflammatory cytokines, such as interleukin 6 (IL-6), TNF-α, and C-reactive protein (McElwain et al., 2021). The role of placenta is indisputable as it may act as a mediator between obesity, GDM and inflammation. The function of placenta may change in response to obesity; it may produce inflammatory markers and act as a site of inflammation (Pantham et al., 2015). On the other hand, placenta may adapt to the changes caused by maternal obesity and thus limit the transport of inflammatory markers to the foetus (Pantham et al., 2015).

The main factors in the development of GDM are β-cell dysfunction and insulin resistance. In GDM complicated pregnancies β-cells cannot response the increased requirement of insulin either due to an inability to release sufficient amount of insulin or to sense the increased glucose level. Insulin resistance develops when the cells do not response to the insulin and thus the transfer of glucose from the blood to the cells is diminished. Both these changes result in an elevated glucose level in the maternal blood. (Plows et al., 2018)

In the next chapters the previous literature on the association between maternal obesity and GDM with the growth and neurodevelopment of children will be reviewed.

### 2.2.3 Implications to growth of children

It is well known that children of mothers with overweight or obesity have an increased risk for developing overweight. This has been shown in a meta-analysis by Helsehurst et al. (2019), which included 79 studies and an age range of investigated children was 1–16 years (Heslehurst et al., 2019). They detected that both maternal overweight and obesity, defined by pre- or early pregnancy BMI, increased a child's risk for obesity while only maternal obesity increased a child's risk for overweight when compared to the group of mothers with normal weight. Another meta-analysis, including 45 studies, investigated the effects of maternal obesity, defined by pre-pregnancy BMI, on a child's birth weight and later overweight risk (Yu et al., 2013). The investigators demonstrated that children of mothers with overweight or obesity had a higher birth weight, a higher risk for macrosomia (birth weight >4500g) and large-for-gestational age (LGA, birth weight >2SD) as well as overweight/obesity when compared to children of mothers with normal weight. It was noted that there were various factors, such as maternal education level, age, GDM, and smoking status, which likely contribute to the detected associations and should be taken into account in future studies (Yu et al., 2013).

The link between GDM and a new-born growth measures has been studied in a recent meta-analysis including 156 studies (Ye et al., 2022). It was seen that GDM led to macrosomia and LGA of a new-born. The association between GDM and a child's growth up to 12 months has been inspected in another meta-analysis, which included 25 studies (Manerkar et al., 2020). The study showed that GDM associated with a higher body fat mass of children aged one to six months and a reduced height from one to 12 months. In contrast, no association was found between GDM and a BMI-value of children aged one to 12 months. (Manerkar et al., 2020)

In conclusion, although there is evidence that both maternal obesity and GDM may lead to a higher birth weight and later on a higher risk for overweight or excess adiposity in children, some disagreement exists and long-term follow up studies on an overall growth of children, including height, weight, head circumference, are lacking. In addition, no prior studies have investigated the potential association between maternal body composition, which describes adiposity more detail than a BMI-value, and a child's growth. The differences in past findings could be due to limited information on the potential confounders (e.g., socio-economic and lifestyle factors), sample size, determination of overweight/obesity in mothers and children, and cut-off values to diagnose GDM. As the prevalence of overweight is increasing in pregnant women more knowledge is needed especially on those children's long-term growth who belong to a risk group for adverse health outcomes, i.e., those born to mothers with obesity and/or GDM.

### 2.2.4 Implications to neurodevelopment of children

Considering maternal overweight and obesity their association with a child's neurodevelopment has been investigated in a previous meta-analysis (Sanchez et al., 2017). The study included 32 articles and an age range of the investigated children was 0.8–27 years. The outcomes were autism spectrum disorder, attention deficit hyperactivity disorder, cognitive and intellectual delay as well as emotional or behavioural problems. It was seen that children of mothers with pre-pregnancy overweight or obesity, defined by BMI, experienced a higher risk for developmental delay, emotional and behavioural problems, and attention deficit disorder when compared to the children of mothers with normal weight. (Sanchez et al., 2017) The association between maternal pre-pregnancy obesity, defined by BMI, and motor development of children is not clear as shown in a prior systematic review, including 10 studies (Adane et al., 2016). The investigators showed that maternal obesity or overweight were associated with poorer gross motor skills of children aged four months to five years, although this relation was not demonstrated in all studies. In addition, no association was detected with fine motor skills of children. It was pointed out that the variation in the results may be due to a child's age, confounders, such as parental socio-economic or genetic factors and smoking habits, or differences in the determination of overweight and obesity within the study populations. (Adane et al., 2016)

Considering the role of GDM in the neurodevelopment of children, the results are not completely cohesive. In one meta-analysis, including 10 cohorts, the relation between GDM and neurodevelopmental, cognitive, and behavioural development of children (age range 3–13 years) was inspected (Pretorius et al., 2025). It was found that GDM associated with a higher level of attention hyperactive disorder symptoms (4–6 and 7–10 years), externalising (4–6 and 7–10 years) and internalising (7–10 and 11–13 years) problems in children. However, after adjustments for confounders the associations between GDM, and externalising and internalising problems were diminished in the age groups of 7–10 and 11–13 years. On the other hand, GDM was not found to associate with motor development or nonverbal intelligence of children. The authors noted that limitations could arise from parent-reported outcomes as well as from the lack of information on potential confounders especially socio-economic factors but also other dietary and lifestyle factors such as smoking habits. (Pretorius et al., 2025)

All in all, previous research suggests that maternal obesity and GDM may lead to lower neurodevelopmental performance of children although disagreement exists. The different assessment methods as well as the age of children at the time of the neurodevelopmental assessment likely influence the findings. Additionally, potential confounding factors, sample size and the population likely have influence. Prior studies have used a BMI-value to assess maternal obesity, thus in future research body composition could be used instead as it is a more precise method to define adiposity. More research is needed especially on neurodevelopment of children whose mothers have overweight or obesity and thus a higher risk for developing GDM.

## 2.3 Diet in pregnancy

Dietary intake and the development of obesity are linked with each other as excess energy intake is the main reason for the weight gain. The importance of a health-promoting diet, such as consumption of vegetables, fruits, berries, whole-grains and fish, during pregnancy is indisputable as it may help prevent excessive gestational weight gain, affect beneficially the body composition (Pellonperä et al., 2019b), and lower the risk of developing GDM (Pajunen et al., 2022) in women with overweight or obesity. Besides that, the purpose of pregnancy diet is to ensure the proper growth and neurodevelopment of a foetus. The dietary recommendations for pregnant women in Finland largely follow the general recommendations for the adult population, although some restrictions exist (Eating together - Food recommendations for Families with Children, 2019). The diet is recommended to include whole-grains, vegetables, legumes, fruits and berries, which are good sources of fibre and many vitamins, as well as fish that includes PUFAs, iodine and vitamin D. In addition, low-fat meat and dairy products should be favoured. On the other hand, the consumption of foods rich in saturated fatty acids (SFAs), salt and sugar are recommended to be limited. It is of note that the energy requirements of pregnant women only elevate slightly. Previously, it has been shown that Finnish pregnant women, at risk for GDM, e.g., due to obesity, do not meet the dietary recommendation in all aspects; they consume an excess amount of SFAs while an intake of carbohydrates, fibre and PUFAs are at too low level (Korpi-Hyövälti et al., 2012; Meinilä et al., 2015; Saros et al., 2025).

Diet also has an important role in the management of GDM. The mothers with GDM are instructed to follow the general dietary recommendations, including consumption of vegetables, fruits, whole-grains, vegetable-based oils, fish, as well as low-fat dairy and meat products. The aim of the dietary therapy is, e.g., to maintain blood glucose at normal level, prevent the need for medication, and excess weight gain. (Gestational diabetes: Current care guideline, 2024)

In the next chapters, the association between maternal diet during pregnancy and the growth and neurodevelopment of children will be discussed.

### 2.3.1 Implications to growth of children

The most relevant studies for this thesis, from the past 10 years, investigating the association between maternal diet and a child's growth are listed in **Table 1**. A healthy diet during pregnancy, as measured by different indexes (i.e., Mediterranean diet score or healthy eating index), has been shown to associate with a lower BMI-value (Monthé-Drèze, et al., 2021) and a lower risk for overweight or obesity in children (Chen et al., 2021; Díaz-López et al., 2024). Further, associations between a better dietary quality and a higher birth weight and length (Yisahak et al., 2021) as well as a lower weight measures and body fat mass in children (Tahir et al., 2019) have been reported. However, disagreement also exists as not all studies have found relations between dietary indexes and a child's adiposity (Gonzalez-Nahm et al., 2019; Grandy et al., 2017).

Besides dietary quality indexes, data derived dietary patterns also have been shown to relate with a child's growth (**Table 1**). Previous studies have found that healthier dietary patterns associate with a lower BMI and adiposity, a lower risk for overweight or obesity, and a reduced body size in children (Chen et al., 2017; Gonzalez-Nahm et al., 2022). In addition, one study detected that a higher adherence to a prudent dietary pattern in pregnancy was linked with a lower birth weight and risk for LGA while a higher risk for small-for-gestational-age (SGA, birthweight <-2SD) (Englund-Ögge et al., 2019). On the other hand, unhealthier dietary patterns have been found to associate with a higher risk for SGA (Teixeira et al., 2021) and overweight/obesity in children (Hu et al., 2020). Nevertheless, in some studies no associations have been detected or the associations have been diminished after adjustments for confounders, such as socio-economic factors, primiparity, BMI, smoking, folic acid supplementation, breast feeding and a child's sex (Martin et al., 2016; Van Den Broek et al., 2015; Yisahak et al., 2021).

A few previous studies have investigated the association between maternal nutrient intakes and a child's growth (**Table 1**). The findings are somewhat consistent as a higher intake of fat and SFAs have been linked with a higher body fat mass and percentage in children (Damen et al., 2021; Meinilä et al., 2021; Nagel et al., 2021). However, one report found an inverse relation; a higher intake of n-3 PUFA in women with GDM was associated with a higher body fat mass and percentage in children while an opposite finding was detected in normoglycemic women (Brei et al., 2018). There are also studies that have not found relations between nutrient intakes, such as SFA or monounsaturated fatty acids (MUFA) and a child's growth measures or adiposity (Arslanian et al., 2020; Grandy et al., 2017; Hakola et al., 2017).

To conclude, a healthy diet in pregnancy seems to lower overweight risk, weight or adiposity in children. Yet, less in known on its effects on other growth measures, and disagreement also exists within the prior research. The reason for divergent findings could relate to the varying assessment methods for maternal diet (food frequency questionnaire, food diary, 24-hour recall) and a child's growth and adiposity (e.g., from medical records, study visits, dual-energy X-ray absorptiometry, skin-fold callipers), as well as age of children. In addition, the information on potential confounding factors (e.g., maternal socio-economic factors and smoking) and the population and sample size may influence the findings. Hence, long-term follow-up studies are needed to clarify the link between maternal diet during pregnancy and an overall growth (height, weight, head circumference) in children.

**Table 1.** Studies investigating the associations between maternal diet during pregnancy and a growth or adiposity of children.

| Reference | Study design | Study subjects | Methods | Findings |
|---|---|---|---|---|
| (Van Den Broek et al., 2015)<br>The Netherlands | Prospective cohort study | n=2695<br>Children aged 6 years<br>Mothers with mean BMI 23.3 ± 4.2 kg/m$^2$ | -Growth measures from study visit, body composition by dual-energy X-ray absorptiometry<br>-Dietary patterns from semi-quantitative food-frequency questionnaire (during pregnancy) | -Higher adherence to “vegetable, fish, and oil” and “nuts, soy, and high-fibre cereals” patterns: ↓ body mass index, fat mass index, and risk of overweight (unadjusted models)<br>-After adjustments NS |
| (Martin et al., 2016)<br>USA | Prospective cohort study | n=389<br>Children from birth until 3 years<br>Mothers with underweight, normal weight, overweight or obesity | -Birth variables form medical records and after that during paediatric or research visits<br>-Dietary patterns from food-frequency questionnaire (26-29 GW) | -Higher adherence to “White bread, red and processed meats, fried chicken, French fries, and vitamin C–rich drinks” compared to “fruits, vegetables, baked chicken, whole-wheat bread, low-fat dairy, and water” pattern:<br>↑ BMI-for-age SD-score (1 and 3 years), odds for overweight and obesity (3 years) After adjustments NS<br>-Higher adherence to “White bread, red and processed meats, fried chicken, French fries, and vitamin C–rich drinks”: ↓ BMI-for-age SD-score at birth |
| (Chen et al., 2017)<br>Singapore | Prospective cohort study | n=1247<br>Children from birth until 54 months<br>Mothers with mean BMI 22.7 ± 4.4 kg/m$^2$ | -Weight and height during research visits. Abdominal circumference, subscapular skinfold, and triceps skinfold (skin-fold callipers)<br>-Dietary patterns from 24-h dietary recalls (26-28 GW) | -Higher adherence to “Vegetables-fruit-and-white rice” pattern: ↓ triceps skinfold (longitudinal analyses),<br>↓ BMI SD-score, triceps skinfold, subscapular skinfold, and sum of skinfolds at 18 months and older<br>-Higher adherence to “Higher fruits and vegetables, lower fast-food pattern”: ↓ adiposity |

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| (Hakola et al., 2017)<br>Finland | Prospective cohort study | n=3807<br>Children aged 2 to 7 years<br>Mothers with median BMI 23.4 (21.4-26.2)–23.5 (21.5-26.3) kg/m$^2$ according to child's sex | -Weight and height from study visits<br>-Nutrient intakes from food frequency questionnaire (late pregnancy) | -High n-6:n-3 ratio: U-shape association with obesity in girls<br>-Arachidonic acid: DHA + EPA ratio association with obesity in boys<br>-SFA, MUFA intakes: NS |
| (Grandy et al., 2017)<br>USA | Prospective pilot study | n=41<br>Children at birth<br>Mothers with normal weight, overweight or obesity | -Birth weight and height, skin fold thickness, fat mass<br>-Dietary quality by HEI and nutrient intakes from 24-h recall during pregnancy | -Lower dietary quality: ↑ birth weight and height<br>-Dietary quality, macronutrients: NS body fat percentage, abdominal circumference, ponderal index |
| (Brei et al., 2018)<br>Germany | Randomised controlled trial | n=208<br>Children from birth to 5 years<br>Mothers with underweight, normal weight, overweight or obesity | -Growth measures from health records and study visits<br>-Skinfold thickness based on Holtain Calliper and abdominal subcutaneous and preperitoneal fat areas based on sonography or MRI<br>-7-day food diaries (15 and 32 GW) | Late pregnancy, higher intake of:<br>-PUFA: ↓ birth weight and fat mass, ↓ subcutaneous fat area at 5 years<br>-Total fat and saturated fatty acids: ↓ subcutaneous fat area at 1 and 5 years<br>-Protein: ↓ BMI SD-score at 3 and 5 years<br>-Fibre: ↑ abdominal subcutaneous fat at 1, fat mass at 3, BMI SD-score at 5 years |
| (Englund-Ögge et al., 2019)<br>Sweden | Prospective cohort study | n=65 904<br>Children at birth<br>Mothers with mean BMI 23.1 ± 3.6–24.6±4.6 kg/m$^2$ depending on dietary pattern | -SGA/LGA based on 1) ultrasound (>2 SD-score above or below), 2) the Norwegian new-born population growth curves, 3) ultrasound-derived growth curves<br>-Dietary patterns from food frequency questionnaire (mid-pregnancy) | -Higher adherence to Prudent compared to Western pattern: ↓ birth weight and LGA risk, ↑ SGA risk,<br>- Higher adherence to Tradition compared to Western pattern: ↑ birth weight and LGA risk, ↓ SGA risk |
| (Gonzalez-Nahm et al., 2019)<br>USA | Prospective cohort study | n=817<br>Children from birth to 12 months<br>Mothers with mean BMI 30.1 ± 9.3kg/m$^2$ | -Growth variables from medical records or study visits<br>-Block food frequency questionnaire, and assessed diet quality using a modified A-HEI (during pregnancy) | -Higher A-HEI: ↑ birth weight for gestational age SD-score and macrosomia (unadjusted)<br>-After adjustments NS |

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| (Tahir et al., 2019)<br>USA | Prospective cohort study | n=354<br>Children from birth until 6 months<br>Mothers with mean BMI 26.4 ± 5.4kg/m$^2$ | -Growth measures from study visits (0, 3, 6 months)<br>-Body composition by dual-energy X-ray absorptiometry (6 months)<br>-Dietary quality by HEI (during pregnancy and 1- and 3-months post-partum) | -Higher dietary quality during pregnancy and post-partum: ↓ weight-for-length (each time point) and body fat percentage<br>-Higher dietary quality post-partum: ↓ body fat mass |
| (Hu et al., 2020)<br>USA | Prospective cohort study | n=1257<br>Children aged 0-4 years<br>Mothers with mean BMI 27.5 ± 7.5kg/m$^2$ | -Growth variables from medical records or study visits<br>-Dietary patterns from food frequency questionnaire (2$^{nd}$ trimester) | -Higher adherence to “Fast food” pattern:<br>↑ risk for rising-high BMI trajectory, overweight/obesity at 4 years<br>-“Processed” pattern: NS |
| (Arslanian et al., 2020)<br>Samoa | Prospective cohort study | n=107<br>Children aged 1-14 days<br>Mothers with normal weight, overweight, obesity | -Body composition using dual-energy X-ray absorptiometry<br>-Nutrient intake from food frequency questionnaire (34-41 GW) | -Nutrient intake: NS adiposity |
| (Chen et al., 2021)<br>Ireland, France, the Netherlands, Poland, UK | Seven European cohort studies | n=16 295<br>Children from early to late childhood<br>Mothers with mean BMI 22.3 ± 3.7–26.2 ± 4.5 kg/m$^2$ depending on the cohort | -Growth measures from medical records or study visits<br>-Sum of skinfold thickness, fat mass index and fat-free mass index by bioelectrical impedance analysis or dual-energy X-ray absorptiometry<br>-Food frequency questionnaire, DASH score, energy-adjusted E-DII™ (pre- early and late pregnancy) | -Higher E-DII early pregnancy: ↑ odds for overweight/obesity (inverse relationship in late pregnancy)<br>-Higher DASH score in early and late pregnancy: ↓ odds for overweight/obesity |
| (Damen et al., 2021)<br>USA | Prospective cohort study | n=79<br>Children at birth<br>Mothers with mean BMI 27.4 ± 6.16 kg/m$^2$ | -Growth measures from medical records, skinfold thickness by Lange skinfold callipers<br>-Diet by Block food frequency online questionnaire (each trimester) | -Higher intake of total fat and saturated fatty acids (total average intake during pregnancy): ↑ body fat percentage<br>-Higher intake of total fat, saturated fatty acids, unsaturated fatty acids (total average intake in second trimester): ↑ body fat percentage |

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| (Meinilä et al., 2021)<br>Finland | Randomized controlled trial | n=301<br>Children aged 5 years<br>Mothers with BMI≥30kg/$^2$ and/or previous GDM | -Body fat mass and fat percentage by bioimpedance<br>-Macronutrient intakes from 3-day food-diaries (5-18 GW, 3rd trimester and postpartum) | -Higher n-3 PUFA intake in normoglycemic women: ↓ body fat mass and percentage<br>-Higher n-3 PUFA intake in GDM women: ↑ body fat mass and percentage<br>-Higher SFA intake: ↑ body fat mass and percentage<br>-Higher carbohydrate intake: ↓ body fat mass and percentage |
| (Monthé-Drèze et al., 2021)<br>USA | Prospective cohort study | n=1459<br>Children from birth to adulthood<br>Mothers with normal weight, underweight, overweight, obesity | -Growth measures from study visits and medical records<br>Trajectories: birth to 1 months, 1–6 months, 6 months to 3 years, 3–10 years, and >10 years<br>-DII, A-HEI, and MDS from food frequency questionnaires (mean 9.9 and 27.9 GW) | -Highest vs lowest DII quartile: ↑ BMI SD growth rate 3-10 years and BMI SD-score 7-10 years<br>-Lower adherence to MDS: ↑ BMI SD-score 3-15 years<br>A-HEI: NS |
| (Nagel et al., 2021)<br>USA | Prospective cohort study | n=349<br>Children aged 6 months<br>Mothers with normal weight, overweight or obesity | -Growth measures from study visits<br>-Body composition by dual-energy X-ray absorptiometry<br>-Nutrient intakes from food frequency questionnaire (1st trimester and at 1 and 3 months postpartum) | -Higher intake of total fat and saturated fatty acids: ↑ body fat percentage<br>-Higher intake of added/excess sugar: ↑ weight-for-length SD-score and body fat percentage |
| (Teixeira et al., 2021)<br>Brazil | Prospective cohort study | n=299<br>Children at birth<br>Mothers with normal weight, overweight or obesity | -Growth measures from study visit<br>-Dietary patterns from food frequency questionnaire (pre-pregnancy) | -Higher adherence to “Snacks, sandwiches, sweets and soft drinks” pattern”: ↑ odds of SGA |
| (Yisahak et al., 2021)<br>USA | Prospective cohort study | n=1948<br>Children at birth<br>Mothers with mean BMI 24.0 ± 4.0–26.3 ± 5.3 kg/m$^2$ depending on dietary variable | -Growth measures from medical records and study visits<br>-Food frequency questionnaire (8–13 GW), A-HEI-2010, aMed, DASH, dietary patterns | -Higher A-HEI, aMed, DASH: ↑ birth weight<br>-Higher aMed: ↓ odds of low birth weight<br>-Higher aMed and DASH: ↑ length and upper arm length<br>-Dietary patterns (“solid fats, non-whole grains, white potatoes, meat” and “different vegetables, seafood”): NS |

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|---|---|---|---|---|
| (Gonzalez-Nahm et al., 2022)<br>USA | Prospective cohort study | n=929<br>Children from birth to 8 years<br>Mothers with mean BMI 27.5 ± 7.1 kg/m$^2$ | -Growth measures from medical records<br>-Mediterranean diet adherence from food frequency questionnaire (during pregnancy) | -Higher adherence to Mediterranean diet: ↓ body size at birth, 3-5 years and 6-8 years |
| (Díaz-López et al., 2024)<br>Spain | Randomised controlled trial | n=272<br>Children aged 4 years<br>Mothers with mean BMI 25.1 ± 4.4 kg/m$^2$ | -Growth measures from study visits<br>-Mediterranean diet adherence from food frequency questionnaire during pregnancy | -Higher adherence to Mediterranean diet: ↓ risk for overweight/obesity at 4 years |

A-HEI=Alternative Healthy Eating Index, aMED=Alternate Mediterranean Diet Score, DII=Dietary Inflammatory Index, BMI=Body mass index, DASH=Dietary approaches to stop hypertension, GW=Gestational week, LGA=large for gestational age, MDS=Mediterranean Diet Score, NS=Not significant, SD-score, standard deviation score, SGA=Small-for-gestational age, ↑=higher/greater, ↓=lower/smaller

### 2.3.2 Implications to neurodevelopment of children

The association between maternal diet and neurodevelopment of children have been investigated by several studies. The most relevant research for this thesis that has been published within the past 10 years is shown in **Table 2**. Two recent studies have found that a healthy diet, as defined by a higher Mediterranean diet score (e.g., consumption of vegetables, legumes, fruits, nuts, and fish), was associated with better communication, intelligence, problem-solving and personal-social skills from early to mid-childhood (Dai et al., 2023; Mahmassani et al., 2022). However, Dai et al. did not detect a relation with motor gross or fine motor skills. Besides that, better prenatal diet quality (as measured by Alternative Healthy Eating, a good nutrition index or New Nordic Diet Score), has been linked with better visual spatial skills, executive functions as well as better verbal and motor skills in children (Mahmassani et al., 2022; Malin et al., 2018; Vejrup et al., 2022).

In addition to different dietary indexes, data driven dietary patterns have been linked with the neurodevelopment of children (**Table 2**). Previous research has found that healthy dietary patterns, including fruits, berries, vegetables, nuts and seafood, associate with better language, gross motor and cognitive skills in children (Freitas-Vilela et al., 2018; Lv et al., 2022). In contrast, maternal unhealthier dietary patterns have been linked with poorer neurodevelopment, such as communication skills, and attention, externalizing and depressive problems, in children (Cendra-Duarte et al., 2024; De Lauzon-Guillain et al., 2022; Puig-Vallverdú et al., 2022). However, Lv et al. (2022) did not find associations between dietary patterns including sweets or citruses or fruits with cognitive, language or motor skills in children.

Besides above mentioned, individual foods have been inspected and particularly higher fish consumption during pregnancy has been linked with beneficial effects on children's neurodevelopment, such as superior problem solving, communication and fine motor skills, and intelligence (Conway et al., 2023; Hamazaki et al., 2020; Inoue et al., 2024; Normia et al., 2019). However, no such association was seen with gross motor skills (Inoue et al., 2024). (**Table 2**) Fish is a great source of PUFAs, especially long-chain n-3 PUFAs, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are pivotal for the foetal brain development (Swanson et al., 2012). Some studies have reported a link between a higher maternal intake of n-3 PUFAs and more favourable neurodevelopment of children (Hamazaki et al., 2020; Tahaei et al., 2022), yet non-significant findings also exist (Kim et al., 2017; Miyake et al., 2018).

In conclusion, although evidence emerges that a healthy diet in pregnancy could benefit a child's neurodevelopment, also inconsistent results have been reported, which could be due to different assessment methods for maternal diet (food frequency questionnaires, food diaries) and a child's neurodevelopment (e.g., Ages & Stages Questionnaires, Bayley Infant and Toddler Development), as well as a child's age. Also, adjustments for potential confounding factors (maternal socio-economic factors, smoking, usage of dietary supplements), the population, and sample size could contribute to the findings. Indeed, more research is needed to identify what kind of a diet and which foods or nutrients during pregnancy could support the neurodevelopment of children, particularly those born to mothers with overweight or obesity.

**Table 2**. Studies investigating the associations between maternal diet during pregnancy and neurodevelopment of children.

| Reference | Study design | Study subjects | Methods | Findings |
|---|---|---|---|---|
| (Kim et al., 2017)<br>Suth Korea | Prospective cohort study | n=960<br>Children aged 6 months<br>Mothers with mean BMI 21.3±3.5 kg/$m^2$ | -Korean Bayley scales of infant development edition II<br>-n-6/n-3 PUFAs from 24-h recall (20 GW) | -Higher n-6/n-3 PUFAs ratio: ↓ mental and psychomotor development<br>-n-6 and n-3 PUFA: NS |
| (Freitas-Vilela et al., 2018)<br>UK | Prospective cohort study | n=12195<br>Children aged 8 years<br>Mothers with mean BMI 22.9 ± 3.7 kg/$m^2$ | -Wechsler Intelligence Scale for Children-III<br>-Dietary patterns from food frequency questionnaire and cluster analysis (32 GW) | -Higher adherence to “Fruit and vegetables” cluster compared to “meat and potatoes” and “white bread and coffee” clusters: ↑ total IQ, verbal IQ and performance IQ |
| (Malin et al., 2018)<br>Mexico | Prospective cohort study | n=65<br>Children aged 4-6 years<br>Mothers: no information on BMI | -McCarthy Scales of Children’s Abilities<br>-Diet quality from food frequency questionnaire (3rd trimester) | -Good nutrition index: ↑ memory, quantitative, motor, perception, verbal scores and global composite index |
| (Miyake et al., 2018)<br>Japan | Prospective cohort study | n=1199<br>Children aged 5 years<br>Mothers: no information on BMI | -Strengths and Difficulties Questionnaire<br>-A diet history questionnaire (pregnancy) | -Higher intake of MUFA, α-linolenic acid, n-6 PUFA, and linoleic acid: ↑ risk for emotional problems<br>-Intake of total fat, SFA, n-3 PUFA, EPA, DHA, arachidonic acid, cholesterol, n-3/n-6 PUFA ratio: NS |
| (Normia et al., 2019)<br>Finland | Randomised controlled trial | n=56<br>Children aged 2 years<br>Mothers with mean BMI 23.8 ± 3.8 kg/$m^2$ | -Pattern-reversal visual evoked potentials<br>-Nutrient intakes from food diaries and fish consumption from a questionnaire (1st, 2nd and 3rd trimester) | -Fish intake (≥3 per week) 3rd trimester: ↑ pVEP component P100 amplitude for 60' and 30' of arcminute check sizes |

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| (Hamazaki et al., 2020)<br>Japan | Prospective cohort study | n=77751-81697<br>Children aged 6-months to 1 year old<br>Mothers with normal weight and overweight | -Ages & Stages Questionnaires<br>-Food frequency questionnaire to assess fish and PUFA intake (mid-late pregnancy) | -Higher fish intake: ↓ risk of problem-solving (6 and 12 months) and fine motor (12 months) skills delay<br>-Higher intake of total n-6 PUFA: ↓ risk for delay in communication (6 months), fine motor (6 and 12 months), gross motor (12 months) and problem solving (12 months) skills<br>-Higher intake of total n-3 PUFA: ↓ risk for delay in problem solving (12 months) and fine motor (6 and 12 months) skills<br>-Higher dietary n6/n3 ratio: ↑ risk for delay in problem solving (12 months) |
| (De Lauzon-Guillain et al., 2022)<br>France | Prospective cohort study | n=9992<br>Children aged 1, 2.5 and 3.5 years<br>Mothers with mean BMI 23.4 ± 4.7 kg/$m^2$ | -Child Development Inventory (1 and 3.5 years)<br>-MacArthur–Bates Communicative Development Inventories (2 years)<br>-Food frequency questionnaire from which food groups, dietary patterns, a diet quality score, a nutrient intake score (3rd trimester) | -Higher nutrient intake score: ↑ neurodevelopment at 1 and 3.5 years<br>-Higher intake of fruits, vegetables, fish: ↑ neurodevelopment at 3.5 years<br>-Higher adherence to processed food patterns: ↓ neurodevelopment at 1 years |
| (Lv et al., 2022)<br>China | Prospective cohort study | n=1178<br>Children aged 1 year<br>Mothers with underweight, normal weight, overweight, obesity | -Bayley Infant and Toddler Development III<br>-Dietary patterns from a semiquantitative food frequency questionnaire (22-26 and 30-34 GW) | -Higher adherence to "Aquatic products, Fresh vegetables and Homonemeae" pattern: ↑ cognitive, gross motor skills and receptive language skills<br>-Higher adherent "Nut" pattern: ↑ expressive language skills<br>-"Pome, Berry and Melon fruits", "Citrus", "Haslet, Beans, Shells, Molluscs", and "Sweets" patterns: NS |

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| (Mahmassani et al., 2022)<br>USA | Prospective cohort study | n=1580<br>Children from infancy to mid-childhood<br>Mothers with underweight, normal weight, overweight, obesity | -Infancy: visual recognition memory (VRM) paradigm<br>-Early childhood: Peabody Picture Vocabulary Test—Third Edition, Wide Range Assessment of Visual Motor Abilities<br>-Mid-childhood: Kaufman Brief Intelligence Test, second edition, WRAVMA drawing subtest, Behavioral Rating Inventory of Executive Function, Strengths and Difficulties Questionnaire<br>-MDS, A-HEI from food frequency questionnaire (early and mid-pregnancy) | -Higher MDS: ↑ nonverbal and verbal scores, ↓ metacognition problems<br>-Higher A-HEI: ↑ visual spatial skills, verbal intelligence and executive function |
| (Puig-Vallverdú et al., 2022)<br>Spain | Prospective cohort study | n=2377<br>Children aged 1 and 4–5 years<br>Mothers: no information on BMI | -Bayley Scales of Infant and Toddler Development (1 year)<br>-McCarthy Scales of Children's Abilities (4-5 years)<br>-Ultra-processed food consumption from food frequency questionnaire (3rd trimester) | -High consumption of ultra-processed food: ↓ communication skills 4-5 years (McCarthy Scales)<br>-Bayley scales: NS |
| (Tahaei et al., 2022)<br>Spain | Prospective cohort study | n=2644<br>Children aged 1, 4 and 7 years<br>Mothers with mean BMI 23.29 ± 3.86–24.04 ± 4.70 kg/m$^2$) | -Bayley Scales of Infant Development I (1 year)<br>-McCarthy Scale of Children's Abilities (4 years),<br>-Attention Network Test (7 years)<br>-Food frequency questionnaire (1st and 3rd trimester) | -High vs low n-3 PUFA intake in 1st trimester: ↑ cognitive, verbal, executive function score (McCarthy scale) and ↓ attention network test hit reaction time standard error<br>-3rd trimester: NS |

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| (Vejrup et al., 2022)<br>Norway | Prospective cohort Study | n=83800<br>Children aged 6, 18 months and 3, 5 years<br>Mothers with underweight, normal weight, overweight or obesity | -Ages and Stages Questionnaires and Child Development Inventory<br>-New Nordic Diet (NND) adherence from food frequency questionnaire (22 GW) | -High NND score: ↑ neurodevelopment at 6, 18 months, 3 and 5 years<br>-High vs low or medium adherence to NND: ↑ neurodevelopment at 6, 18 months, 3 years and motor development at 5 years |
| (Conway et al., 2023)<br>Seychelles | Prospective cohort study | n=229<br>Children aged 9 and 30 months and 5 and 9 years<br>Mothers: no information on BMI | -Bayley Scales of Infant Development II (9 and 30 months)<br>-Finger Tapping, Preschool Language Scale, Woodcock–Johnson (WJ) Tests of Achievement, Achenbach Child Behaviour Checklist, Kaufman Brief Intelligence Test (5 years)<br>-CBCL, Bender Visual Motor Gestalt, Conners' Attention Deficit Hyperactivity Disorder, Expressive Vocabulary Test, KBIT, Peabody Picture Vocabulary, Stroop, Trail Making Time, and the WJ Tests of Achievement (9 years)<br>-Fish consumption from 4-day food diaries (28 GW) | -Higher fish consumption: ↑ Kaufman Brief Intelligence Test scores (5 years)<br>-Fish consumption as tertials: NS |
| (Dai et al., 2023)<br>China | Prospective cohort study | n=1471<br>Children aged 1 year<br>Mothers with BMI < 24 kg/m$^2$ or ≥24 kg/m$^2$ | -Ages and Stages Questionnaires, Third Edition<br>-MDS from food frequency questionnaire (16-23 GW) | -High MDS: ↓ risk for failure in communication, problem-solving, personal-social domains (after adjustments only communication domain remained significant)<br>-Gross and fine motor domains: NS |

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| (Cendra-Duarte et al., 2024)<br>Spain | Randomised controlled trial | n=205<br>Children aged 4 years<br>Mothers with mean BMI 25.02 kg/$m^2$ | -Child Behavior Checklist<br>-Teacher's Report Form<br>-Behavior Rating Inventory of Executive Function – Preschool Version<br>-Dietary patterns from food frequency questionnaire (mean 12, 24, and 36 GW) | -Higher adherence to "Sweet and Superfluous" pattern: ↑ externalizing and depressive problems<br>-Higher adherence to "Meat and Cereals" pattern: ↑ attention, hyperactivity and depressive problems<br>-Higher adherence to "Fish and Vegetables" pattern: ↓ hyperactivity problems |
| (Inoue et al., 2024)<br>Japan | Prospective cohort study | n= 91909<br>Children aged 3 years<br>Mothers with underweight, normal weight, overweight or obesity) | -Ages & Stages Questionnaire<br>-Fish consumption from food frequency questionnaire during pregnancy | -Higher fish intake: ↑ communication, fine motor, problem-solving, personal-social skills<br>-Gross motor skills: NS |

A-HEI=Alternative Healthy Eating Index, MDS=Mediterranean Diet Score, BMI=Body mass index, DHA=Docosahexaenoic acid, DII=Dietary Inflammatory Index, DASH=Dietary approaches to stop hypertension, EPA=Eicosapentaenoic acid, GW=Gestational week, NS=Not significant, PUFA=Polyunsaturated fatty acid, SFA=Saturated fatty acid, ↑=better/higher/more, ↓=poorer/lower/less

## 2.4 Dietary supplements in pregnancy

During pregnancy, and already pre-conception, the adequate intake of various nutrients is vital to ensure the foetal growth and neurodevelopment. In Finland, pregnant women are recommended to use folic acid (400mg/day pre-conception and 1$^{st}$ trimester) and vitamin D (10µg/day throughout pregnancy) supplements. Other supplements, such as iodine or iron, are recommended in some cases, for example, due to a vegan diet. A recent study reported that among Finnish pregnant women 93% consumed folic acid and 97% vitamin D supplement. In addition, over 80% consumed vitamin B6, vitamin E, iodine, zinc and magnesium supplements (Koivuniemi et al., 2022). Also, other dietary supplements have raised interest, namely fish oil and probiotics that potentially have beneficial health effects. Fish oil is rich in PUFAs, especially EPA and DHA, while probiotics are defined as live micro-organisms with potential health benefits. The most common probiotics are *Lactobacillus* and *Bifidobacterium* spp (Sarita et al., 2024) that are shown to affect beneficially blood glucose levels and decrease systemic low-grade inflammation in the body (He et al., 2023; Laitinen et al., 2008; Shah et al., 2024). According to a recent study, 20.4% and 18.1% of Finnish pregnant women (n=535) consumed fish oil and probiotics supplements, respectively, during pregnancy (Jaakkola et al., 2025). Currently, there is no official recommendation in Finland for the use of fish oil and probiotics supplements during pregnancy, as the scientific evidence is considered insufficient. However, fish oil as well as probiotics supplements are shown to be well-tolerated among pregnant women (Navarro-tapia et al., 2020; von Schacky, 2020). As pregnancy is considered to be "a window for opportunity" it might be possible to yield beneficial effects on the children's growth by modifying early life circumstances, importantly maternal diet. One approach is the administration of dietary supplements, fish oil and probiotics, to pregnant women.

In the next chapters, the previous literature on the associations between a fish oil and probiotics supplementation to the growth of children will be reviewed.

### 2.4.1 Fish oil supplementation in pregnancy and implications to growth of children

The findings on the association between fish oil supplementation or intake in pregnancy and the growth of children are inconsistent. The most important studies relevant for this thesis, published within the last decade, has been listed in **Table 3**. In one study, fish oil administration to the pregnant women lowered a BMI-value and weight measures of children when compared to placebo (De Toro et al., 2024). In contrast, other studies have found that a fish oil supplementation increased a BMI-value, weight, overweight risk, fat percentage and fat mass in children at birth and up to 10 years of age (Hull et al., 2024; Keenan et al., 2016; Monthé-Drèze et al., 2021; Satokar et al., 2023; Vinding et al., 2018, 2019, 2024). However, there also are studies that have not found any effect of a fish oil supplementation on the weight, height, head circumference, BMI or adiposity in children from birth until 7 years of age (Foster et al., 2017; Gonzalez-Casanova et al., 2015; Gualtieri et al., 2024; Khandelwal et al., 2021; Muhlhausler et al., 2016; Ostadrahimi et al., 2018; Wood et al., 2018). (**Table 3**)

All in all, the findings on the relation between fish oil supplementation in pregnancy and the growth of children are not consistent, although preliminary evidence suggest that it may lower a child's weight measures. On the other hand, less in known about the impacts on a child's height and head circumference. In the prior studies, the composition of fish oil supplements, the length of the intervention, the population, and sample size differed, which could affect the results. Besides that, the varying assessment methods for a child's growth and adiposity (from medical records or study visits, bioelectrical impedance spectroscopy, dual energy x ray absorptiometry), the age of children, and the information on potential confounders (e.g., maternal lifestyle and socio-economic factors) could explain the divergent findings. Thus, long-term follow-up studies on the effects of consuming fish oil supplements during pregnancy on an overall growth of children are needed.

**Table 3.** Studies investigating the associations between fish oil supplementation during pregnancy and growth or adiposity of children.

| Reference | Study design | Study subjects | Methods | Findings |
|---|---|---|---|---|
| (Gonzalez-Casanova et al., 2015)<br>Mexico | Randomised controlled trial | n=802<br>Children aged 0 to 60 months<br>Mothers with mean BMI 26.0 ± 4.3 fish oil and 26.3 ± 4.4 $kg/m^2$ placebo | -Growth measures from study visits<br>-Fish oil (400mg DHA/day) or placebo (soy/corn oil) from 18-22 GW until delivery | -Fish oil vs placebo: NS weight, height, BMI |
| (Foster et al., 2017)<br>USA | Randomised controlled trial | n=63<br>Children aged 0, 2 and 4 years<br>Mothers with mean BMI 33.9 ± 4.2 fish oil and 34.8 ± 3.5 $kg/m^2$ placebo | -Growth measures from hospital records, skinfold measurements by calliper<br>-Fish oil (800mg DHA/day) or placebo (corn/soy oil) from 25-29 GW until delivery | -Fish oil vs placebo: NS BMI, weight, height, arm skinfold or circumference at birth, 2 or 4 years |
| (Muhlhausler et al., 2016)<br>Australia | Randomised controlled trial | n=1531<br>Children aged 3 and 5 years<br>Mothers with median BMI 26.2 (23.5-30.1) fish oil and 26.3 (23.2-30.5) $kg/m^2$ placebo | -Body composition by bioelectrical impedance spectroscopy, height and weight at research visits<br>-Fish oil (800mg DHA/day) or placebo (vegetable oil) from 2$^{nd}$ trimester until birth | -Fish oil vs placebo: NS BMI, body fat percentage |
| (Keenan et al., 2016)<br>USA | Randomised controlled trial | n=49<br>Children aged 3 months<br>Mothers: no information on BMI | -Birth measures from medical records<br>-Fish oil (DHA 450mg/day) or placebo (soybean) from 16-21 GW until delivery | -Fish oil vs placebo: ↑ birth weight |
| (Ostadrahimi et al., 2018)<br>Iran | Randomised controlled trial | n=150<br>Children aged 4 and 6 months<br>Mothers with mean BMI 23.8 ± 3.5 fish oil and 23.9 ± 3.7 $kg/m^2$ placebo | -Growth measures from study visits<br>-Fish oil (120mg DHA, 180mg EPA/day) or placebo, 20$^{th}$ GW until 30 days postpartum | -Fish oil vs placebo: NS weight, height, head circumference |
| (Vinding et al., 2018)<br>Denmark | Randomised controlled trial | n=688<br>Children aged 0 to 6 years<br>Mothers with mean BMI 24.6 ± 4.4 $kg/m^2$ | -Growth measured from study visits<br>-Body composition by dual energy x ray absorptiometry<br>-Fish oil (4g of which 2.4g PUFA, 37% DHA/day) or placebo (olive oil) from 24 GW until 1 week postpartum | -Fish oil vs placebo: BMI increased from 0 to 6 years, ↑ BMI, weight/height, waist circumference at 6 years<br>-Obesity: NS |

| | | | | |
|---|---|---|---|---|
| (Wood et al., 2018)<br>Australia | Randomised controlled trial | n=252<br>Children aged 7 years<br>Mothers with mean BMI 27.6 ± 5.8 $kg/m^2$ | -Body composition by air displacement plethysmography and bioelectrical impedance spectroscopy, growth measures at research visits<br>-Fish oil (800mg DHA/day) or placebo (500mg vegetable oil) from 20$^{th}$ GW until delivery | -Fish oil vs placebo: NS body fat, BMI, weight, height or hip and waist circumference |
| (Vinding et al., 2019)<br>Denmark | Randomised controlled trial | n=699<br>Children at birth<br>Mothers with mean BMI 24.6 ± 4.4 $kg/m^2$ | -Growth measured from study visits<br>-Fish oil (4g of which 2.4g PUFA, 37% DHA/day) or placebo (olive oil) from 24 GW until 1 week postpartum | -Fish oil vs placebo: ↑ weight, size for gestational age |
| (Khandelwal et al., 2021)<br>India | Randomised controlled trial | n=880<br>Children at birth<br>Mothers with mean BMI 20.5 ± 3.5 fish oil and 20.7±3.6 $kg/m^2$ placebo | -Growth measured from study visits<br>-Fish oil (400mg DHA/day) or placebo (soy/corn oil) from ≤20$^{th}$ GW until delivery | -Fish oil vs placebo: NS weight, height and head circumference |
| (Monthé-Drèze et al., 2021)<br>USA | Pilot randomised controlled trial | n=48<br>Children at birth<br>Mothers with median BMI 30.2 (28.2–35.4) $kg/m^2$ | -Body composition by air displacement plethysmography (PeaPod -system), growth measures at birth<br>-Fish oil (DHA 800mg, EPA 1200mg/day) or placebo (wheat germ oil) from 10-16 GW until delivery | -Fish oil vs placebo: ↑ fat free mass, weight at birth<br>-Fat mass and fat percentage: NS |
| (Satokar et al., 2023)<br>New Zealand | Randomised controlled trial | n=98<br>Children aged 2 weeks and 3 months<br>Mothers with overweight or obesity | -Body composition by dual-energy X-ray absorptiometry<br>-Fish oil (3.55g n-3 PUFA/day) or placebo (olive oil) from mid-pregnancy until 3 months post-partum | -Fish oil vs placebo: NS body composition<br>-Fish oil vs placebo: ↑ BMI, ponderal index at 3 months |
| (Gualtieri et al., 2024)<br>Italy | Prospective cohort study | n=404<br>Children at birth<br>Mothers with underweight, normal weight, overweight or obesity | -Growth measures from questionnaires<br>-Fish oil supplement consumption from questionnaires during pregnancy | -Fish oil: NS birth height or weight |

| | | | | |
|---|---|---|---|---|
| (Hull et al., 2024)<br>USA | Randomised controlled trial | n=250<br>Children aged 24 months<br>Mothers with normal weight, overweight or obesity | -Growth measures from study visits<br>-Fish oil (high dose 1000mg or low dose 200mg/day) during the 2nd and 3rd trimester | -Higher fish oil dose vs low dose: ↑ fat mass |
| (De Toro et al., 2024)<br>Chile | Randomised controlled trial | n=169<br>Children aged of 4 months<br>Mothers with overweight or obesity | -Growth measures from study visits<br>-Fish oil (800mg or 200mg/day) from <15 GW until delivery | -Higher fish oil dose vs low dose: ↓ weight-for-length, BMI |
| (Vinding et al., 2024)<br>Denmark | Randomised controlled trial | n=597<br>Children aged 10 years<br>Mothers with mean BMI 24.6 ± 4.5 kg/m$^2$ | -Growth measures from study visits<br>-Body composition by Bioelectrical Impedance Analysis<br>-Fish oil (4g of which 2.4g PUFA, 37% DHA/day) or placebo (olive oil) from 24 GW until 1 week postpartum | -Fish oi vs placebol: ↑ BMI, overweight risk, fat percentage, fat mass, lean mass |

BMI=body mass index, DHA= Docosahexaenoic acid, EPA=eicosapentaenoic acid, GW=gestational week NS=non-significant, PUFA=polyunsaturated fatty acid, ↑=higher/greater, ↓=lower/smaller

### 2.4.2 Probiotics supplementation in pregnancy and implications to growth of children

Previous research has investigated the impacts of probiotics supplementation in pregnancy mainly on the birth measures of children. The most relevant studies for this thesis are presented in **Table 4**. In the majority of these studies, probiotics had no effects on birth weight, height or head circumference of children (Callaway et al., 2019; Halkjær et al., 2020; Kijmanawat et al., 2018; Lindsay et al., 2014; Wickens et al., 2017), although one study found a negative association with a birth weight and the rate of macrosomia (Sahhaf Ebrahimi et al., 2019). Similarly, no effects have been detected on body composition of a new-born (Halkjær et al., 2023; Okesene-Gafa et al., 2019). However, in one study probiotics consumption in pregnancy decreased the rate of SGA (Callaway et al., 2019). The long-term effects of probiotics consumption during pregnancy on the growth of children are less investigated. One study reported that children of mothers who consumed probiotics during their pregnancies and six months post-partum (probiotics administrated to the child if mother did not breast-feed) had a lower weight-gain and BMI especially at the age of four years (Luoto et al., 2010). Oppositely, another study showed that probiotics supplementation during pregnancy may lead to a higher weight and height of children aged 12 months (Mantaring et al., 2018). Again, non-significant findings have also been reported (Pastor-Villaescusa et al., 2020). (**Table 4**)

All in all, the prior findings on the association between probiotics supplementation in pregnancy and the growth of children are far inconsistent and have mainly focused on a new-born growth measures. Yet, there is some evidence that probiotics administration during pregnancy could lower the weight measures of children. The differences in the prior studies could be due to different probiotic strains and the length of the intervention as well as the population and sample size. Also, the assessment methods for a child's growth and adiposity (from medical records or study visits, air displacement plethysmography, dual-energy X-ray absorptiometry) as well as adjustments for potential confounders (e.g., maternal lifestyle and socio-economic factors) are not consistent. Altogether, it is evident that more research is needed to clarify the possible effects of probiotics and especially longer follow-up studies are required.

**Table 4.** The studies investigating the association between maternal probiotics consumption and growth or adiposity of children.

| Reference | Study design | Study subjects | Methods | Findings |
|---|---|---|---|---|
| (Luoto et al., 2010)<br>Finland | Randomised controlled trial | n=159<br>Children until 10 years of age<br>Mothers with normal weight, overweight, obesity | -Growth measures from study visits or by school nurse<br>-Probiotics (*Lactobacillus rhamnosus* GG, ATCC 53103 $1x10^{10}$ CFU/day) or placebo from 4 weeks before delivery until 6 months post-partum | -Probiotics vs placebo: ↓ excess weight-gain especially in those who became overweight<br>-BMI at 4 years (tendency) ↓ |
| (Lindsay et al., 2014)<br>Ireland | Randomised controlled trial | n=175<br>Children at birth<br>Mothers with obesity | -Growth measures form medical records<br>-Probiotics (100 mg *Lactobacillussalivarius* UCC118 $10^9$ CFU/day) or placebo from 24 until 28 GW | -Probiotics vs placebo: NS birth weight |
| (Wickens et al., 2017)<br>New Zealand | Randomised controlled trial | n=373<br>Children at birth<br>Mothers with median BMI 26 (23-30) probiotics and 25 (23-29) kg/m$^2$ placebo | -Birth measures from medical records or assessed by a researcher<br>-Probiotics (*Lacticaseibacillus rhamnosus* HN001, $6×10^9$ CFU/day) or placebo from 14$^{th}$ to 16$^{th}$ GW | -Probotics vs placeo: NS birth weight, height and head circumference |
| (Kijmanawat et al., 2018)<br>Thailand | Randomised controlled trial | n=57<br>Children at birth<br>Mothers with GDM and BMI 22.74 ± 3.73 probiotics and 22.04 ± 3.12 kg/m$^2$ placebo | -Birth measures from medical records<br>-Probiotics (*Lactobacillus acidophilus* and *Bifidobacterium bifidum* 1,000 million CFU/day) or placebo for 4 weeks between late 2$^{nd}$ and early 3$^{rd}$ trimester | -Probiotics vs placebo: NS birth weight |
| (Mantaring et al., 2018)<br>Philippines | Randomised controlled trial | n=183<br>Children from birth to 12 months<br>Mothers with mean BMI 20.6±2.9 supplement, 20.7 ± 7.7 supplement + probiotics and 21.1±3.3 kg/m$^2$ no-supplement | -Growth measures from research visits<br>-Probiotics (*Bifidobacterium lactis* CNCC I-3446 $7x10^8$ CFU and *Lactobacillus rhamnosus* CGMCC 1.3724 $7x10^8$ CFU), + supplement (protein, fats, carbohydrates, vitamins and minerals) or supplement/twice per day or no-supplement from 3$^{rd}$ trimester until 2 months postpartum | -Combined supplement+probiotics + supplement vs no-supplement: ↑ weight, height and weight-for-age at 12 months |

| | | | | |
|---|---|---|---|---|
| (Callaway et al., 2019)<br>Australia | Randomised controlled trial | n=411<br>Children at birth<br>Mothers with overweight or obesity | -Birth measures and body composition by air displacement plethysmography<br>-Probiotics (*Lactobacillus rhamnosus* (LGG) and *Bifidobacterium animalis* subspecies lactis (BB-12) $1 \times 10^9$ CFU/day) or placebo from 2nd trimester until delivery | -Probiotics vs placebo: NS birth weight, ↓ risk for small-for-gestational age |
| (Sahhaf Ebrahimi et al., 2019)<br>Iran | Randomised controlled trial | n=84<br>Children at birth<br>Mothers with GDM and BMI 31.67 ± 5.44 probiotics and 29.67 ± 3.03 kg/m$^2$ no-probiotics | -Birth measures from medical records<br>-Probiotics yogurt (*Lactobacillus acidophilus* and *Bifidobacterium lactis* $10^6$ CFU/day) or conventional yogurt for 8 weeks | -Probiotics vs no-probiotics: ↓ weight, rate of macrosomia<br>-height or head circumference: NS |
| (Okesene-Gafa et al., 2019)<br>New Zealand | Randomised controlled trial | n=230<br>Children at birth<br>Mothers with overweight or obesity | -Growth measures within 72 hours from birth<br>-Body composition by air-displacement plethysmography (Pea Pod -system)<br>-Probiotics (*Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* BB12, minimum $6.5 \times 10^9$ CFU/day) or placebo from 12-17 GW until birth | -Probiotics vs placebo: NS anthropometrics or body composition |
| (Halkjær et al., 2020)<br>Denmark | Randomised controlled trial | n=50<br>Children at birth<br>Mothers with BMI ≥30 but < 35 kg/m$^2$ | -Birth measures from medical records<br>-Probiotics (Vivomixx®m, 450 billion CFU/day) or placebo from 14-20 GW until delivery | -Probiotics vs placebo: NS birth weight |
| (Pastor-Villaescusa et al., 2020)<br>Spain | Randomised controlled trial | n=291<br>Children from birth until 16 weeks old<br>Mothers with mean BMI 24.4 ± 4.3 probiotics, 24.5 ± 4.9 kg/m$^2$ placebo | -Growth measures from study visits<br>-Probiotics (*Lactobacillus fermentum* CECT5716 Lc40, 3×109 CFU/day) or placebo (maltodextrin) from birth until 16 weeks | -Probiotics vs placebo: NS height, weight, BMI |
| (Halkjær et al., 2023)<br>Denmark | Randomised controlled trial | n=36<br>Children at birth<br>Mothers with BMI ≥30-< 35 kg/m$^2$ | -Body composition by dual-energy X-ray absorptiometry<br>-Probiotics (Vivomixx®, 450 billion CFU/day) or placebo from 14-20 GW until delivery | -Probiotics vs placebo: NS body composition |

BMI=body mass index, CFU=Colony forming unit, GW=gestational week, NS=non-significant, ↑=higher/greater, ↓=lower/smaller

## 2.5 Summary of the literature

Unfavourable early life circumstances may adversely affect the health of children through programming mechanisms. More children are predisposed to obesity and GDM during pregnancy as these conditions have become increasingly common. Previous studies have shown that obesity and GDM associate with weaker neurodevelopment of children and increase a child's risk for higher weight and later obesity, but these studies have included both women with normal weight and overweight or obesity. It is likely that dietary counselling of pregnant women could benefit the mother herself but also her child's growth and neurodevelopment. Consumption of foods with health-benefits, such as vegetables, fruits, whole grains and fish, during pregnancy has been shown to benefit neurodevelopment of children and lower the adiposity and overweight risk, but less is known about the overall growth, i.e., height, weight and head circumference, of children. Thus, more research is needed to elucidate what kind of a diet and which nutrients could support the optimal growth and neurodevelopment of children, especially in those belonging a risk-group for later adverse health effects due to their mothers' overweight or obesity. This also raises the need to develop new means to modify maternal diet and thus beneficially influence the health of children. There is some evidence that fish oil and probiotics supplements may benefit the growth of children, but the findings are far inconclusive and more studies are needed to clarify the potential associations. In addition, there are no prior studies that have investigated the potential co-effects of fish oil and probiotics on the growth of children.

## 2.6 Hypotheses

The hypotheses of this thesis are that maternal adiposity, GDM and diet during pregnancy influence the growth and neurodevelopment of children up to 5– 6 years of age (**Figure 1**). The children of mothers with higher adiposity (obesity, higher body fat mass or percentage) or GDM may have less favourable neurodevelopmental skills and higher weight and adiposity when compared to the children of mothers with less adiposity and/or without GDM. Maternal consumption of a health-promoting diet, including vegetables, fruits, whole-grains, and fish, during pregnancy may associate with better neurodevelopmental performance and lower adiposity in children. In addition, administration of fish oil and/or probiotics during pregnancy to mothers may lead to a lowered adiposity and overweight risk in their children.

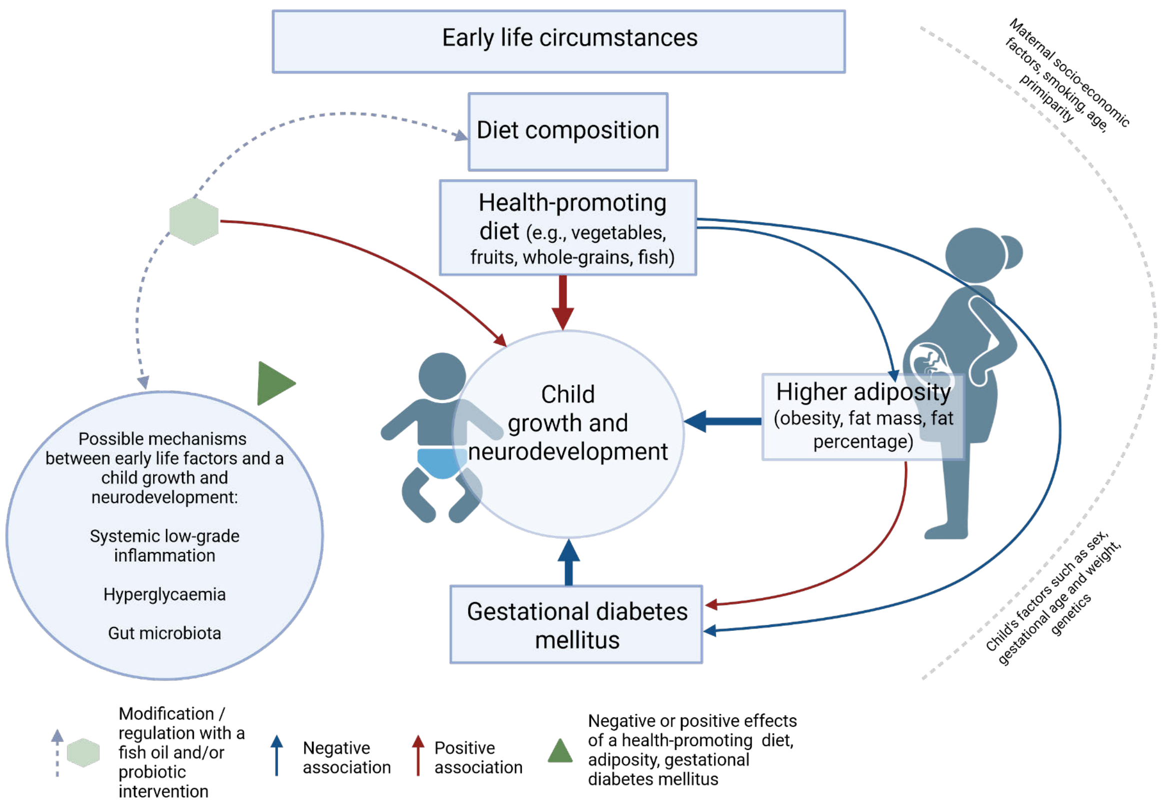


**Figure 1.** Hypotheses of this thesis. Early-life factors, i.e., maternal adiposity, gestational diabetes mellitus, and diet that putatively affect the long-term growth and neurodevelopment of children through foetal programming by affecting the level of low-grade inflammation, hyperglycaemia as well as gut microbiota. Modification of maternal diet by fish oil and/or probiotics supplements during pregnancy could provide an opportunity to beneficially influence a child's growth and neurodevelopment by lowering systemic low-grade inflammation and hyperglycaemia while affecting beneficially the gut microbiota. Created in BioRender. Saros, L. (2025) https://BioRender.com/9qmd0vu

# 3 Aims

The overall aim in this thesis was to investigate the extent to which maternal adiposity, GDM and diet, including an intervention with fish oil and/or probiotics, during pregnancy influence the growth and neurodevelopment of children up to 5–6 years of age.

The specific aims were to investigate:

1) the impact of the fish oil and/or probiotics supplementation to the pregnant women and six months postpartum on the growth of children from 3 to 24 months of age, and particularly on the risk for overweight at the age of 24 months (study I)
2) the extent to which maternal diet, GDM, and adiposity (pre-pregnancy BMI and body composition) during pregnancy influence the growth of children from birth until 24 months of age (study II)
3) the association between maternal diet, GDM and adiposity (pre-pregnancy BMI and body composition) during pregnancy and the neurodevelopment of children at the ages of 2 and 5–6 years (studies III and IV)

# 4 Materials and Methods

## 4.1 Study design and subjects

The data for this thesis originates from a mother-child clinical trial that is a randomized, double-blinded, placebo-controlled study (ClinicalTrials.gov Identifier: NCT01922791). Recruitment of study subjects took place between October 2013 and July 2017 in Turku and nearby cities. Recruitment included advertisement leaflets that were delivered to maternal welfare clinics as well as to ultrasound units. Additionally, the study was promoted in print media and social media platforms. The inclusion criteria for the study were: <18 gestational week (GW), age 18–45 years, pre-pregnancy BMI ≥25kg/m$^2$, singleton pregnancy, no presence of chronic diseases (asthma and allergies were accepted), and a signed consent form. The exclusion criteria were: normal weight (BMI<25kg/m$^2$), >18 GW, intake of other probiotic or fish oil/vegetable oil supplements, chronic diseases and bleeding tendency. Altogether 439 mothers fulfilled the inclusion criteria; however, one mother was later excluded due to familiar hypercholesterolemia. Thus, 438 mothers were included in the study.

The mothers visited study center twice during their pregnancies; in early pregnancy and in late pregnancy. The allocation to the four intervention groups was performed in the early pregnancy study visit: fish oil + placebo, probiotics + placebo, fish oil + probiotics, placebo + placebo. The allocation was performed based on the mother's parity and history of GDM (primipara, multipara, multipara + previous GDM). Stratified randomization was conducted (random permuted blocks of four) and randomisation lists of the three blocks were created by a statistician (T. Poussa, STAT-Consulting, Nokia, Finland). The intervention begun in early pregnancy and lasted until six months postpartum. The mothers with their children attended study visits at three, six, 12 and 24 months after delivery during which children's growth was assessed. Neurodevelopmental assessments of children were performed at two and 5–6 years (**Figure 2**).

The follow-up study was carried-out between November 2020 and March 2023 for the mothers and their 5–6-year-old children. The inclusion criteria were that the mother had participated in both study visits during her pregnancy, and if the mother was pregnant during the follow-up visit only her child could participate. Of the 438 mothers, 378 were invited to participate with their children. Total of 162 children and 156 mothers were willing to participate in the study.

## 4.2 Ethics

The study was conducted in accordance to the guidelines laid down in the Declaration of Helsinki and the Ethics Committee of the Hospital District of South-West Finland approved all procedures involving human subjects. Written informed consent was asked from each woman before the participation.

## 4.3 Clinical measures of mothers

### 4.3.1 Adiposity

Mother's adiposity was defined in two ways: pre-pregnancy BMI and body composition.

Mother's pre-pregnancy weight was self-reported and was obtained from maternal welfare clinic cards. Height was measured during the early pregnancy study visit with a wall stadiometer to the nearest 0.1 cm. Pre-pregnancy BMI was calculated based on this information and the mothers were categorised to have overweight (BMI $\geq$25kg/m$^2$) or obesity (BMI $\geq$30kg/m$^2$).

The body composition of mothers was measured in early and late pregnancy by an air displacement plethysmography (the Bod Pod system, software version 5.4.0, COSMED, Inc., Concord, USA) as instructed by the manufacturer. The equations by van Raaij et al (Van Raaij et al., 1988) were utilized to calculate the proportion of fat. The protocol for body composition measurement has been depicted more accurately earlier (Pellonperä et al., 2019a).

### 4.3.2 Gestational diabetes mellitus

A 75 g two-hour oral glucose tolerance test was offered for all mothers in the maternal welfare clinics or during the study visit in mid-pregnancy and/or already in early pregnancy if a mother's risk was elevated (Gestational diabetes: Current care guideline, 2024). GDM was diagnosed if one or more value was: 0h $\geq$5.3, 1h $\geq$10.0 and 2h $\geq$8.6 mmol/l.

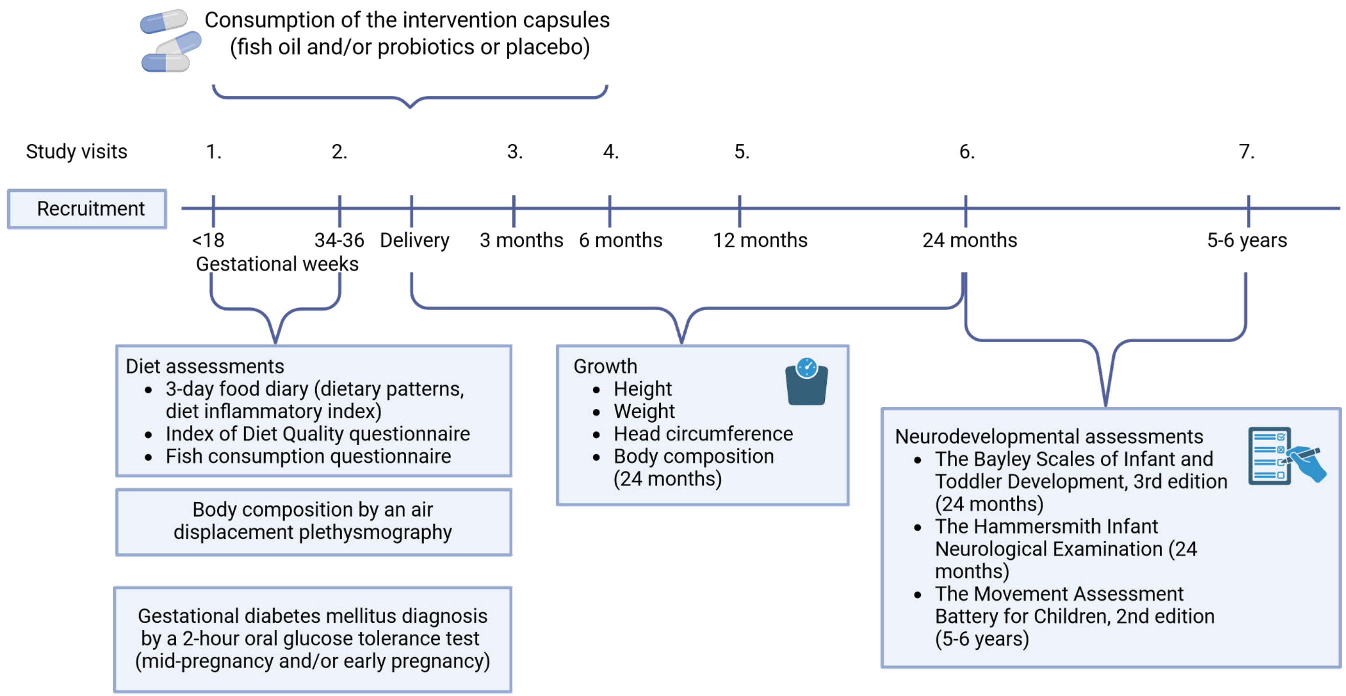


**Figure 2.** Study timeline and summary of the study design, data collection, and methods used in studies I-IV. Created in BioRender. Saros, L. (2025) https://BioRender.com/cdfgo36

## 4.4 Dietary intake

### 4.4.1 Food diaries

Dietary intake of mothers was assessed by three-day food diaries, including two weekdays and one weekend day. The mothers kept the diary during the week prior to the early and late pregnancy study visits, and they received verbal and written instructions. They were advised to write down all foods and beverages consumed. The study personnel checked the accuracy of the food diaries by using an illustrated portion picture booklet during the study visits. Intakes of energy and nutrients per day were calculated using computerized software AivoDiet (version 2.0.2.3; Aivo, Turku, Finland), which utilizes the Finnish Food Composition Database Fineli.

### 4.4.2 Dietary patterns

Dietary patterns were extracted from the three-day food diaries and using the food group classification in the Finnish Food Composition Database Fineli. The formation of dietary pattern has been described in detail earlier (Pajunen et al., 2022). Briefly, nutritionally similar food groups were combined (n=29) and of these 22 and 21, in early and late pregnancy respectively, were used in the final dietary pattern analysis. Principal component analysis with Varimax rotation was used to form the two dietary patterns. Dietary patterns were named as a healthier and an unhealthier based on the loadings of different food groups. The composition of dietary patterns in early and late pregnancy is shown in **Figure 3**. The component coefficient score of both components were addressed to each woman. The pattern with a higher score was decided to be the predominant pattern for each woman.

### 4.4.3 Dietary Inflammatory Index

The dietary inflammatory index (DII) scores were calculated based on the three-day food diaries. DII composes of 45 food parameters and it assesses diet-associated inflammation (Hébert et al., 2019; Shivappa et al., 2014). In this study, 28 nutrients were utilised to calculate DII and energy-adjusted DII (E-DII): energy, carbohydrate, protein, total fat, alcohol, fiber, cholesterol, SFA, MUFA, PUFA, n-3 and n-6 fatty acids, trans-fatty acids, niacin, thiamine, riboflavin, vitamins B12, B6, A, C, D, and E, iron, magnesium, zinc, selenium, folic acid, and beta-carotene.

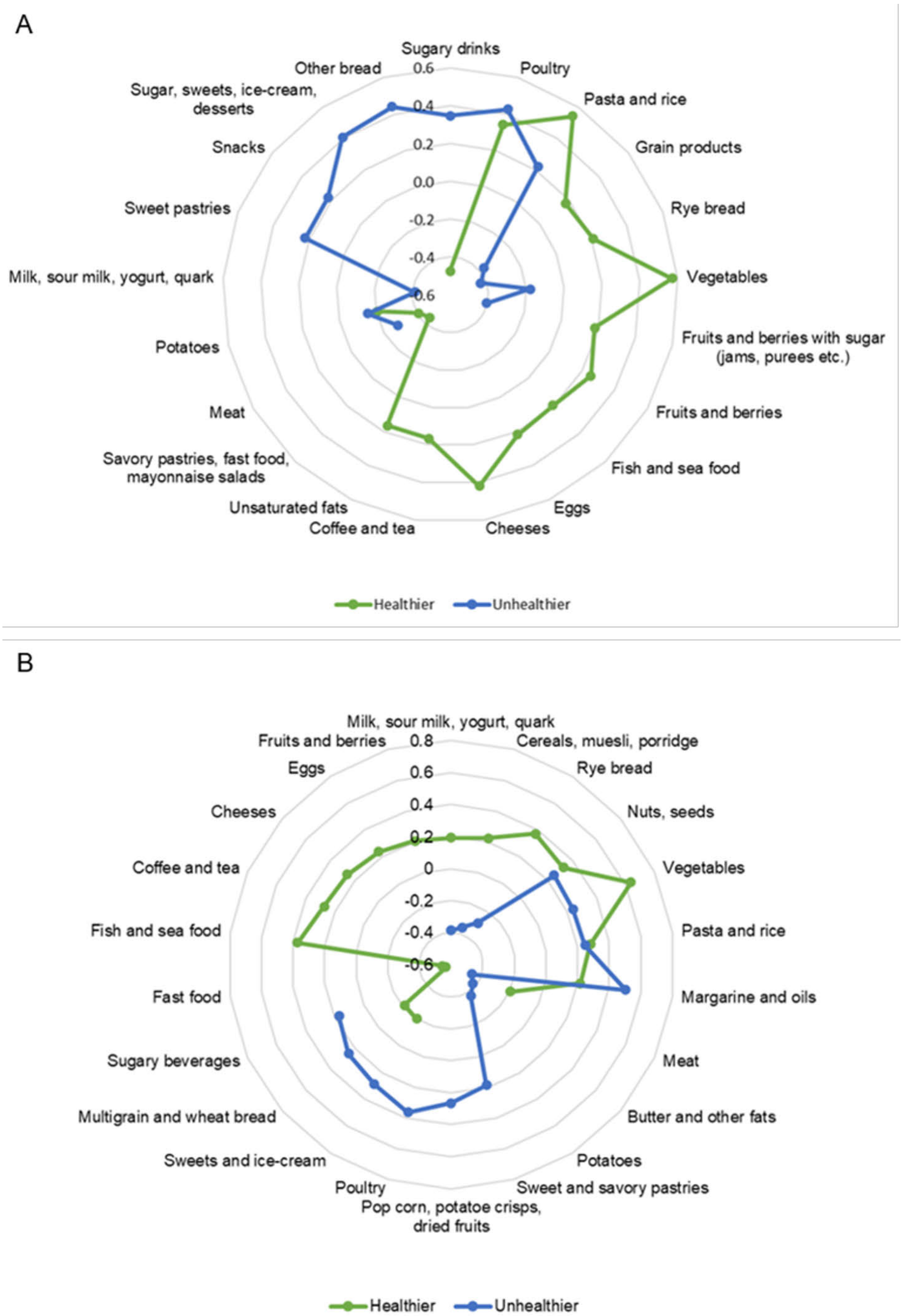


**Figure 3.** Dietary patterns in A) early and B) late pregnancy derived with principal component analysis from food diaries and factor loadings of different food groups (>0.15 and <-0.15). The higher the value of the food group, better it represents each the dietary pattern.

### 4.4.4 Index of Diet Quality

The validated Index of Diet Quality (IDQ) questionnaire (Leppälä et al., 2010) was used to define an overall quality of diet. The questionnaire includes 18 questions, which assess the frequency and consumption of food products, such as vegetables, fruits and berries, whole-grains, fish, spreads, and sugar-rich foods or beverages, during the week prior to study visit. Each question was scored and the scores ≥10/15 and <10/15 indicated good and poor dietary quality, respectively (Leppälä et al., 2010).

### 4.4.5 Fish consumption

The consumption of fish was determined by a frequency questionnaire. The mothers were asked to record their fish consumption (times per week) during the two weeks prior to the study visits.

## 4.5 Dietary supplements

The fish oil capsules (Croda Europe Ltd., Leek, U.K) included total of 2.4g of n-3 fatty acids of which 1.9g were docosahexaenoic acid (DHA, 22:6-n-3), 0.22g were eicosapentaenoic acid (EPA, 20:5-n-3), and the rest were other n-3 fatty acids such as docosapentaenoic acid. The placebo capsules for fish oil included medium-chain fatty acids, e.g., capric and caprylic acid. The probiotic capsule contained *Lacticaseibacillus rhamnosus* HN001 (formerly *Lactobacillus rhamnosus* HN001) (ATCC SD5675; DuPont, Niebüll, Germany) and *Bifidobacterium animalis* ssp. *lactis* 420 (DSM 22089; DuPont), $10^{10}$ colony forming units per capsule. The placebo capsules for probiotics included microcrystalline cellulose. The placebo capsules were similar to the intervention capsules in terms of size, shape, colour and flavour. The mothers were instructed to take two fish oil capsules and one probiotic capsule daily.

## 4.6 Other maternal data

The mothers filled in questionnaires regarding their general background information and health. The questions covered, for example, age, education level (college or university education), history of GDM (yes, no), smoking status (before or during pregnancy), and primiparity (primipara or multipara).

## 4.7 Growth of children

The information on growth (height, weight and head circumference) of children was collected from welfare clinic cards during three-, six-, 12- and 24-months study visits. Weight-for-height% and SD-scores for weight-for-age, height-for-age, head circumference-for-age, and BMI-for-age were calculated according to the Finnish growth references (Karvonen et al., 2012; Saari et al., 2011). For the children born prematurely (n=24), appropriate growth references were utilized (Sankilampi et al., 2013). The BMI-for-age SD-score (n=149) was possible to determine for the children whose age was ≥two years. BMI-for-age SD-score and weight-for-height% were categorized into normal weight or underweight, overweight, and obesity as shown in **Table 5** (Saari et al., 2011). One child with abnormal growth data was excluded from the analysis (studies I and II). For studies I and II, the children with overweight and obesity were combined in one group that is hereafter referred as “overweight group”. Likewise, the children with normal weight and underweight were combined and the group is referred as “normal weight group”.

The body composition was measured by an air displacement plethysmography, by using the paediatric option in the Bod Pod-system. Children wore a tight cap and underwear or swimming trunks during the measurement. They were allowed to eat and drink before the measurement. The density model devised by Fomon et al. was utilized in the fat percentage calculation (Fomon et al., 1982).

**Table 5.** Cut-off values for normal weight or underweight, overweigh and obesity.

| Growth variable | Normal weight or underweight | Overweight | Obesity |
|---|---|---|---|
| Weight-for-height % | < +10 % | +10–20 % | >+20 % |
| BMI-for-age SD-score | | | |
| girls | <1.1629 SD-score | 1.1629–2.1064 SD-score | ≥2.1065 SD-score |
| boys | <0.7784 SD-score | 0.7784–1.7015 SD-score | ≥1.7016 SD-score |

SD-score=standard deviation score

## 4.8 Neurodevelopmental assessments of children

### 4.8.1 The Bayley Scales of Infant and Toddler Development – Third Edition

The Bayley-III (Bayley Salo, S., Munck, P., Uusitalo, N., & Korja, R., 2006) was used to assess neurodevelopment of children at the age of two years. Trained psychology students or a physiotherapist (gross motor subscale) performed the tests. The test included 1) cognitive, 2) language (receptive and expressive communication subscales) and 3) motor (fine and gross motor subscales) scales. Index scores were calculated (mean=100, SD=15) for the composite cognitive, language and motor scales while standard scores (mean=10, SD=3) were calculated for the language and motor subscales as depicted in the manual. Corrected age was used for children born preterm (gestational age <37 weeks, n=13).

### 4.8.2 The Hammersmith Infant Neurological Examination

The Hammersmith Infant Neurological Examination (HINE) (Haataja et al., 1999) was performed by a trained physiotherapist at two years of age. The assessment included three sections: 1) neurologic examination, 2) developmental milestones, and 3) behaviour. The first section consisted of 26 items assessing five subsections: cranial nerve function, posture, movements, tone and reflexes. After scoring each item, the item scores were added up to get the subsection scores and further the global score (minimum=0, maximum=78). The global score was divided into optimal score (≥74) and suboptimal score (<74) (Haataja et al., 1999). The children born preterm (n=13) were excluded from this categorization. The second and third sections were excluded from the global scores and therefore not used in the analyses.

### 4.8.3 The Movement Assessment Battery for Children – Second Edition

The Movement ABC-2 was used to assess motor development of children at the age of 5–6 years (Henderson et al., 2007). The assessment was performed by researchers trained by a child neurologist. The Movement ABC-2 included three subscales: 1) manual dexterity (three items), 2) aiming and catching (two items), and 3) balance (three items). The age band 1 (3–6 years) was used and the test was scored according to the test norms for 5–6-year-old children. All items were scored according to the best attempt (out of maximum of two attempts). These raw scores were transformed into standard scores comparing to percentiles of subscales and total test score, accordingly. Percentiles ≤15$^{th}$ for total test score referred to developmental coordination disorder (DCD) or motor impairment on subscales. Oppositely, percentiles >15th represented age-appropriate motor development (Henderson et al., 2007). Higher percentiles indicated a better motor performance.

## 4.9 Statistics

The outcomes and independent variables, statistical tests, and the number of subjects in each study are described in **Table 6**. In all studies, skewness <1 was used to define the normality of the data. Normally distributed continuous variables were described as mean (SD, standard deviation) and those not normally distributed as median (interquartile range, IQR). Independent samples T-test or Mann Whitney U-test were used to compare the groups. Categorical variables were described as frequency (percentage) and Fisher exact or Chi squared test was used in the comparisons. The variables that were not normally distributed were natural log transformed for the analyses. The associations between categorical outcomes and categorical or continuous dependent variables were analysed by using adjusted logistic regression models while those between continuous outcomes and categorical dependent variables with adjusted general linear regression models. Associations between two continuous variables were analysed by using Pearson or Spearman correlations. The correlations between dietary inflammatory index and the motor development of children are only presented in this thesis and are not included in the Original publications.

For the study I, the mothers in four intervention groups were re-grouped; the mothers in groups receiving fish oil (fish oil + placebo, fish oil + probiotics) and those who did not received (probiotics + placebo, placebo + placebo) were combined. Similarly, the mothers in groups receiving probiotics (probiotics + placebo, fish oil + probiotics) and those who did not (fish oil + placebo, placebo + placebo) were combined. The main effects of fish oil and probiotics and a fish oil×probiotics interaction effect was checked by binary logistic regression models. The re-grouping was possible due to two factorial study design. In studies II-IV, the intervention groups were combined into one group and the data were analysed as an observational cohort study design. The intervention groups were included as a confounding factor in the analyses.

The statistical analyses were performed with IBM SPSS Statistics version 26 (study III) or 27 (studies I, II and IV) for Windows (IBM Corp, Armonk, NY, USA). Statistical significance was set at P-value $<0.05$.

**Table 6.** Summary of the data analysed in the studies I-IV, including number of subjects, variables, and statistical tests.

| Study | Outcomes and number of subjects | Dependent variables | Adjustments | Statistical tests |
|---|---|---|---|---|
| **I** | Overweight/obesity at 24 months of age<br>(n=250)<br>Growth at 3–24 months of age (n=330)<br>Fat percentage at 24 months of age (n=73) | Intervention with fish oil and/or probiotics or placebo | Pre-pregnancy smoking status, birth weight, age of children | Linear regression models<br>Logistic regression models<br>Analyses of covariance for repeated measurements |
| **II** | Growth at 0–24 months of age (n=378)<br>Fat percentage, fat mass, fat free mass at 24 months of age (n=73) | Diet:<br>Dietary quality [a]<br>Dietary inflammatory index<br>GDM [b]<br>Adiposity:<br>Overweight/obesity [c]<br>Body composition | Birth weight, age of children, intervention groups<br>Education, pre-pregnancy smoking status, age of mothers [a]<br>Education, pre-pregnancy BMI, gestational weeks at delivery [b]<br>Gestational diabetes mellitus diagnosis, gestational weeks at delivery [c] | General linear models<br>Pearson Partial or Spearman Partial correlation coefficient [1] |
| **III** | Neurodevelopment at 2 years of age (n=243) | Diet:<br>Dietary quality<br>Dietary inflammatory index<br>Fish consumption<br>GDM [d]<br>Adiposity:<br>Overweight/obesity [e]<br>Body composition | Education, employee status, marital status, pre-pregnancy smoking status, primiparity, child's sex, pre-pregnancy BMI, intervention groups<br>Gestational weeks at delivery [d]<br>Gestational diabetes mellitus diagnosis, age of children [e] | General linear models<br>Logistic regression models<br>Pearson Partial or Spearman Partial correlation coefficient |

| | | | | |
|---|---|---|---|---|
| **IV** | Neurodevelopment at 5–6 years of age<br>(n=159) | Diet:<br>Dietary patterns<br>Fish consumption<br>GDM [f]<br>Adiposity:<br>Overweight/obesity [g]<br>Body composition [h] | Education, age, smoking status, sex of children, intervention groups<br>Pre-pregnancy BMI, gestational weeks at delivery [f]<br>Gestational diabetes diagnosis [g]<br>Gestational weeks at delivery [h] | General linear models<br>Logistic regression models<br>Pearson Partial or Spearman Partial correlation coefficient |

[1] Adjusted for multiple comparisons: dietary inflammatory index and body composition analyses (Benjamini-Hochberg procedure, false discovery rate 0.05).

# 5 Results

## 5.1 Clinical characteristics

The clinical characteristics of the mothers, with overweight or obesity, and their children in studies I–IV are presented in **Table 7**. In study I, characteristics of mothers and their children were compared between the intervention groups. The characteristics were similar among the groups, except for smoking before pregnancy, which was more common in the placebo group (see details in Original publication I).

In studies II and III, the mothers were divided into two groups based on their GDM diagnosis (II no n=263, yes n=107, III no=169, yes=68,). In both studies, mothers without GDM had a higher education level, lower pre-pregnancy BMI and a longer duration of pregnancy when compared to mothers with GDM. In study II, the mothers were also divided according to their dietary quality in early pregnancy (good n=178, poor n=197). The mothers with a good dietary quality had a higher education level, they smoked less often before and during pregnancy, and breastfed for longer duration when compared to mothers with a poor dietary quality (see details in Original publication II). In study III, the mothers were also divided based on their pre-pregnancy BMI (overweight n=149, obesity n=94). The mothers with obesity had more often GDM diagnosis and their children were older at the time of the two-year neurodevelopmental assessment when compared to mothers with overweight and their children (see details in Original publication III).

The children's and mothers' characteristics in study IV were compared according to whether a child was denoted to have DCD (n=22) or not (n=132). The mothers of children with an age-appropriate motor development at 5–6 years had higher education level when compared to those whose children were denoted to have DCD. Also, children with age-appropriate motor development were more often girls and they were older at the motor assessment when compared to children denoted to have DCD (see details in Original publication IV).

**Table 7**. Clinical characteristics of mothers and their children included in the studies I-IV. Modified from Original publications I-IV.

| Characteristics | Study I (n=330) | Study II (n=378) | Study III (n=243) | Study IV (n=159) |
|---|---|---|---|---|
| **Mothers** | | | | |
| Age (years) [a] | 30.7 ± 4.5 | 30.6 ± 4.5 | 30.9 ± 4.6 | 30.6 ± 4.3 |
| College or university education [b] | 211 (63.9) | 228 (61.5) | 169 (70) | 107 (67.7) |
| Primiparity [b] | 161 (48.8) | 183 (48.4) | 133 (54.7) | 82 (51.6) |
| Smoking before pregnancy [b] | 57 (17.3) | 79 (21.2) | 38 (15.6) | 31 (19.6) |
| Pre-pregnancy BMI | 28.7 (26.5–31.8) [c] | 28.7 (26.5–32.0) [c] | 29.4 ± 3.8 [a] | 28.8 (26.5–31.6) [c] |
| With obesity [b] | 130 (39.4) | 150 (39.7) | 94 (38.7) | 59 (37.1) |
| Gestational diabetes mellitus [b] | 93 (28.9) | 107 (28.9) | 68 (28.7) | 38 (24.5) |
| Smoking during pregnancy [b] | 13 (3.9) | 19 (5.1) | 8 (3.3) | 7 (4.5) |
| Gestational weeks at delivery [c] | 39.7 (39.0–40.6) | 39.6 (39.0–40.6) | 40.0 (39.0–40.7) | 39.9 (39.1–40.9) |
| Delivery <37+0 gestational weeks [b] | 19 (5.8) | 22 (5.8) | 13 (5.3) | 7 (4.4) |
| Unassisted vaginal delivery [b] | 239 (72.4) | 277 (73.3) | 174 (71.6) | 115 (72.3) |
| **Children** | | | | |
| Child sex, girl [b] | 165 (50.0) | 193 (51.1) | 119 (49.0) | 75 (47.2) |
| **At 2 years** | | | | |
| Age at the Bayley-III assessment (years) [a] | - | - | 2.0 ± 0.03 | - |
| Age at the HINE and gross motor assessment of the Bayley-III (years) [a] | - | - | 2.0 ± 0.1 | - |
| **At 5–6 years** | | | | |
| Age at the Movement ABC-2 (years) [a] | - | - | - | 5.5 ± 0.5 |

[a] mean ± standard deviation, [b] frequency (percentage), [c] median (interquartile range)

Bayley-III=Bayley Scales of Infant and Toddler Development, Third Edition, HINE=Hammersmith Infant Neurological Examination, Movement ABC-2= Movement Assessment Battery for Children, Second edition.

## 5.2 Overview of growth and neurodevelopment of children

### 5.2.1 Growth (studies I & II)

The mean growth of children from birth until 24 months of age was within the normal reference range as shown in **Table 8**. Most children had normal weight (81.6%, n=204) at the age of 24 months, and the rest had overweight (18.4%, n=46) as assessed by weight-for-age%. A mean fat percentage was 24.6 (SD 8.87) while the numbers for fat mass and fat free mass were 3.30 (SD 1.48) and 9.78 (SD 1.01) kg, respectively, in children aged 24 months.

**Table 8.** Growth measures of children from birth until 24 months of age. Modified from Original publications I and II.

| Time point | Height-for-age SD-score<br>Mean ± SD | Weight-for-height%<br>Mean ± SD | Head circumference-for-age SD-score<br>Mean ± SD |
|---|---|---|---|
| Birth (n=339-361) | 0.04 ± 1.00 | 2.14 ± 9.37 | 0.21 ± 1.03 |
| 3 months (n=321-327) | -0.20 ± 1.11 | 3.14 ± 8.40 | -0.07 ± 1.10 |
| 6 months (n=295-300) | -0.26 ± 1.11 | 4.34 ± 8.47 | -0.03 ± 1.08 |
| 12 months (n=275-282) | -0.19 ± 1.08 | 2.76 ± 8.30 | -0.10 ± 1.09 |
| 24 months (n=236-250) | -0.17 ± 1.06 | 2.91 ± 8.52 | -0.06 ± 1.06 |

SD-score=standard deviation score.

### 5.2.2 Neurodevelopment (studies III & IV)

The results of neurodevelopmental assessment of children are presented in **Table 9**. The children's mean neurodevelopment was normal at the age of two years as assessed by the Bayley-III or the HINE. Yet, few children scored ≤ 1SD below the normative mean in the Bayley-III on the composite cognitive and language scales and receptive language subscale while the number of children was higher on the expressive language subscale. The number of children with suboptimal score (<74) in the HINE was 16.7% (n=38).

At the age of 5–6 years the mean percentiles for total test scores in the Movement ABC-2 were age-appropriate (47.5 ± 28.3). The number of children with DCD (total score ≤15th percentile) was 14.3% (n=22). The numbers for subscales are presented in **Table 9**.

**Table 9**. Neurodevelopmental assessment scores or percentiles in 2 and 5–6 years old children. Modified from Original publications III and IV.

| **Bayley-III (2 years) (n=171-235)** | **Mean ± SD** | **≤ 1SD n (%)** |
|---|---|---|
| Composite cognitive | 112 ± 12.7 | 3 (1.3) |
| Composite language | 110 ± 15.0 | 10 (2.3) |
| Expressive language | 10.3 ± 3.1 | 27 (6.2) |
| Receptive language | 13.1 ± 2.7 | 2 (0.4) |
| Composite motor | 115 ± 12.2 | - |
| Fine motor | 12.8 ± 2.4 | - |
| Gross motor | 12.2 ± 2.8 | - |
| **HINE (2 years) (n=241)** | **Median (IQR)** | **Suboptimal score (<74) n (%)** |
| Global score | 76.0 (74.5–76.8) | 38 (16.7) |
| **Movement ABC-2 percentiles (5–6 years) (n=154-158)** | **Mean ± SD** | **≤ 15th percentile n (%)** |
| Total score | 47.5 ± 28.3 | 22 (14.3) |
| Manual Dexterity | 40.8 ± 28.9 | 39 (24.7) |
| Aiming & catching | 46.9 ± 27.2 | 23 (14.6) |
| Balance | 58.9 ± 28.8 | 14 (9.0) |

Bayley-III=Bayley Scales of Infant and Toddler Development, Third Edition, HINE=Hammersmith Infant Neurological Examination, IQR=Interquartile range, Movement ABC-2=Movement Assessment Battery for Children, Second edition.
≤15th percentile denotes developmental coordination disorder (total score) or an age-inappropriate motor development (subscales).

## 5.3 Adiposity in pregnancy in association with

### 5.3.1 Growth of children (study II)

An inspection of maternal body composition in early (fat percentage mean 43.2, SD 5.6, fat mass mean 36.9, SD 10.0 kg) and late (fat percentage mean 40.7, SD 5.2, fat mass mean 38.4, SD 9.7 kg) pregnancy revealed statistically significant associations with the growth of children from birth to 24 months after adjustments for confounders (**Figure 4**). A higher fat mass in early and late pregnancy correlated positively with a head circumference-for-age SD-score and a height-for-age SD-score. Maternal body composition in early or late pregnancy did not affect the body composition of children at the age of 24 months (**Figure 4**). No statistically significant associations were seen between maternal overweight or obesity, as defined by pre-pregnancy BMI, and the growth or body composition of children during the first 24 months of life (adjusted models, see details in Original publication II).

### 5.3.2 Neurodevelopment of children (studies III & IV)

A higher maternal adiposity in pregnancy associated negatively with the results of the neurodevelopmental assessments of children at two and 5–6 years of age, after adjustments for confounders, as shown in **Table 10**. However, not all the associations were statistically significant. A higher body fat percentage in early pregnancy (mean 42.9, SD 5.5) correlated with lower composite cognition, expressive language, composite motor and gross motor scores of the Bayley-III in two-year-old children. In late pregnancy, negative correlations were seen between body fat percentage (mean 40.4, SD 5.1) and composite cognitive and receptive language scores of children. No statistically significant associations were seen with the global score of the HINE in the adjusted models (**Table 10**).

At the age of 5–6 years, a higher maternal fat mass in early (mean 36.5, SD 9.3 kg) and late (mean 37.8, SD 9.3 kg) pregnancy was associated with higher odds for a child having DCD as assessed by the Movement ABC-2 (adjusted model). In addition, a higher maternal body fat percentage in late (mean 40.5, SD 5.4) but not in early (mean 43.1, SD 5.5) pregnancy associated with increased odds for DCD and motor impairment on the manual dexterity subscale, after adjustments for confounders (**Table 11**).

Pre-pregnancy obesity or overweight, as determined by BMI, did not influence the results of the neurodevelopmental assessments, after adjustments for confounders, at two or 5–6 years of age (see details in Original publications III and IV).


**Figure 4.** The heatmap describing Pearson's partial correlations between maternal body composition, in early and late pregnancy, and the growth and body composition of children from birth until 24 months of age. Red colour indicates a positive correlation and blue colour indicates a negative correlation (not corrected for multiple testing, *p<0.05). Adjusted for birth weight (except for birth weight variables), and for child's age (weight-for-height%, 3–24 months). Corrected for multiple testing by the Benjamini-Hochberg procedure (†corrected p<0.05). Modified from Original publication II.

**Table 10**. Correlation between maternal body composition, in early and late pregnancy, and the neurodevelopment of children at 2 years of age as assessed by the Bayley-III and the HINE. Modified from Original publication III.

| | **Early pregnancy** | | **Late pregnancy** | |
|---|---|---|---|---|
| **Bayley-III (2 years)** | Correlation (r / rho) | Adjusted p | Correlation (r / rho) | Adjusted p |
| Fat percentage | Composite cognitive -0.16 | 0.02 | Composite cognitive -0.18 | 0.01 |
| Fat percentage | Composite language -0.13 | 0.06 | Composite language -0.14 | 0.06 |
| Fat percentage | Expressive language -0.14 | 0.046 | Expressive language -0.10 | 0.16 |
| Fat percentage | Receptive language -0.12 | 0.10 | Receptive language -0.15 | 0.03 |
| Fat percentage | Composite motor -0.16 | 0.04 | Composite motor -0.14 | 0.07 |
| Fat percentage | Fine motor -0.03 | 0.70 | Fine motor -0.04 | 0.62 |
| Fat percentage | Gross motor -0.13 | 0.04 | Gross motor -0.12 | 0.06 |
| **HINE (2 years)** | | | | |
| Fat percentage | Global score -0.11 | 0.09 | Global score -0.09 | 0.16 |

Pearson or Spearman correlation, adjusted for: maternal education, maternal employee and marital status, primiparity, pre-pregnancy smoking status, and child’s sex.
Bayley-III=Bayley Scales of Infant and Toddler Development, Third edition, HINE=Hammersmith Infant Neurological Examination.

**Table 11.** Associations between maternal body composition, in early and late pregnancy, and the neurodevelopment of children at 5–6 years of age as assessed by the Movement ABC-2. Modified from Original publication IV.

| | **Early pregnancy** | | **Late pregnancy** | |
|---|---|---|---|---|
| **Movement ABC-2 (5-6 years)** | Adjusted OR (CI 95%) for ≤15$^{th}$ percentile | Adjusted p | Adjusted OR (CI 95%) for ≤15$^{th}$ percentile | Adjusted p |
| | **Total test score** | | **Total test score** | |
| Fat mass | 1.07 (1.01–1.13) | 0.02 | 1.08 (1.02–1.14) | 0.01 |
| Fat percentage | 1.10 (0.99–1.22) | 0.08 | 1.12 (1.09–1.24) | 0.03 |
| | **Manual Dexterity** | | **Manual Dexterity** | |
| Fat mass | 1.02 (0.98–1.06) | 0.45 | 1.04 (0.997–1.08) | 0.07 |
| Fat percentage | 1.03 (0.96–1.11) | 0.41 | 1.09 (1.01–1.18) | 0.04 |
| | **Aiming & catching** | | **Aiming & catching** | |
| Fat mass | 1.00 (0.95–1.05) | 0.95 | 1.00 (0.96–1.06) | 0.85 |
| Fat percentage | 0.97 (0.89–1.06) | 0.56 | 0.99 (0.90–1.08) | 0.78 |
| | **Balance** | | **Balance** | |
| Fat mass | 1.06 (0.995–1.12) | 0.10 | 1.05 (0.99–1.11) | 0.12 |
| Fat percentage | 1.10 (0.98–1.24) | 0.17 | 1.06 (0.95–1.19) | 0.30 |

Logistic regression model, adjusted for: maternal education level, age, pre-pregnancy smoking status, child's sex, and intervention groups and additionally models on early pregnancy fat mass and fat percentage for gestational weeks at delivery.
≤15$^{th}$ percentile denotes developmental coordination disorder (total score) or an age-inappropriate motor development (subscales).
CI=confidence interval, Movement ABC-2= Movement Assessment Battery for Children, Second edition, OR=odds ratio, SE=standard error

## 5.4 Gestational diabetes mellitus in pregnancy in association with

### 5.4.1 Growth of children (study II)

The associations between maternal GDM and the growth markers of children are described in **Figure 5**. A mean head circumference SD-score was lower at birth and at six months in those children whose mothers were diagnosed with GDM during pregnancy when compared to those whose mothers were without GDM, after adjustments for confounders. No other statistically significant associations were detected between GDM and the growth markers of children. GDM did not associate with the body composition of children at the age of 24 months, after adjustments for confounders (**Figure 5**).

### 5.4.2 Neurodevelopment of children (study III & IV)

The associations between maternal GDM and the neurodevelopment of the children at two and 5–6 years of age are shown in **Table 12**. Children of mothers with GDM scored lower on expressive language subscale of the Bayley-III when compared to children of mothers without GDM at the age of two years, after adjustments for confounders. No statistically significant associations were seen between GDM and the optimal / suboptimal scores of the HINE (adjusted model).

No differences were seen in motor performance in 5–6 years old children of mothers with and without GDM, after adjustments for confounders (**Table 12**). Motor impairment (total score <15$^{th}$ percentiles) was found in 14.9% and 13.9% of children of mothers with and without GDM, respectively, with no statistically significant difference. The number of children with impaired manual dexterity, aiming and catching or balance did not differ between the maternal GDM groups (adjusted models, see details in Original publication IV).

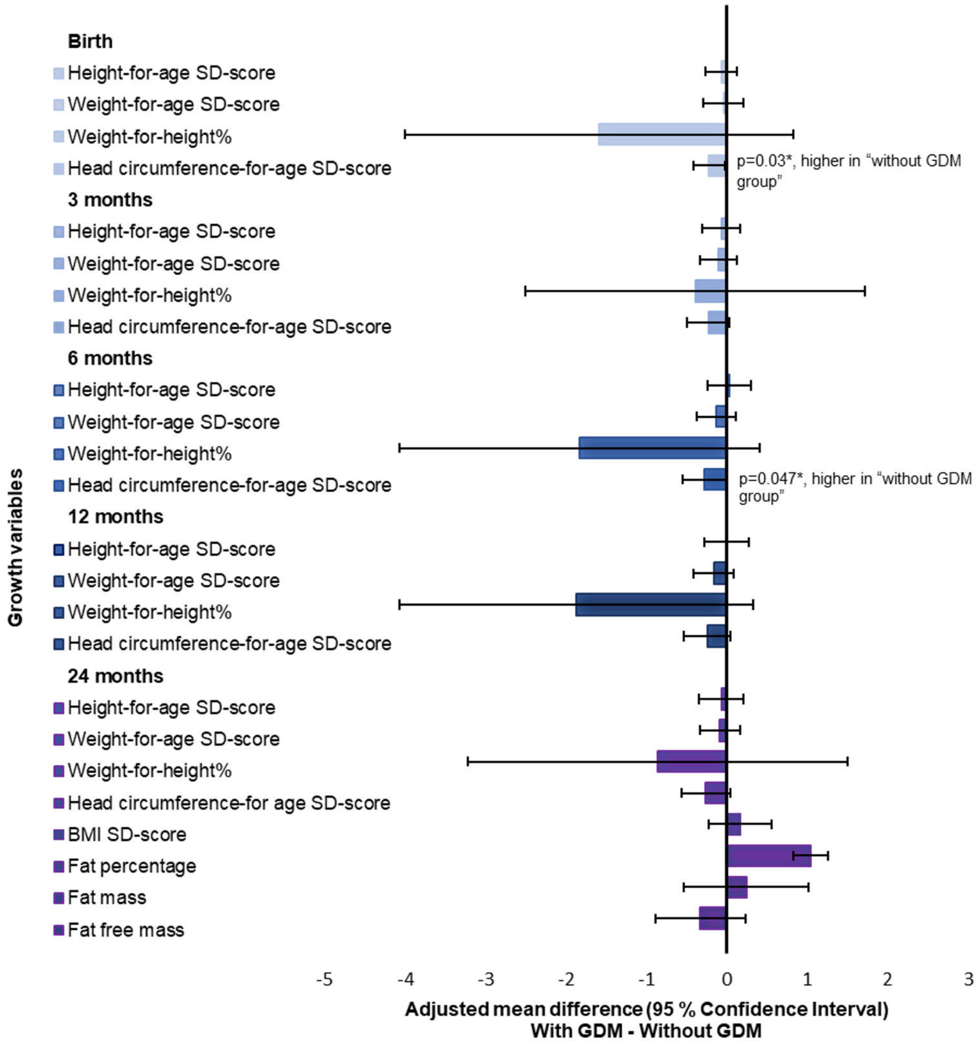


**Figure 5.** Associations between maternal GDM diagnosis (yes or no) and the growth of children from birth until 24 months of age. General linear model, adjusted for maternal pre-pregnancy BMI, education level, child's birth weight (except for birth weight variables) or gestational weeks at delivery (weight-for-age SD-score and weight-for-height% at birth), child's age (weight-for-height%, 3-24 months), and intervention groups. Modified from Original publication II.

**Table 12.** Associations between GDM and the neurodevelopment of children at 2 and 5–6 years of age as assessed by the Bayley-III, the HINE and the Movement ABC-2. Modified from original publications III and IV.

| | **Without GDM adjusted mean (SE)** | **With GDM adjusted mean (SE)** | **Adjusted mean difference / [a] OR (95% CI)** | **Adjusted p** |
|---|---|---|---|---|
| **Bayley-III (2 years)** | n = 126–169 | n = 45–66 | | |
| Composite cognitive | 112 (2.69) | 111 (2.85) | -1.39 (-5.36–2.58) | 0.49 |
| Composite language | 108 (3.13) | 104 (3.33) | -4.34 (-9.07–0.39) | 0.07 |
| Expressive language | 10.2 (0.65) | 9.09 (0.69) | -1.12 (-2.10–(-0.15)) | 0.02 |
| Receptive language | 12.5 (0.57) | 12.2 (0.60) | -0.30 (-1.15–0.56) | 0.50 |
| Composite motor | 112 (3.09) | 109 (3.24) | -3.65 (-8.04–0.74) | 0.10 |
| Fine motor | 13.1 (0.63) | 12.5 (0.66) | -0.64 (-1.54–0.26) | 0.16 |
| Gross motor | 11.8 (0.55) | 11.2 (0.59) | -0.63 (-1.47–0.21) | 0.14 |
| **HINE (2 years)** | | | | |
| Suboptimal score<br>Optimal score [a] | 22 (13.8)<br>137 (86.2) | 15 (23.8)<br>48 (76.2) | 2.12 (0.92–4.88) | 0.08 |
| **Movement ABC-2 (5-6 years) Percentiles** | n = 114–115 | n = 36–38 | | |
| Total test score | 43.3 (3.29) | 45.8 (5.30) | 2.52 (-8.65–13.7) | 0.66 |
| Manual Dexterity | 40.1 (3.38) | 38.8 (5.30) | -1.28 (-12.7–10.1) | 0.83 |
| Aiming & catching | 43.3 (3.11) | 48.8 (4.92) | 5.52 (-5.08–16.1) | 0.31 |
| Balance | 52.7 (3.30) | 51.2 (5.37) | -1.51 (-12.9–9.85) | 0.79 |

General linear models (with GDM–without GDM) or [a] binary logistic regression model (HINE as categorical variable, Optimal score of HINE ≥74, suboptimal score of HINE <74).
Bayley-III and HINE adjusted for: maternal education level, employee status, marital status, pre-pregnancy BMI, gestational weeks at delivery, pre-pregnancy smoking status, primiparity, child's sex, and intervention groups. N=171-235.
Movement ABC-2 adjusted for: maternal education level, age, pre-pregnancy smoking status, child's sex, pre-pregnancy BMI, gestational weeks at delivery, and intervention groups. N=150-154.
Bayley-III= Bayley Scales of Infant and Toddler Development, Third edition, CI=Confidence Interval, HINE=Hammersmith Infant Neurological Examination, GDM=Gestational diabetes mellitus, Movement ABC-2=Movement Assessment Battery for Children, Second edition, SE=standard error.

# 5.5 Diet in pregnancy in association with

## 5.5.1 Growth of children (study II)

The associations between maternal dietary quality, based on the Index of Diet Quality, in early pregnancy and the growth of children from birth until 24 months of age are shown in **Figure 6**. The SD-scores for height-for-age were higher at each timepoint in children whose mothers had a good dietary quality in early pregnancy when compared to those of mothers with a poor dietary quality, after adjustments for confounders. In addition, SD-scores for head circumference-for-age were higher at the age of 12 and 24 months in children who belonged to maternal good dietary quality group (adjusted model). No other statistically significant associations were seen. Considering late pregnancy, a good dietary quality associated with a lower fat mass of children at the age of 24 months (adjusted mean difference -0.69, 95% confidence interval (-1.35; -0.10)). No other statistically significant associations were seen with the growth markers of children from birth until 24 months (see details in Original publication II).

When maternal dietary inflammatory index (mean -0.49, SD 1.78 and mean -0.52, SD 1.74 in early and late pregnancy, respectively) in relation to the growth of children was investigated, statistically significant correlations were seen after adjustments for confounders (**Figure 7**). A higher DII score in early and/or late pregnancy correlated with lower height-for-age SD-scores but higher weight-for-height% and BMI-for-age SD-scores in children. A higher E-DII score in early (mean -1.16, SD 1.61) but not in late (mean -1.10, SD 1.63) pregnancy, correlated with a lower height-for-age SD-score at 12 months in children. Neither DII nor E-DII in early and late pregnancy was associated with the body composition of children at 24 months of age, after adjustments for confounders (**Figure 7**).

To see whether a good dietary quality is less inflammatory in the original publication II, the correlations between IDQ and DII were inspected; negative associations were detected in early ($r=-0.38$, $p<0.001$) and late ($r=-0.29$, $p<0.001$) pregnancy.

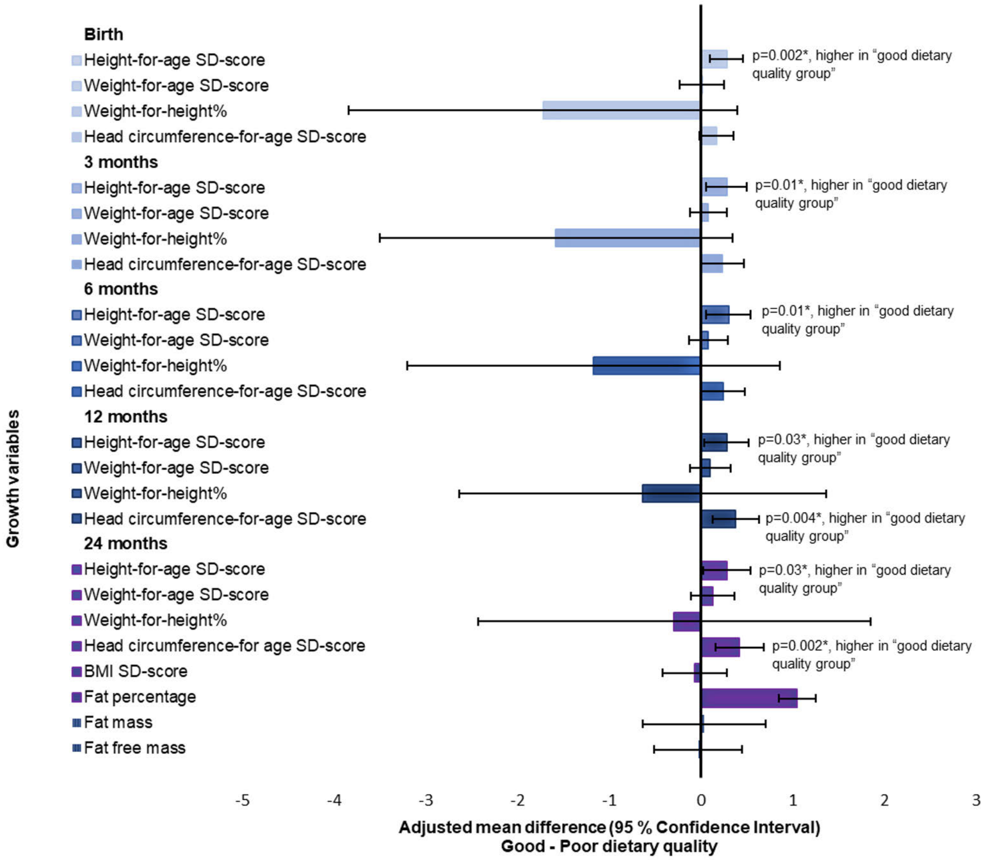


**Figure 6.** Association between maternal dietary quality (good or poor) in early pregnancy and the growth of children from birth until 24 months of age. General linear model, adjusted for maternal education level, pre-pregnancy smoking status, child's birth weight (except for birth weight variables), child's age (weight-for-height%, 3-24 months), and intervention groups. Modified from Original publication II.

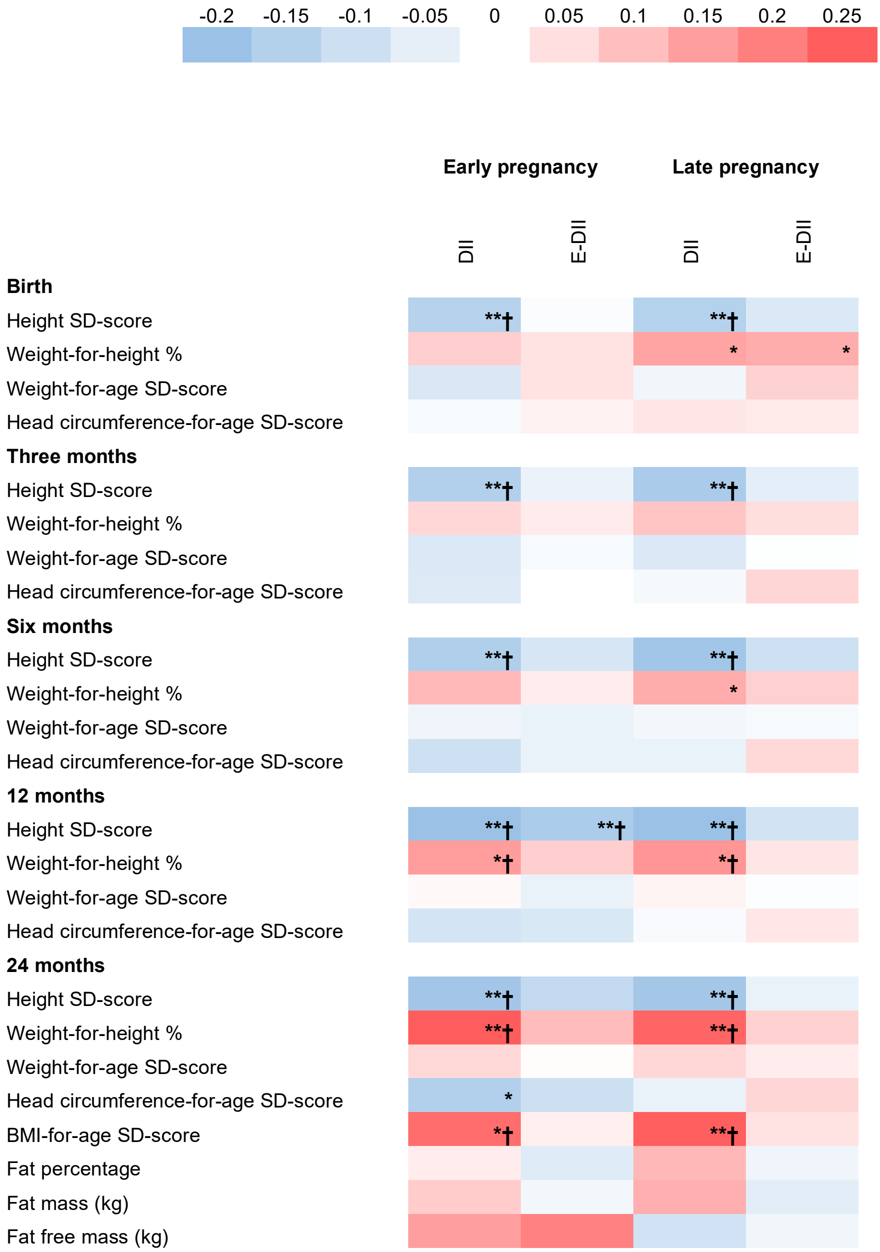


**Figure 7.** The heatmap describing Pearson's partial correlations between the growth of children and dietary inflammatory potential (DII and E-DII) in early and late pregnancy. Red colour indicates a positive correlation and blue colour indicates a negative correlation (not corrected for multiple testing, *p<0.05, **p<0.01). Adjusted for birth weight (except for birth weight variables), and for child's age (weight-for-height%, 3-24 months). Corrected for multiple testing by the Benjamini-Hochberg procedure (†corrected p<0.05). Modified from Original publication II.

### 5.5.2 Neurodevelopment of children (studies III & IV)

The associations between maternal diet during pregnancy and the results of the neurodevelopmental assessments of the children are presented in **Table 13**. Maternal good dietary quality, based on the Index of Diet Quality, in late pregnancy associated with higher scores on expressive language subscale of the Bayley-III in two-year-old children, after adjustments for confounders. No statistically significant associations were found between dietary quality in early pregnancy and the Bayley-III results (adjusted models, see details in Original publication III). Maternal dietary quality in early or late pregnancy did not affect the optimal / suboptimal scores of the HINE (adjusted models).

At the age of 5–6 years, the children of mothers with a healthier dietary pattern, defined from food diaries, in early pregnancy had better motor performance as assessed by the Movement ABC-2, after adjustments for confounders (**Table 13**). The percentages of children with motor impairment (<$15^{th}$ percentiles, total score) were 15.2% and 13.1% in the maternal healthier and unhealthier dietary pattern groups, with no statistically significant difference in the adjusted models. Accordingly, the number of children with impaired manual dexterity, aiming and catching or balance, did not differ between the maternal dietary pattern groups. Maternal dietary patterns in late pregnancy were not associated with the motor performance in 5–6-year-old children (adjusted models, see details in Original publication IV).

When mothers' diets were investigated in more detail, it was seen that higher fish consumption in early (study III median 2.2, IQR 1.0–3.0, study IV 2.0, 1.0–3.0 times/week) or late (study III median 2.0, IQR 1.0–3.0 and study IV 2.0, 1.0–3.0 times/week) pregnancy associated with a better neurodevelopment of children, after adjustments for confounders (**Table 14**). More closely, greater fish consumption in late pregnancy associated with higher expressive language scores in two-year-old children as assessed by the Bayley-III. In addition, greater fish consumption in early pregnancy was associated with lower odds for impaired manual dexterity and aiming and catching as assessed by the Movement ABC-2 at 5–6 years of age (**Table 14**). No statistically significant associations were seen between a fish consumption and the global score of the HINE at two years of age (adjusted models).

Considering mothers' diet inflammatory potential, no associations were seen with the results of the neurodevelopmental assessments (the Bayley-III and the HINE) at two years of age in the adjusted models. At 5–6 years, negative correlations were detected with percentiles for total score and manual dexterity, after adjustments for confounders (**Figure 8**). When correlations between IDQ and DII scores were investigated to see whether a good diet quality is less inflammatory in the Original publication III, significant associations were seen in early ($r=-0.40$, $p<0.001$) and late pregnancy ($r=-0.25$, $p<0.001$).

**Table 13**. Association between maternal dietary quality (good or poor) or dietary patterns (healthier or unhealthier) in early and late pregnancy and neurodevelopment of children at 2 and 5–6 years of age as assessed by the Bayley-III, the HINE and the Movement ABC-2. Modified from Original publications III and IV.

| | **Early pregnancy** | | | | **Late pregnancy** | | | |
|---|---|---|---|---|---|---|---|---|
| **Bayley-III (2 years)** | Good dietary quality Adjusted mean (SE) | Poor dietary quality Adjusted mean (SE) | Adjusted mean difference / [a] OR (95% CI) | Adjusted p | Good diet quality Adjusted mean (SE) | Poor diet quality Adjusted mean (SE) | Adjusted mean difference / [a] OR (95% CI) | Adjusted p |
| Composite cognition | 110 (2.71) | 112 (2.64) | -1.43 (-4.87–2.00) | 0.41 | 112 (2.65) | 110 (2.65) | 2.49 (-0.92–5.90) | 0.15 |
| Composite language | 107 (3.21) | 106 (3.11) | 1.18 (-2.98–5.34) | 0.58 | 108 (3.13) | 104 (3.15) | 3.92 (-0.25–8.10) | 0.07 |
| Expressive language | 10.1 (0.67) | 9.48 (0.65) | 0.60 (-0.27–1.46) | 0.18 | 10.1 (0.65) | 9.25 (0.66) | 0.87 (0.004–1.73) | 0.049 |
| Receptive language | 12.3 (0.58) | 12.5 (0.56) | -0.17 (-0.92–0.57) | 0.65 | 12.5 (0.57) | 12.2 (0.57) | 0.33 (-0.42–1.08) | 0.39 |
| Composite motor | 110 (3.30) | 112 (3.05) | -2.08 (-5.88–1.72) | 0.28 | 111 (3.24) | 111 (3.13) | 0.23 (-3.65–4.11) | 0.91 |
| Fine motor | 12.8 (0.67) | 13.0 (0.62) | -0.22 (-0.99–0.55) | 0.57 | 13.0 (0.66) | 12.7 (0.64) | 0.32 (-0.48–1.12) | 0.43 |
| Gross motor | 11.4 (0.58) | 11.8 (055) | -0.39 (-1.13–0.36) | 0.31 | 11.6 (0.57) | 11.7 (0.56) | -0.05 (-0.81–0.71) | 0.90 |
| **HINE (2 years)** | | | | | | | | |
| Suboptimal/optimal score [a] | 18 (17.1)<br>87 (82.9) | 19 (15.7)<br>102 (84.3) | 0.84 (0.39–1.81) | 0.66 | 20 (16.0)<br>105 (84.0) | 16 (16.0)<br>84 (84.0) | 0.93 (0.42–2.05) | 0.86 |
| **Movement ABC-2 (5-6 years) Percentiles** | Healthier Dietary pattern Adjusted mean (SE) | Unhealthier Dietary pattern Adjusted mean (SE) | Adjusted mean difference (95% CI) | Adjusted p | Healthier Dietary pattern Adjusted mean (SE) | Unhealthier Dietary pattern Adjusted mean (SE) | Adjusted mean difference (95% CI) | Adjusted p |
| Total test score | 49.5 (4.05) | 39.7 (3.55) | 9.80 (0.66–19.0) | 0.04 | 44.3 (3.86) | 43.1 (3.87) | 1.16 (-8.00–10.3) | 0.80 |
| Manual Dexterity | 42.7 (4.17) | 37.7 (3.64) | 4.95 (-4.46–14.3) | 0.30 | 37.0 (3.73) | 40.0 (3.85) | -3.03 (-12.1–6.05) | 0.51 |
| Aiming & catching | 50.9 (3.77) | 41.3 (3.34) | 9.57 (0.95–18.2) | 0.03 | 47.9 (3.52) | 43.8 (3.58) | 4.05 (-4.51–12.6) | 0.35 |
| Balance | 55.7 (4.09) | 50.5 (3.60) | 5.20 (-4.17–14.6) | 0.27 | 52.7 (3.90) | 52.3 (3.85) | 0.41 (-8.82–9.64) | 0.93 |

Data are presented as adjusted mean (SE), adjusted mean difference (95% CI)

General linear models (good quality / healthier diet – poor quality / unhealthier diet) or [a] binary logistic regression models (HINE as categorical variable, Optimal score of HINE ≥74, suboptimal score of HINE <74).
Bayley-III and HINE adjusted for: maternal education level, employee status, marital status, pre-pregnancy BMI, pre-pregnancy smoking status, primiparity, child's sex, and intervention groups. Number of subjects early pregnancy 173-239 and late pregnancy 171-235.
Movement ABC-2: maternal education level, age, pre-pregnancy smoking status, child's sex, and intervention groups. Number of subjects in early pregnancy 150-153 and in late pregnancy 150-154.
Bayley-III=Bayley Scales of Infant and Toddler Development, Third edition, CI=Confidence Interval, HINE=Hammersmith Infant Neurological Examination, Movement ABC-2=Movement Assessment Battery for Children, second edition, OR=odds ratio, SE=standard error.

**Table 14.** Associations between maternal fish consumption in early and late pregnancy and neurodevelopment of children at 2 and 5–6 years of age as assessed by the Bayley-III, the HINE and the Movement ABC-2. Modified from Original publications III and IV.

| | **Maternal fish consumption in early pregnancy** | | **Maternal fish consumption in late pregnancy** | |
|---|---|---|---|---|
| **Bayley-III (2 years)** | Correlation (r / rho) | Adjusted p | Correlation (r / rho) | Adjusted p |
| Composite cognitive | 0.13 | 0.051 | 0.08 | 0.23 |
| Composite language | 0.06 | 0.41 | 0.12 | 0.09 |
| Expressive language | 0.04 | 0.59 | 0.17 | 0.02 |
| Receptive language | 0.07 | 0.29 | 0.02 | 0.83 |
| Composite motor | 0.05 | 0.56 | 0.07 | 0.36 |
| Fine motor | 0.12 | 0.14 | 0.05 | 0.58 |
| Gross motor | -0.004 | 0.96 | 0.05 | 0.50 |
| **HINE (2 years)** | | | | |
| Global score | 0.06 | 0.39 | 0.06 | 0.39 |
| **Movement ABC-2 (5-6 years) Percentiles** | Adjusted OR (95% CI) for ≤15th percentile | Adjusted p | Adjusted OR (95% CI) for ≤15th percentile | Adjusted p |
| Total test score | 0.85 (0.59–1.22) | 0.37 | 0.86 (0.61–1.23) | 0.41 |
| Manual Dexterity | 0.72 (0.54–0.97) | 0.03 | 0.86 (0.64–1.14) | 0.29 |
| Aiming & catching | 0.64 (0.44–0.94) | 0.02 | 0.87 (0.61–1.23) | 0.42 |
| Balance | 1.15 (0.82–1.62) | 0.41 | 0.70 (0.43–1.14) | 0.15 |

Pearson or Spearman partial correlation:
Bayley-III and HINE adjusted for: maternal education level, maternal employee and marital status, primiparity, pre-pregnancy smoking status, pre-pregnancy BMI, child sex.
Logistic regression model:
Movement ABC-2 adjusted for: maternal education level, age, pre-pregnancy smoking status, child sex, and intervention groups.
Bayley-III=Bayley Scales of Infant and Toddler Development, Third edition, CI=Confidence Interval, HINE=Hammersmith Infant Neurological Examination, Movement ABC-2=Movement Assessment Battery for Children, Second edition, OR=odds ratio.
≤15th percentile denotes developmental coordination disorder (total score) or impaired motor development (subscales).

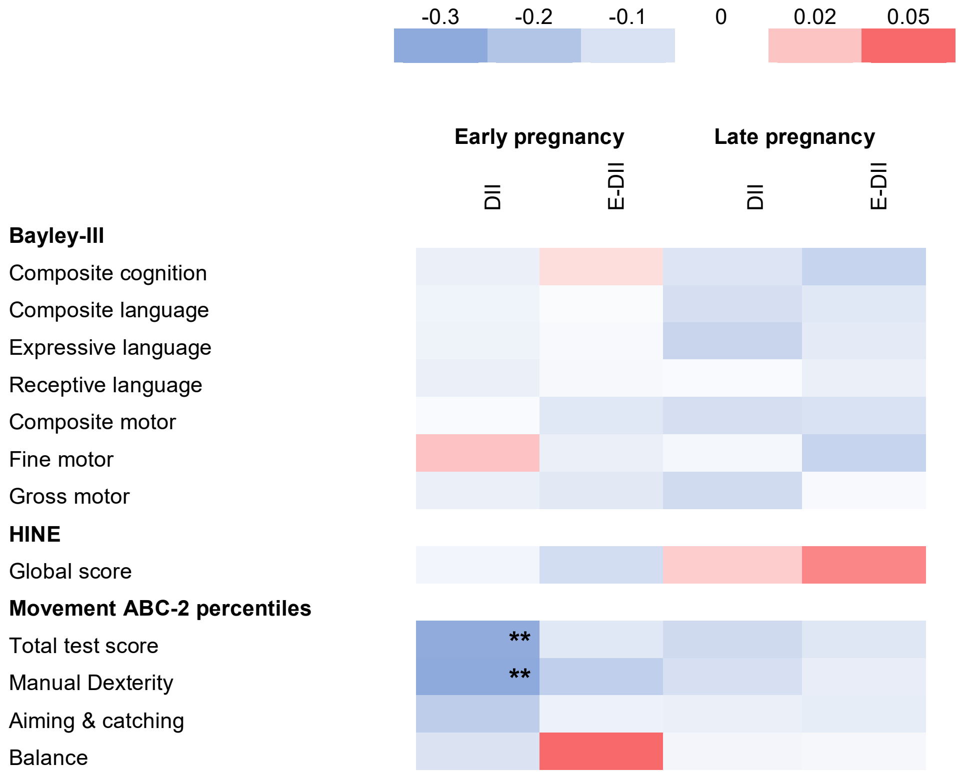


**Figure 8.** The heatmap describing Pearson's partial correlations between the neurodevelopment of children and diet inflammatory indexes (DII and E-DII) in early and late pregnancy. Red colour indicates a positive correlation and blue colour indicates a negative correlation (not corrected for multiple testing, **p<0.01). Adjusted for maternal education level, pre-pregnancy BMI, child's sex (Bayley-III and HINE) or for maternal education level, age, pre-pregnancy smoking status, child's sex (Movement ABC-2). Bayley-III=Bayley Scales of Infant and Toddler Development, Third edition, DII=diet inflammatory index, E-DII=energy-adjusted diet inflammatory index, HINE=Hammersmith Infant Neurological Examination, Movement ABC-2=Movement Assessment Battery for Children, Second edition.

## 5.6 Fish oil and probiotics supplementation in pregnancy in association with growth of children (study I)

The consumption of probiotics during pregnancy and six months postpartum lowered the odds for overweight in children at the age of 24 months by using weight-for-height% as an outcome in the adjusted models (**Figure 9**). When effects of fish oil and/or probiotics on the children's growth markers (height, weight, head circumference) were investigated, no statistically significant associations were detected (adjusted models, see details in Original publication I).

When the groups receiving probiotics (probiotics + placebo and fish oil + probiotics) were combined and compared to those that did not receive probiotics (fish oil + placebo and placebo + placebo), statistically significant associations were seen between probiotics and a lower weight-for-height% and weight-for-age SD-score of children at the age of 24 months (**Table 15**) but not at 3–12 months timepoints, after adjustments for confounders (see details in Original publication I). In addition, probiotics consumption was associated with lower overweight odds in children at the age of 24 months when compared to non-probiotics (weight-for-height%: adjusted OR 0.48 (95% CI 0.25–0.95), Original publication I). When groups receiving fish oil (fish oil + placebo and fish oil + probiotics) and groups that did not receive fish oil (probiotics + placebo and placebo) were combined no statistically significant associations were found between fish oil and the growth markers from three to 24 months of age, after adjustments for confounders (**Table 15** and original publication I). The interaction effect between fish oil and probiotics was not significant in the analyses (see Original publication I).

When investigating the interaction effect between the intervention group and time a statistically significant effect was seen on a child's height-for-age SD-score but not on other growth markers, after adjustments for confounders, as shown in **Figure 10**. In more detail, the decrease in mean height-for-age SD-score was greater in the probiotics + fish oil group when compared to the placebo + placebo group.

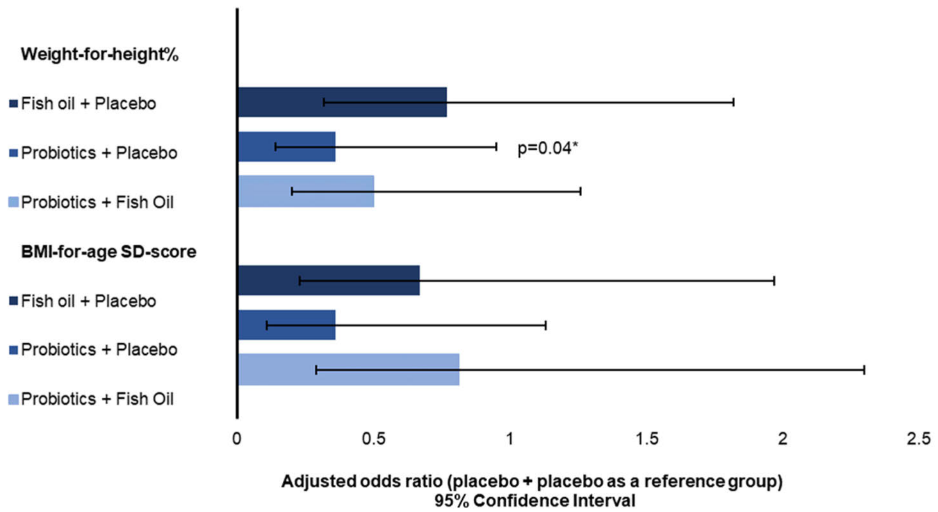


**Figure 9**. Associations between fish oil and/or probiotics intervention and overweight odds of children at the age of 24 months. Logistic regression model, adjusted for maternal pre-pregnancy smoking status, child's birth weight, and child's age at the measurement (weight-for-height%). SD-score=standard deviation score. Modified from Original publication I.

**Table 15** Associations between fish oil and/or probiotics intervention in pregnancy and six months postpartum with growth markers of children at the age of 24 months. Modified from Original publication I.

| Growth variable | Fish oil | Non-fish oil | Fish oil effect | | Probiotics | Non-probiotics | Probiotics effect | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted mean (SE) or geometric mean (95% CI) | Adjusted mean (SE) or geometric mean (95% CI) | Adjusted mean difference or proportional difference (95% CI) | Adjusted p † | Adjusted mean (SE) or geometric mean (95% CI) | Adjusted mean (SE) or geometric mean (95% CI) | Adjusted mean difference or proportional difference (95% CI) | Adjusted p † |
| Height-for-age SD-score | -0.21 (0.11) | 0.03 (0.10) | -0.24 (-0.50–0.02) | 0.07 | -0.19 (0.11) | 0.001 (0.11) | -0.19 (-0.44–0.07) | 0.15 |
| Weight-for-height% | 4.85 (0.92) | 3.40 (0.80) | 1.45 (-0.65–3.55) | 0.18 | 2.93 (0.86) | 5.32 (0.86) | -2.39 (-4.44–(-0.34)) | 0.02 |
| Weight-for-age SD-score | 0.19 (0.11) | 0.21 (0.10) | -0.02 (-0.26–0.21) | 0.84 | 0.05 (0.10) | 0.34 (0.10) | -0.29 (-0.52–(-0.06)) | 0.02 |
| Head circumference-for-age SD-score | -0.15 (0.12) | 0.11 (0.10) | -0.26 (-0.53–0.01) | 0.06 | -0.07 (0.11) | 0.03 (0.11) | -0.09 (-0.36–0.17) | 0.49 |
| BMI-for-age SD-score | 0.45 (0.15) | 0.38 (0.13) | 0.07 (-0.27–0.41) | 0.70 | 0.27 (0.14) | 0.55 (0.14) | -0.28 (-0.62–0.06) | 0.11 |
| Fat percentage[1] | 22.4 (19.4; 25.8) | 22.4 (19.5; 25.8) | 1.00 (0.84–1.20) | 0.99 | 22.3 (19.2; 25.8) | 22.6 (19.7; 25.8) | 0.99 (0.82–1.19) | 0.88 |

[1] Adjusted geometric mean (95% CI), proportional difference for adjusted geometric mean (95% CI) for fat percentage, which was ln transformed for the analysis due to its skewed distribution.

† General linear model, adjusted for: maternal pre-pregnancy smoking status, child's birth weight, and child's age at the measurement (weight-for-height%).

Number of subjects fish oil/non-fish oil 122/114-125/125 (BMI-for-age SD-score 72/77, fat percentage 36/37) and probiotics/non probiotics 118/118-125/125 (BMI-for-age SD-score 75/74, fat percentage 34/39). BMI=body mass index; CI=confidence interval; SD-score=standard deviation score; SE=standard error. Fish oil (fish oil + placebo and fish oil + probiotics), non-fish oil (probiotics + placebo and placebo + placebo).

Probiotics (probiotics + placebo and probiotics + fish oil), non-probiotics (placebo + fish oil and placebo + placebo).

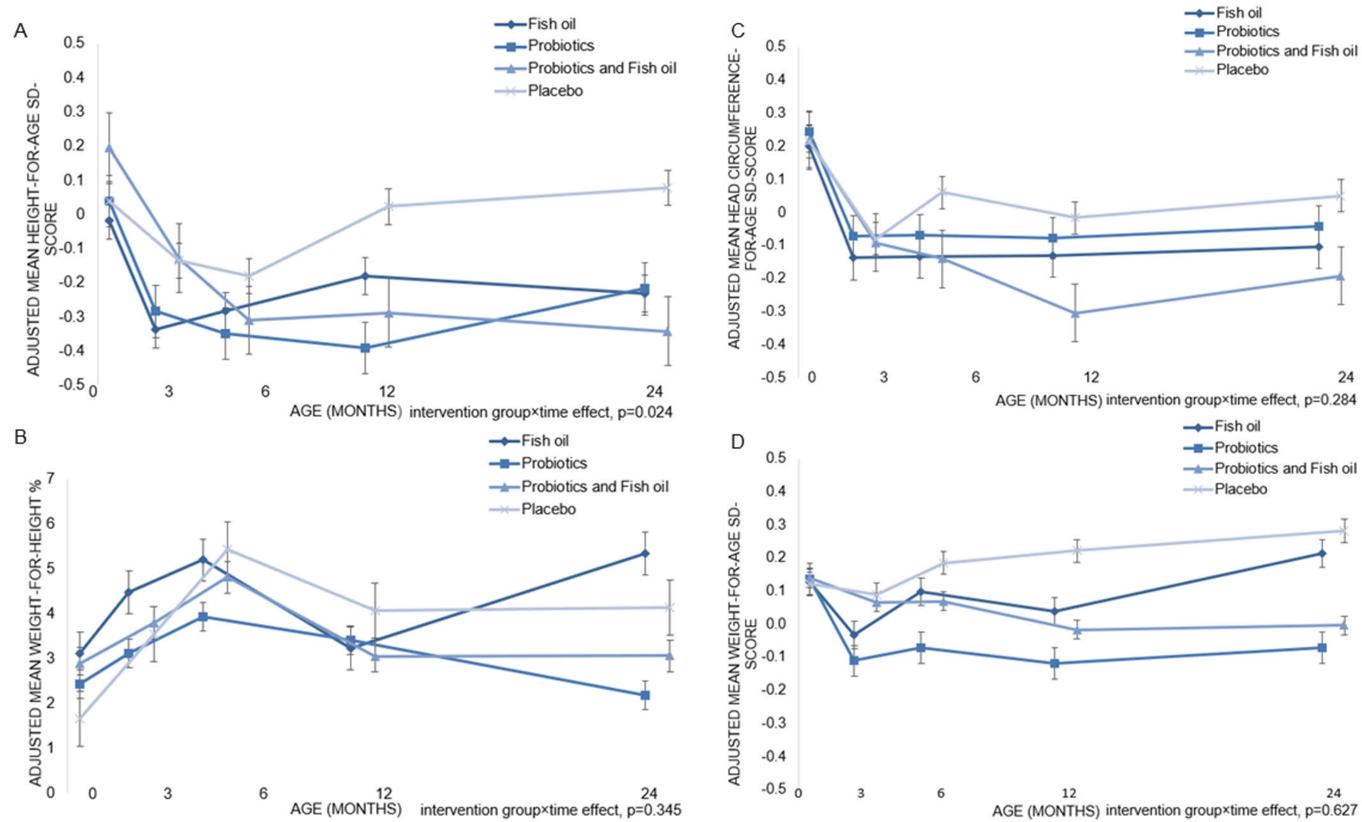


**Figure 10.** Interaction between intervention with fish oil and/or probiotics and time on the growth markers of children from birth to 24 months. A) height-for-age SD-score (p=0.024), B) weight-for-height % (p=0.345), C) head circumference-for-age SD-score (p=0.284), D) weight-for-age SD-score (p=627). Analyses of covariance for repeated measurements, adjusted for maternal pre-pregnancy smoking status and child's birth weight. Modified from Original publication I.

# 6 Discussion

## 6.1 Summary of the results

In this thesis, the associations between adiposity, GDM, and diet in mothers with overweight or obesity in pregnancy and the growth and neurodevelopment of children were investigated. The mean growth of children was within the reference values from birth until 24 months of age. The number of 24-month-old children living with overweight or obesity was 18.4%, which is in accordance with the prevalence reported in Finnish children aged 2–6 years (14% and 24% in girls and boys, respectively) in 2023 (Official statistics of Finland: Child and adolescent overweight and obesity, 2023). The results showed that greater adiposity during pregnancy was associated with a greater height and head circumference in children aged three to 12 months (**Figure 11**). Foetal predisposition to GDM in pregnancy led to a smaller head circumference in early infancy. Maternal consumption of a good quality diet during pregnancy resulted to a greater height and head circumference up to 24 months of age but lower levels of adiposity in children aged 24 months. The children whose mothers consumed probiotics during pregnancy and six months postpartum had lower odds for developing overweight as well as a lower weight at the age of 24 months. Maternal adiposity, GDM or the intervention did not affect the body composition of children at the age of 24 months (**Figure 11**).

The neurodevelopmental performance of the children at the age of two years was within the mean normative, yet few children (0.4–6.2%) scored below that on the cognitive and language scales. The number of children with DCD at the age of 5–6 years was 14.3%, a number that is nearly threefold higher than the generally reported prevalence in children (5–6%) (Blank et al., 2019). It was seen that greater adiposity during pregnancy was related to poorer cognitive, language and motor skills in two and 5–6 years old children (**Figure 11**). In addition, GDM was associated with less favourable neurodevelopment, namely expressive language skills, in children aged two years. On the other hand, children of mothers who consumed a healthy diet, including a greater fish consumption, during pregnancy, had better expressive language and motor skills at the age of two and 5–6 years, respectively (**Figure 11**).

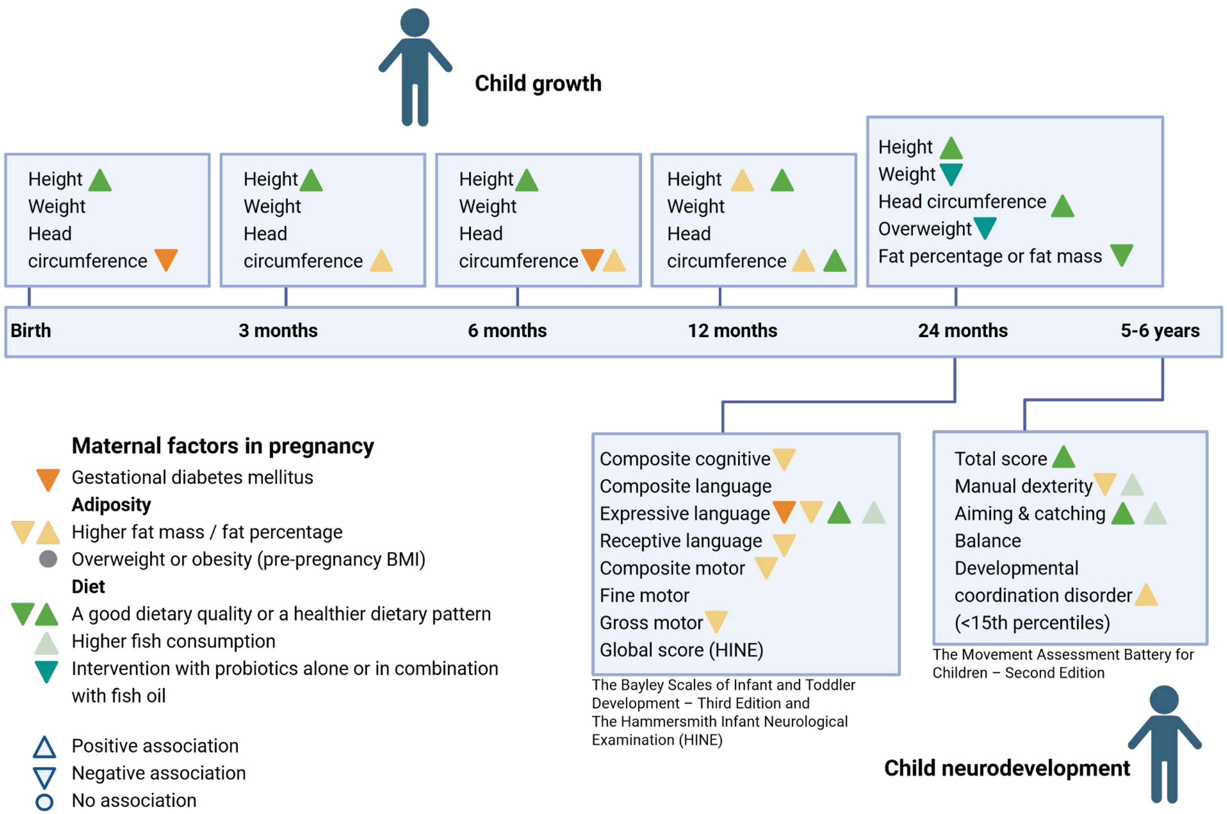


**Figure 11.** Summary of the key findings on the associations between maternal factors in pregnancy and the growth and neurodevelopment of children from birth until 5–6 years of age. Positive or negative statistically significant association ($p<0.05$). Created in BioRender. Saros, L. (2025) https://BioRender.com/26d3q0k

## 6.2 Adiposity and gestational diabetes mellitus in pregnancy: the relations to growth and neurodevelopment of children

### 6.2.1 Adiposity

The findings of this thesis indicate that greater adiposity, as measured by body composition analysis, during pregnancy led to a greater height and head circumference of children, although the latter did not remain significant after multiple correction. No such findings have been observed in previous literature. Prior research has mainly linked maternal obesity, as defined by a BMI-value, with a higher weight, BMI, fat mass and the risk for obesity in children aged 0–7 years (Bider-Canfield et al., 2017; Chiavaroli et al., 2021; Hu et al., 2019; Österroos et al., 2024). It is possible that no associations in this thesis were detected between maternal obesity and a child's weight or adiposity as no mothers with normal weight were available as a reference group unlike in previous studies. In addition, the age of children when their growth or adiposity was assessed and various assessment methods and outcomes (BMI, weight SD-score, dual-energy x-ray absorptiometry) likely influence the results.

Considering the neurodevelopment, greater adiposity during pregnancy, as measured by body composition analysis, was related to less favourable language, cognitive and motor skills as well as higher odds for DCD in children aged two and 5–6 years. These findings are unique as no previous studies have researched the link between maternal body composition and the neurodevelopment of children. The findings are, however, somewhat supported by previous literature, which indicates that maternal obesity, as measured by a BMI-value, is associated with impaired cognitive, language, problem-solving and motor skills, as assessed by various methods, in 3.5–9 years old children (Adane et al., 2018; Daraki et al., 2017; Girchenko et al., 2018; Widen et al., 2018). However, not all studies demonstrated the association between maternal higher BMI-value and the neurodevelopment of children, after adjustments for confounders (Krzeczkowski et al., 2018). Similarly, in this thesis, no association was seen between maternal obesity, as defined by pre-pregnancy BMI, and a child's neurodevelopment. Interestingly, one study suggests that the relation with a delayed neurodevelopment was observed only in those children whose mothers had a very high BMI-value ($\geq$35 kg/m$^2$) (Hinkle et al., 2012).

The findings of this thesis indicate that assessment of body composition provides deeper insights in the study on obesity when compared to a commonly used BMI-value. This explanation could lie in the fact that a BMI-value does not take into account the amount of fat mass, which putatively mediates, to a great extent, the putative harmful effects on a child's health.

### 6.2.2 Gestational diabetes mellitus

The findings of this thesis suggest that GDM, in mothers with overweight or obesity, may lead to a smaller infantile head circumference, although within the reference values. This is a novel, hence, a surprising finding as no other studies have found similar result. However, some support arises from a study, which found that glucose intolerance, including GDM and type 2 diabetes, in pregnancy resulted to a child's lower growth measures (height, weight, BMI) in first years of life (Titmuss et al., 2022). In contrast to hypothesis, no association was seen between GDM and a higher adiposity or weight of children, which has been shown in prior literature (Hu et al., 2021; Hu et al., 2019; Mantzorou et al., 2023). The reason is not clear but may relate to the fact that in this thesis no mothers with normal weight were included, thus no "normal weight/no-GDM" reference group was available unlike in most prior studies. Second putative explanation could be that all mothers who were diagnosed with GDM received dietary therapy in the maternal clinics according to Finnish current care guidelines (Gestational diabetes: Current care guideline, 2024), which may have resulted to a good glycaemic control. An inspection of a head circumference growth could also provide an interesting link to a child's neurodevelopment as there is some evidence that these interrelate.

When considering the neurodevelopment, the findings of this thesis point out that the children who exposed to hyperglycaemia due to their mothers' GDM during pregnancy had less favourable expressive language skills at the age of two years when compared to their counterparts who did not expose to GDM. Similar results arise from prior studies; GDM has been linked with poorer communication and cognitive performance in 1–7 years old children (Bolaños et al., 2015; Dionne et al., 2008; Girchenko et al., 2018), although disagreement also exists as not all studies demonstrated an association between maternal hyperglycaemia and a child's neurodevelopment (Daraki et al., 2017; Krzeczkowski et al., 2018). At the age of 5–6 years, no relations were detected between maternal GDM during pregnancy and a child's motor performance. It may be possible that GDM hinders mainly the language or cognitive development as shown previously rather than motor development. Also, the harmful effects of GDM may be shorth-term and thus do not persist into later childhood, although this cannot be concluded based on the findings of this thesis as no language assessment, of 5–6 years old children, was included in this thesis.

The findings of this thesis could be interpreted so that predisposition to GDM during early life may disturb the neurodevelopment of children through impacts on a head circumference growth. This association has been shown previously, as a smaller head circumference at birth predicted poorer neurodevelopment (Räikkönen et al., 2009; Selvanathan et al., 2022). Further, GDM has been shown to affect the maturation of the brain and caused anatomical brain structure differences, which were linked with an impaired neurodevelopment of children (Rodolaki et al., 2023). All in all, the long-term effects of GDM on the growth and neurodevelopment of children should be further investigated especially in the population of women with overweight or obesity.

### 6.2.3 Potential mechanisms

One underlying mechanism linking maternal adiposity and GDM with growth and neurodevelopment of children may be the systemic low-grade inflammation. As described earlier in this thesis, normal pregnancy is characterised by a slight increase in the inflammatory markers but in pregnancies complicated by excess adiposity or GDM, the level of systemic low-grade inflammation is even higher (Pantham et al., 2015). The babies of mothers with obesity or GDM likely predispose to inflammation as there is a higher level of pro-inflammatory cytokines in the placentas of their mothers (Van Der Burg et al., 2016). These cytokines can pass through the placenta and influence the development of foetal central nervous system by causing alterations in the brain structure (Jiang et al., 2018). In fact, previously it has been shown that elevated levels of IL-1 and IL-8 in maternal circulation were associated with poorer neurodevelopmental performance in children (Dozmorov et al., 2018; Mac Giollabhui et al., 2019). In addition, systemic low-grade inflammation may affect the nutrient supply from mother to foetus as an elevated level of inflammatory markers has been shown to increase the capability of placenta to transfer nutrients, for example, fatty acids that has been linked with faster growth of a baby (Parisi et al., 2021). On the other hand, previous research has pointed out that DHA transport from mother to foetus is diminished in GDM complicated pregnancies due to a lower expression of DHA transporter in the placentas (Sánchez-Campillo et al., 2020). This is particularly alarming as DHA is a crucial nutrient for the brain development and neither the foetus nor the placenta can synthesize DHA (Rodolaki et al., 2023).

Another plausible mechanism may be the hyperglycaemia that is seen both in the women with GDM and excess adiposity, as it may cause epigenetic changes such as DNA methylation, which is a potential mediator for a child's poorer neurodevelopment (Chu & Godfrey, 2020). Although GDM has been generally linked with a greater size of a baby due to hyperglycaemia (Metzger et al., 2008) there is evidence that GDM may cause intrauterine growth restriction. This occurs when placental small blood vessels are damaged, leading to an impaired nutrient transfer to foetus and thus growth restriction (Fasoulakis et al., 2023). This pathway could explain the smaller head circumference detected in the infants of mothers with GDM. Besides that, no association was seen between maternal adiposity and higher weight measures of children; however, hyperglycaemia could still potentially explain the higher height and head circumference measures detected in the children whose mothers had a higher fat mass during pregnancy. Lastly, a higher leptin level that is seen in mothers with overweight or obesity, may disturb placental functions and affect the brain development, and eventually the growth and neurodevelopment of children (Godfrey et al., 2017; Sullivan et al., 2014).

It is of note that there are several other putative mechanisms and confounders, such as maternal socio-economic status and lifestyle choices during and after pregnancy that are involved in the neurodevelopment and growth of children.

## 6.3 Diet in pregnancy: the relations to growth and neurodevelopment of children

### 6.3.1 Diet composition

The findings of this thesis indicate that a good dietary quality, in mothers with overweight or obesity, during early pregnancy associated with a greater height and head circumference of children from birth until 24 months of age. In addition, a good dietary quality in late pregnancy led to lower levels of adiposity in 24-month-old children. In line with these findings, previous research has shown that maternal good quality diet and seafood consumption were associated with a greater height, weight and head circumference in children, yet the assessment point was only at birth (Brantsæter et al., 2012; Rodríguez-Bernal et al., 2010; Yisahak et al., 2021). Considering a child's adiposity, prior studies have also found that a healthy diet, as measured by the Healthy Eating Index or dietary pattern, in pregnancy was associated with a lower fat mass in children aged six months and six years (Tahir et al., 2019; Van Den Broek et al., 2015), although in the study by van den Broek et al. the association did not remain significant after adjustments for confounders.

In respect to the neurodevelopment, the results suggest that the children of mothers with a good dietary quality in late pregnancy had better expressive language skills at two years of age when compared to children of mothers with a poor dietary quality. In addition, a healthier dietary pattern in early pregnancy led to superior motor skills in children aged 5–6 years. More detailed evaluation of maternal diet revealed that a greater fish consumption during pregnancy associated with better neurodevelopment in two and 5–6 years old children. These results are largely in line with prior studies that have detected a link between a health-promoting diet and a higher fish consumption in pregnancy and superior neurodevelopment of children (Freitas-Vilela et al., 2018; Hamazaki et al., 2020; Lv et al., 2022; Mahmassani et al., 2022; Normia et al., 2019).

All in all, the findings point out that consuming a health-promoting diet by mothers with overweight or obesity during pregnancy, including foods, such as vegetables, fruits, berries, whole grains and fish, would likely improve the growth and neurodevelopment of children, particularly in those whose mothers had overweight or obesity during pregnancy.

### 6.3.2 Potential mechanisms

One feasible link between maternal diet and the neurodevelopment and growth of children is the nutritional content of a healthy dietary pattern or a good quality diet. These both are characterised by a high consumption of whole-grains, vegetables, fruits, berries, low-fat dairy products and fish. Indeed, these food groups are important sources for nutrients, vitamins and minerals needed in the child's growth and neurodevelopment. For example, folate and iodine are vital in the development of foetal central nervous system (Abel et al., 2017; Naninck et al., 2019; Zou et al., 2021), while vitamin D is needed in the foetal and postnatal growth (Miliku et al., 2016). In addition, fibre has beneficial effects on glucose metabolism, that is especially important in the GDM complicated pregnancies (Weickert & Pfeiffer, 2008). Fish is a good source of n-3 PUFAs, particularly EPA and DHA, which are vital for the developing brain and retina (Martinat et al., 2021), and their beneficial effects on the neurodevelopment have been shown previously (Hamazaki et al., 2020; Vollet et al., 2017). A good dietary quality and a healthier dietary pattern may also affect beneficially a child's growth and neurodevelopment by their anti-inflammatory effects that are likely attributable to the n-3 PUFAs (Minihane et al., 2015). This may be the case, as IDQ and DII correlated negatively in the studies II and III, which denotes that a good dietary quality has anti-inflammatory effects in the body. Indeed, previous literature has shown that an anti-inflammatory diet already before pregnancy supports a child's neurodevelopment and growth (Chen et al., 2021; Kyozuka et al., 2022). This is in line with the findings of this thesis; it was seen that a higher inflammatory potential of prenatal diet correlated with higher weight, but lower height of children as well as with poorer motor performance.

## 6.4 Fish oil and probiotics supplementation in pregnancy: the relations to growth of children

The findings of this thesis indicate that the consumption of probiotics (*L. rhamnosus* HN001 and *B. animalis* ssp. *lactis* 420, $10^{10}$ colony-forming units) during pregnancy and six months postpartum by mothers with overweight or obesity lowered the overweight odds and weight of children at the age of 24 months. Not many researchers have found similar findings, however some support arises from one prior study in which consumption of probiotics (*Lacticaseibacillus rhamnosus* (formerly *Lactobacillus rhamnosus*) GG, ATCC 53103, $1x10^{10}$ colony-forming units) from pregnancy until six months postpartum (probiotics given to a baby if mother did not breastfeed) was associated with a slower weight-gain from foetal period up to 24–48 months of age and a lower BMI-value in children aged four years, although the latter result was only borderline statistically significant (Luoto et al., 2010). Although probiotics have known health-effects in adults, most studies have not detected that consumption of those during pregnancy would affect a child's growth as described in the literature review of this thesis (e.g., Halkjær et al., 2020, 2023; Okesene-Gafa et al., 2019; Pastor-Villaescusa et al., 2020; Wickens et al., 2017). By contrast to the hypothesis, probiotics consumption in pregnancy did not impact a child's body composition. This is line with two prior studies in which probiotics administration (*Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* BB12, minimum $6.5x10^9$ colony forming units and Vivomixx®, $450x10^9$ colony forming units) to mothers with overweight or obesity did not affect a child's body composition (Halkjær et al., 2023; Okesene-Gafa et al., 2019). However, it is of note that these studies assessed the body composition only at birth. The reason for this finding remains unsolved but explanation could relate to the low number of children who had available body composition data. Also, different bacterial strains of probiotics may exsert differential impacts. As the adipose tissue is likely in the key position in the development of various metabolic diseases in later life, the relation between probiotics consumption by a pregnant mother and her child's adiposity is necessary to investigate in future research.

A one plausible mechanism how probiotics influence the growth of children is through their anti-inflammatory effects as they are able to decrease the production of pro-inflammatory cytokines, such as leptin and TNF-α, while increasing the level of anti-inflammatory markers such as adiponectin (Zheng et al., 2019; Zhou et al., 2021). As mentioned above, the inflammatory markers are able to transfer through the placenta and subsequently influence the development of metabolic pathways, which may result in the development of diseases such as overweight in later childhood. Second putative mechanism may be that probiotics have been linked with benefits in lipid metabolism as they can inhibit cumulation of lipids in children with overweight or obesity (Li et al., 2023). Hence, it may be speculated that, by this mechanism, probiotics when administrated to the mother could also prevent the development of overweight and obesity in children. In addition, probiotics are able to enhance the shorth chain fatty acid production and thus they are able to modify gut microbiota, which may also beneficially affect the programming of metabolic pathways, e.g., development of obesity (Fu et al., 2021; Wiciński et al., 2020; Ziętek et al., 2021). Lastly, probiotics can decrease the DNA-methylation of genes that are related to obesity and weight gain, which leads to silencing of those genes and putatively to lower overweight risk in children (Vähämiko et al., 2019).

Findings of this thesis also point out that administration of probiotics in the combination with fish oil to mothers with overweight or obesity resulted in a lower height of children over the 24 months study period when compared to the children whose mothers received only placebo. The underlying reason for this finding is not known but it may be link to that in the placebo + placebo group the children had more often higher weight when compared to fish oil + probiotics group. Indeed, previously it has been shown that children with obesity tend to be taller (Holmgren et al., 2017; Papadimitriou et al., 2006). It is of note, that height of children is influenced by many other factors, including genetic, i.e., parental height, and environmental factors, such as diet as well as physical activity and sleep (Jelenkovic et al., 2016; Lee et al., 2018). As the mean growth of children was within the reference range, this finding should be interpreted carefully and needs to be confirmed in future studies.

In contrast to hypothesis, the consumption of fish oil (total of 3.8g DHA and 0.4g EPA/day) alone by mothers with overweight or obesity, did not impact the overweight, adiposity or growth measures of children. It is possible that the beneficial effects of fish oil, namely n-3 PUFAs, were diminished as all the women had overweight or obesity in this thesis. Support for this concept arises from one study where women with obesity had a lower concentration of n-3 PUFA when compared to women with normal weight following a supplementation with n-3 PUFAs (Monthé-Drèze et al., 2018). Thus, it could be that the amount of EPA and/or DHA in fish oil capsules should be higher when administrated to women with overweight or obesity. In line with the finding of this thesis, not all the previous studies have detected association between a fish oil supplementation during pregnancy and a child's growth or body composition (Foster et al., 2017; Gonzalez-Casanova et al., 2015; Gualtieri et al., 2024; Khandelwal et al., 2021; Muhlhausler et al., 2016; Wood et al., 2018). However, others have found associations between lower weight, BMI, adiposity or obesity risk and a fish oil supplementation (200mg or 800mg of DHA/day) or DHA+EPA intake from the diet during pregnancy (Bergmann et al., 2007; De Toro et al., 2024; Donahue et al., 2011). These apparent differences could relate to the composition of fish oil supplement (amount of DHA and/or EPA), duration of intervention, the study population (women with normal weight, overweight, obesity), and the assessment point for a child's growth. Thus, further research is needed to elucidate the impact of a fish oil supplementation in pregnancy on the long-term growth of children.

## 6.5 Strengths and limitations

The strengths of this thesis are long-term follow-up of the mothers during pregnancy and children from birth until 5–6 years of age and detailed data collection in a clinical trial setting. A novelty of this thesis is that no prior studies have investigated the co-effects of fish oil and probiotics on the growth of children. Furthermore, previously maternal body composition has not been studied in relation to the growth and neurodevelopment of children. Further advantage lies in the data collection; as the study population was well characterised, it was possible to consider various putative confounding factors in the statistical analyses. Also, a comprehensive approach to investigate the maternal diet was utilised: a validated Index of Diet Quality questionnaire, dietary patterns derived from three-day food diaries, and a fish consumption questionnaire. Also, an advantage was the use of validated and objective neurodevelopmental assessment methods (the Bayley-III, the HINE and the Movement ABC-2). Further, the overall growth of children was evaluated, taking account height, weight, head circumference, and body composition. In this thesis an air displacement plethysmography was used to assess body composition of mothers and children that is considered to be a gold-standard method and it is a more precise measurement of adiposity when compared to a commonly used BMI-value.

One limitation of this thesis was that all mothers had overweight or obesity already before pregnancy, thus no mothers with normal weight were available as a reference group, which may affect the generalisability of the findings to all pregnant women. However, the study sample represents quite well the pregnant women in Finland as around 27% and 20% had pre-pregnancy overweight or obesity, respectively, in 2023 (Official statistics of Finland: Perinatal statistics - parturients, 2023). Another limitation relates to the outcomes of the studies included in this thesis being secondary; thus, no power calculations were performed. In addition, the drop-out over the study course, that is typical for long-term follow-ups, may have influenced the potential to find associations as the number of mothers and children were relatively low after categorisations (e.g., with and without GDM). In the drop-out analyses of studies I and III, differences were detected in the mothers' education level and smoking habits (see details in Original publications I, III and IV). However, these were considered as confounders in the statistical analyses. A further limitation of this thesis is that maternal consumption of supplements other than fish oil/probiotics was not considered. Various vitamins and minerals are pivotal for the child's growth and neurodevelopment, such as folic acid and vitamin D. However, these supplements are generally recommended for Finnish pregnant mothers, and according to a previous report over 90% of them consumed those supplements (Koivuniemi et al., 2022). In line with this study, not all the previous studies (Mahmassani et al., 2022; Monthé-Drèze, Rifas-Shiman, et al., 2021; Normia et al., 2019; Tahir et al., 2019) have considered the consumption of dietary supplements during pregnancy when evaluating a child's growth or neurodevelopment, although some other reports have (Dai et al., 2023; Lv et al., 2022; Van Den Broek et al., 2015).

# 7 Conclusions

In this thesis the growth and neurodevelopment of children born to mothers with overweight or obesity were investigated. Based on the findings, the growth and neurodevelopment of children were an average in the reference range, although this population represented a risk-group of children due to their mother's overweight, obesity and GDM.

This thesis presented the following main conclusions:

1) Maternal higher adiposity during pregnancy associated with a higher height and head circumference of children from three to 12 months. Besides that, maternal higher adiposity exerted negative effects on cognitive, language and motor skills in two- and 5–6-year-old children.
2) The children who predisposed to GDM during pregnancy had a smaller head circumference in early infancy when compared to those who were not predisposed to GDM. In addition, maternal GDM associated less favourable neurodevelopment, especially regarding expressive language skills at two years of age. Maternal GDM did not affect motor development at 5–6 years.
3) An overall healthy diet during pregnancy associated with higher height and head circumference as well as with lower fat mass of children from birth until 24 months of age. Additionally, the children of mothers who followed a good quality diet or a healthy dietary pattern in pregnancy had superior language and motor skills at two and 5–6 years when compared to those whose mothers did not.
4) The children whose mothers consumed probiotics from early pregnancy until six months postpartum had lower odds for developing overweight and lower weight at 24 months. The combination of fish oil and probiotics associated with lower height of children over time period from birth to 24 months. Administration of fish oil alone to mother did not affect the overall growth of children.

## Implications and research needs

The findings of this thesis suggest that more attention should be paid to the means to modify the early life risk factors that may adversely impact the children's growth and neurodevelopment particularly when the mothers have GDM and overweight/obesity during pregnancy. Based on the finding of this thesis, the key element is to support the pregnant mothers to follow a health-promoting diet during pregnancy. Consumption of an overall healthy diet, based on the Index of Dietary Quality and a healthier dietary pattern, including for example vegetables, fruits, berries, whole grains, and fish, during pregnancy could have long-term health benefits for the mother and the child. Thus, the implementation of dietary recommendations during pregnancy, particularly among women with overweight or obesity, warrants greater attention. Secondly, the findings of this thesis, along with those of previous studies, suggest that the consumption of probiotics from early pregnancy onwards may support the children's growth, although this topic requires further research. This information could be utilised in the maternal welfare clinics to guide and support the pregnant women with their dietary choices.

The findings of this thesis further suggest that maternal adiposity may be more accurately assessed using body composition measurement rather than a BMI-value. Based on the findings of this thesis, maternal fat mass or percentage may play a greater role in children's growth and neurodevelopment than pre-pregnancy BMI. This information could be utilised in the future research. In addition, body composition measurement could be a useful tool to screen the high-risk mothers, i.e., those with excess fat mass, to target the dietary counselling for them and to motivate them to follow a health-promoting diet in the maternal welfare clinics.

In the future, more research is needed to elucidate even longer-term effects of maternal diet on the children's growth and neurodevelopment, beyond the ages two and 5–6 years. Secondly, there are no general recommendations regarding the consumption of fish oil and probiotics supplements during pregnancy; therefore, their safety and effects on both the mother and the child should be further investigated to enable the development of these guidelines. Lastly, as this was the first study investigating the relations between maternal body composition during pregnancy and the children's growth and neurodevelopment, these findings should be confirmed in larger studies.

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Lotta Saros

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