

Mediterranean Dietary Patterns During Pregnancy

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Pregnancy outcomes for both mother and child are affected by many environmental factors. The importance of pregnancy for 'early life programming' in the first 1,000 days of life is well established and maternal nutrition is an important factor contributing to a favourable environment for developing offspring. Results show that being on a Mediterranean Diet during pregnancy is associated with favourable outcomes for both maternal and offspring health, particularly for gestational diabetes in mothers and congenital defects in offspring.

Keywords: maternal nutrition ; Mediterranean diet ; offspring health ; Nutrition ; First 1000 Days

1. Introduction

The maternal diet before conception and during pregnancy has long-term implications for maternal and offspring health, from placental development ^[1], risk of developing gestational diabetes ^[2], birth complications ^[3], birth weight ^[4] and risk of developing allergies in childhood ^{[5][6][7][8]}. Exposure to an unfavourable environment in early pregnancy is known to significantly increase the risk of diseases in adult life; this is known as 'early life programming' and one of the most important factors is the maternal diet ^[9]. Pregnancy presents an opportune time window for healthcare professionals' intervention to improve health for both the mother and child, making the evidence surrounding maternal diet an important tool for the healthcare practice.

Maternal diet is a blueprint for the diet which children are likely to follow into adolescence. This is due to the fact that, typically, mothers are responsible for feeding their children. Without intervention, pregnant women who do not follow a healthy diet or lifestyle choices are unlikely to change their patterns of behaviour. Sometimes obstacles to changes in behaviour can present themselves even for well-known harmful habits such as smoking during pregnancy, but as a unique window of opportunity, focusing health service efforts to impact the behaviour of pregnant women is crucial.

The Mediterranean Diet (MD) and Mediterranean Diet Adherence (MDA) is characterized by a high intake of fruits, vegetables, whole grain cereals, legumes, fish and nuts; low-to-moderate consumption of dairy products and limited amounts of red meat and red wine. It is low in saturated fats and high in antioxidants, fibre and mono and polyunsaturated fatty acids mainly derived from extra virgin olive oil (evo) (MUFAs) and oily fish (n-3 PUFAs). The MD is known to have many beneficial effects for longevity and disease prevention, demonstrated in numerous high-quality studies, reviews and meta-analyses, making it the most widely studied and evidence-based dietary approach to healthy eating and disease prevention ^{[10][11][12][13]}. The unique synergy of various health benefitting nutrients makes MD an effective approach to improving health ^[11].

Recording dietary patterns through food diaries and food frequency questionnaires (FFQs) is a valuable tool to analyse eating behaviours and better understand which foods and food groups are consumed. Individual foods, such as extra virgin olive oil (evo), as well as food groups, such as pulses, provide an insight to the nutrients consumed in the recorded foods, such as monounsaturated fatty acids (MUFAs) and fibre, respectively. Asking an individual to recount specific nutrient amounts is more complex than recounting what foods were consumed as part of the daily diet, making dietary pattern analysis more attainable for patients and crucial for research.

Evidence on the impact of diet during pregnancy on health outcomes focusses on either individual nutrients, such as folic acid, or the Mediterranean Diet for their impact on specific disease outcomes such as neural tube defects ^[14] or leukaemia ^[15]. The degree of evidence available for the impact of specific nutrients in pregnancy on outcomes for offspring health is more powerful than that for dietary patterns. For instance, the necessity for appropriate levels of folic acid during gestation is well-documented in the prevention of neural tube defects, and the mechanism by which folic acid prevents neural tube defects is well understood and documented. Whereas supplements are the quicker and easier way to address certain nutritional deficiencies of individual nutrients ^[11], dietary patterns are a useful way of studying the

effects of dietary exposure, in turn, making recommended diets a potential health improvement intervention alongside appropriate and necessary supplementation in pregnancy.

The Mediterranean Diet is well established as beneficial in the literature ^[16]. Previous reviews of the evidence where several dietary patterns have been evaluated highlight that maternal dietary patterns are important factors in early life programming. Maternal dietary patterns which reflect the MD showed consistent associations with a lower risk for allergic disease in children ^[17], appropriate infant birthweight ^[18], and lower risk of pre-eclampsia and preterm birth ^[19]. This Review investigates and presents current evidence exclusively on the Mediterranean Diet's multifactorial impact on overall health outcomes for both the mother and offspring, as the sole dietary pattern of interest.

2. Current Insights on Mediterranean Dietary Patterns During Pregnancy

The mechanisms by which the MD exerts its effect on fetal development and maternal health are complex and need further research. By reviewing the available literature focusing specifically on MD interventions/exposure, as opposed to all dietary patterns as in previous reviews, we have a good overview of how the MD pattern effects mothers and their offspring on a variety of outcomes. Particularly interesting insights can be gleaned from the numerical values associated with some of the risk factors. The studies in this review are of good quality and represent a combined study population >63,000.

The observed heterogeneity of interventions, study populations and outcomes measured, allows for a big picture view of how the MD diet exerts its effects at all gestational ages and in the early years of life. For instance, when looking at behavioural outcomes, this review concluded that adherence to the MD in pregnancy has a statistically significant impact on decreasing the likelihood of offspring exhibiting depressive behaviours (OR 0.28) ^[20] in an ethnically diverse cohort, and another study added to this with a reduced OR of 0.90 ^[21] for developing externalising behaviours (such as aggression) for offspring of mothers with a high MDA.

Though some of the outcome categories we have identified only have 2 or 3 studies, they give a good starting point for future research to build on the current knowledge. Berti et al.'s comprehensive literature review of early life nutritional exposures on life-long health splits its findings into 'sections' ^[22] which, again, give a big picture overview on the vast impact that maternal, early life and even pre-conceptional nutrition can have. Unlike some more focused reviews, investigating the impact of maternal diet on allergic diseases ^[23], for instance, we hope that our review's heterogeneity contributes to a wider understanding of maternal dietary impact.

This review brings together some ideas of how the MD may be contributing to in-utero development through specific mechanistic pathways. The methylation of specific sites in two of the studies present results on how the MD, as opposed to specific nutrients, contribute to this very time-sensitive window of change of DNA methylation during fetal development.

The results on atopy, asthma and eczema highlight that whilst the MD is not always protective, it is associated with a reduced likelihood of allergic disorders as a result of maternal MD diet adherence and compounded further by offspring MD adherence. This type of follow up warrants attention; further investigation into the impacts which MD adherence for offspring of mothers who had high adherence to the MD during pregnancy and lactation, compared to non-MD adherent mother-child pairs would allow for dietary recommendations to be evidence-based through the course of pregnancy and early life as a one-time course. Intuitively, this would be a good way to approach dietary recommendations for improving health, as most children adopt their mother's dietary choices as the main provider of food in early life.

With regards to premature birth, low birth weight and childhood obesity, the evidence is more mixed. The studies that found no association between the MD and decreased likelihood of premature birth were of high quality. Some of the uncertainty is due to the limitations of the studies, some not controlling for confounders of specific outcomes like intrauterine growth, such as smoking. Despite this, the studies that were inconclusive on the impact of the MD on their primary chosen outcome, for instance the INMA birth cohort study for childhood obesity ^[24] and Parlapani et al.'s work ^[25] on birth complications and prematurity, still found statistically significant positive associations between MD adherence and other health outcomes in their results, such as waist circumference and likelihood of pre-eclampsia and necrotizing enterocolitis for each study, respectively.

A strong case for the positive impact of the MD can be seen in the results of the studies focusing on cardiometabolic and congenital defects, GDM and DNA methylation. Though these studies investigated hugely different markers and outcomes, it is clear that the MD has a protective effect on them all. The evidence presented here regarding DNA methylation and biomarkers reflects a novel way to measure the impact of dietary changes and contributes to the understanding of the mechanisms behind the long-term impacts which 'early-life programming' has. The nature of DNA

methylation in the fetal development time-course makes it possible to observe the impact which specific intra-uterine exposures have on offspring DNA methylations 20, 30 or 40 years later. For example, studies on the impact of intra-uterine exposure to famine showed that lower methylation of 5 CpG dinucleotides within the insulin-like growth factor-II differentially methylated region (DMR) [26] was detected in affected offspring decades later. Thus, the potential for future research on the impact of the MD on methylation sites of interest is vast, as dietary exposure has such a large impact.

The pattern of MD that may influence the reduction of adverse effects most appears to be one where there is purposefully added *evoo* and nuts. As seen in the present literature, increased vegetables and oily fish and decreased processed foods delivered positive results, and the effects are seen both in metabolically healthy and compromised gestation, indicating that the MD could be a diet with beneficial outcomes for GDM and metabolically healthy pregnancies.

The results of this review add to the growing body of evidence that the Mediterranean Diet is a beneficial dietary recommendation throughout the life course. By collating the evidence on outcomes of the MD for the mother and child, we highlight the broad range of effects this dietary intervention has. The limitations of this work are the small number of studies per outcome group, with the biggest group here being 'premature birth and birth weight' at only 7 studies total. Regular updates of this review are important as research around the topic is growing, and with an expanding evidence base, the possibility of meta-analysis for each category is likely. The biggest strength of this review is that, even with small numbers of studies, it highlights the impact which MDA in pregnancy and early childhood can have on several different health outcomes. The implications for clinical practice are great, as prescribing an MD pattern to women of reproductive age is a simple intervention, with important clinical potential for both the mother and offspring.

3. Conclusions

The Mediterranean Diet in pregnancy and early infancy is safe and beneficial for a wide range of maternal and offspring outcomes. Further research to ascertain the relationship and mechanisms maternal MD has with health outcomes of interest in different populations is needed to position it as a public health intervention for all populations.

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