

1. Introduction

The metabolic syndrome (MetS) is an substantial public health challenge world wide^{1,2}. The MetS is a clustering of a minimum of 3 of the following features: (abdominal) obesity, dyslipidemia, hypertension and hyperglycemia, which increases the risk of developing type 2 diabetes (T2D), cardiovascular disease (CVD) and all-cause mortality^{1,3,4}. Thus strategies are needed to prevent the increasing prevalence of MetS¹.

Emerging evidence suggest that biomarkers in the one-carbon metabolism (OCM) is closely related to MetS parameters and has a key role in the development of MetS⁵. The OCM is a central pathway that donates methyl groups for various biological functions, including methylation of DNA. Methylation of DNA is one example of epigenetic regulation, and epigenetic regulation has been closely linked to development of human diseases^{6,7}. New hypotheses have emerged that diet may affect metabolism via epigenetic modifications, including methylation of DNA and histones⁵. Among the nutrients that have the capacity to mediate such epigenetic modifications are B-vitamins, including folates, and other bioactive compounds such as betaine and choline^{5,8}. These compounds are involved in multiple reactions within the OCM pathway and through OCM they can affect epigenetics via donation of methyl groups^{8,9}. However, epigenetic mechanisms might not be the only potential way in which OCM might affect MetS development, as methylation reactions are also involved in methylation of phospholipids and proteins which might additionally play a role in MetS development^{10,11}. Furthermore, MetS parameters might also affect OCM flow^{12,13}. Thus it is essential to study the OCM and epigenetics in order to understand whether this can be used in prevention of MetS and related diseases.

Discovery and testing of dietary components that can affect OCM processes are needed in order to examine whether OCM affect the risk of developing MetS. A dietary component such as whole grain foods are considered to be rich in methyl donors for the OCM, including folate, betaine and choline¹⁴. Furthermore, a higher whole grain consumption has been linked to lower plasma homocysteine (Hcy) concentrations¹⁵⁻¹⁷, higher folate¹⁸, higher choline and betaine intake as well as plasma concentration¹⁹⁻²¹. In addition, there is substantial evidence that whole grain play a role in MetS parameters including weight management²², lipid metabolism²³, blood pressure (BP) regulation²⁴, and insulin resistance (IR)^{25,26} possibly through OCM and epigenetic mechanisms^{20,27}. Fish consumption has also been linked to OCM, as it is a rich source of the methyl donors choline¹⁴ and methionine, as well as OCM co-factor vitamin B₁₂²⁸⁻³⁰. Moreover, fish consumption has been associated with lower concentrations of plasma Hcy¹⁷. In addition, fish are also rich in n-3 long chain polyunsaturated fatty acid (n-3 LCPUFA) which have a protective effect on CVD risk and might beneficially affect MetS risk^{31,32}. The fatty acids might also

regulate OCM enzymes³³ and this could explain why human interventions with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have found a lowering of plasma Hcy following supplementation³⁴. Furthermore, n-3 LCPUFAs have also been linked to epigenetic alterations and early life programming of later disease risk³⁵.

More information is needed for understanding the role of OCM in MetS and to elucidate the role of dietary components such as whole grain, fish, and n-3 LCPUFA, on OCM and epigenetic regulation. The aim of this PhD thesis is to investigate how OCM metabolites were related to MetS parameters and further to examine dietary components related to OCM metabolites in two cross-sectional analyses. Moreover, the potential role of whole grains as a donor of methyl groups and the effect of a whole grain intervention on OCM regulation was investigated. Furthermore, the aim was to examine the epigenetic modifications of an early life intervention with fish oil and whether this was related to metabolic changes.

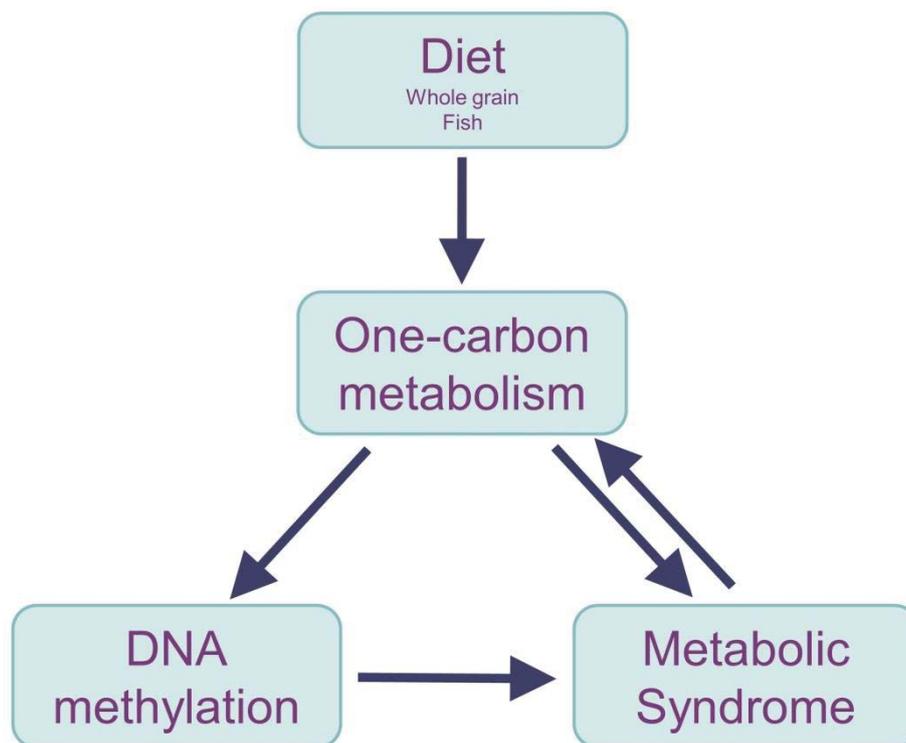


Figure 1 – Scientific framework – Illustrating the overall framework of the thesis. It shows that diet is a main regulator of one-carbon metabolism. Furthermore, there is interplay between one-carbon metabolism and metabolic syndrome, where it is hypothesized that metabolic syndrome can alter one-carbon metabolism flow and that one-carbon metabolism can affect metabolic syndrome development with one of the mechanisms being through epigenetics, especially DNA methylation.