Maternal diet matters

Objective and findings

The prevalence of obesity has nearly doubled since 1980 [1], resulting in 52% of the European Union's (EU's) adult population being overweight and 16% being obese [2]. At the same time, the prevalence of asthma has increased over the past few decades [3], leading to a current asthma prevalence of 5.4% in the EU [4]. Furthermore, respiratory infections are currently the fourth leading cause of both death and burden of disease in the world [5]. Next to their detrimental effects on a patient's health status and quality of life, these conditions have one thing in common: their development is associated with the fat content or fatty acid composition of the maternal diet during pregnancy. Given the increasing prevalences of these metabolic, immunologic and pulmonary conditions, and considering the substantial health care costs that are associated with treating them, society may benefit from preventing these diseases by improving maternal nutrition during pregnancy.

Although the long-term phenotypic effects in offspring of the maternal dietary fat content or fatty acid composition have been studied extensively, the molecular responses and mechanisms that are involved in these effects remain largely unknown. Therefore, this thesis aimed to study the effects of maternal dietary fatty acids and high-fat diet on the molecular responses related to offspring immunologic, metabolic and pulmonary health. In **chapter 2** we showed that a perinatal high-fat diet induced oxidative stress, and altered DNA methylation and gene expression of pathways involved in lipid metabolism, oxidative stress response and cell proliferation in offspring liver. In **chapter 3**, a maternal high-fat diet exacerbated ozone-induced effects on pulmonary oxidant status and the molecular control of mitophagy in female offspring. In **chapter 4**, a maternal fish oil diet, which contained high amounts of n-3 polyunsaturated fatty acids (PUFAs), not only affected *ex vivo* polarization of offspring $CD4^+$ T cells, but also induced anemia in both dams and offspring, and hepatic steatosis in offspring. In **chapter 5**, we used a multivariate statistical approach to demonstrate that maternal fatty acid status was associated with offspring inflammatory markers, and that maternal Mead acid levels correlated with the risk of developing lung conditions.

Scientific relevance

The findings from this thesis may contribute to scientific advancement in a number of ways. For **chapters 2 till 4**, this contribution mainly consists of the addition of fundamental knowledge about the effects of maternal nutrition on offspring health. The effects of a perinatal high-fat diet in **chapter 2** on offspring hepatic DNA methylation and gene expression were related to the known adverse effects on offspring metabolism induced by a maternal high-fat diet. These findings may suggest that the effects of maternal diet on

offspring health are transmitted via epigenetics and the regulation of gene expression. Similarly, the effects of a perinatal high-fat diet in **chapter 2** on oxidative stress in offspring liver and in **chapter 3** on ozone-induced oxidative stress in offspring lung suggest that oxidative stress may play an important role in the effects of maternal high-fat diet on offspring health. The effect of a maternal fish oil diet in **chapter 4** on *ex vivo* polarization of offspring $CD4^+$ T cells may be involved in the anti-asthmatic effects of prenatal supplementation with n-3 PUFAs, given the importance of $CD4^+$ T cell polarization in atopy development. Altogether, these findings contribute to a better understanding of the molecular responses that underlie the long-term phenotypic effects of maternal nutrition. Furthermore, these findings provide new leads for future studies to further unravel the mechanisms by which maternal exposures affect offspring health.

Chapter 5 mainly contributes to scientific advancement by demonstrating the use of a non-standard statistical approach for the examination of associations between prenatal nutrition and offspring health. In this chapter, we applied the statistical model canonical correlation analysis to study the multivariate relation between maternal fatty acid status and child inflammation. Applying this multivariate approach in future studies may aid in discovering new insights in the relation between maternal diet and offspring health.

Societal relevance

Results from this thesis, together with findings from previous and future studies, may contribute to the establishment of new dietary advises that will aid to improve the health of children that are yet to be born. By improving the immunologic, metabolic and pulmonary health, these children will have a better quality of life. Next to this, health care costs may be substantially reduced. For instance, 500 million euros are spent each year in the Netherlands to treat the consequences of obesity and indirect costs are even 2 billion euros each year [6]. For asthma, direct healthcare costs are estimated to be 287 million euros per year, with costs related to sick leave adding another 650 million euros per year [7].

Target groups

On the short term, findings from this thesis are most relevant to policy makers. (Semi-) governmental institutions such as the Research Council (Gezondheidsraad) and the Nutrition Center (Voedingscentrum) will have to collect and critically review results from our studies, as well as from related previous and future studies, and translate them into specific dietary advices. These dietary advices will then be used by healthcare professionals such as midwives, dietitians, general practitioners and gynecologists to inform and advise women who are pregnant, or plan to get pregnant, and their partners about good nutrition

before and during pregnancy. Furthermore, nutrition companies may develop food products and supplements to help women meet the requirements for good perinatal nutrition. In the end, all of this will help to improve the health, and therefore quality of life, of future generations. Society as a whole may benefit from this, through the reduction of health care costs.

Communication of results

The findings presented in this thesis have been shared with other researchers in the field through poster presentations and oral presentations at national and international conferences. Furthermore, results have been or will be published in peer-reviewed scientific journals: chapters 2 and 3 have been published, chapter 4 is under review and chapter 5 is in preparation for submission. All chapters have been or will be published under a Creative Commons license, meaning that they are openly and freely accessible to everyone. For communication to the general public, organizations like the Nutrition Center (Voedingscentrum) will have to translate findings from this thesis and from related publications into specific and understandable dietary advises.

References

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