Abating abdominal adiposity: Modifiable lifestyle risk factors for visceral and liver fat deposition

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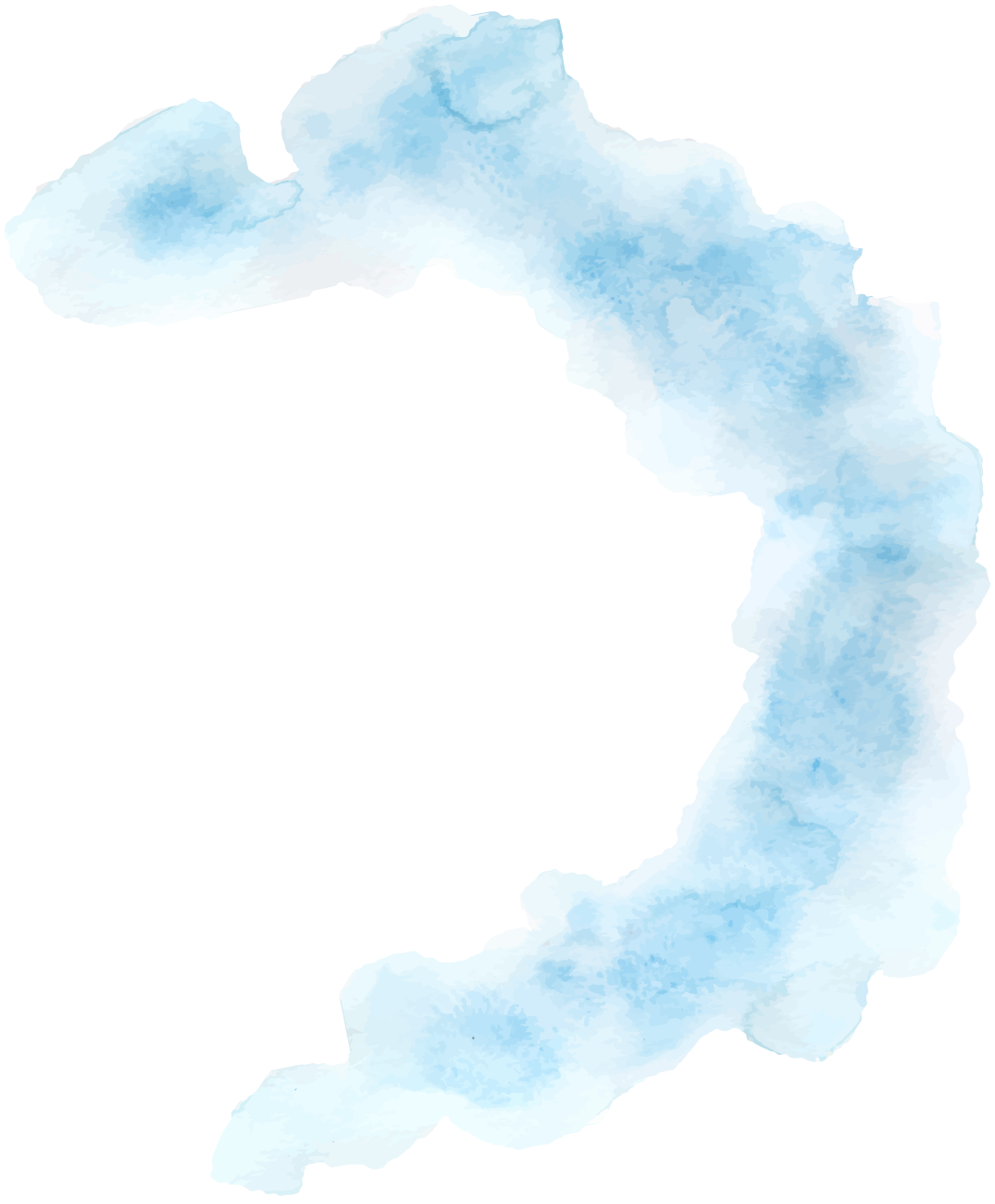

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General discussion and summary

The main aim of this thesis was to study the role of dietary habits and physical activity in the accumulation of visceral fat and liver fat. The majority of the studies described in this thesis were performed in the Netherlands Epidemiology of Obesity study, in which middle-aged participants underwent deep phenotyping, including measures of visceral adipose tissue by magnetic resonance imaging (MRI) and hepatic triglyceride content by magnetic resonance spectroscopy (MRS). We used the baseline measurement of NEO participants to investigate the association between dietary habits or physical activity patterns and visceral fat volume and liver fat content. In this general discussion we summarize our main findings, discuss their interpretation and address implications for future research.

SUMMARY OF MAIN FINDINGS

In **Chapter 2** we show the results of our systematic review and meta-analysis of randomized controlled trials and provide a summary of the evidence on the effect of dietary macronutrient composition on liver fat content as assessed by ^{1}H-MRS, MRI, CT or liver biopsy in adults. We concluded that a diet high in saturated fat leads to more liver fat accumulation than a diet high in unsaturated fat. When a diet high in protein is compared with a diet high in carbohydrates, replacing carbohydrates with proteins decreases liver fat content. Exchanging carbohydrates for dietary fats did not lead to changes in liver fat, although results of different trials were in conflict. Since only a limited number of eligible trials could be included in these meta-analyses, we have identified an essential gap in knowledge on the effect of dietary macronutrient composition on liver fat content.

In **Chapter 3** we describe the relation between dietary intake of multiple food groups and measures of visceral adipose tissue and hepatic triglyceride content. Consumption of fruit and vegetables and plant-based fats and oils was associated with less visceral fat, whereas consumption of sweet snacks was associated with more liver fat in the total study population. Patterns of were similar in men and women. Associations were partly explained by total body fat, as they attenuated after additional adjustment for total body fat, but remained present.

In **Chapter 4** we show that a higher score on the Dutch Healthy Diet Index, which reflects a better adherence to the 2015 Dutch dietary guidelines, was associated with less total body fat, less visceral fat and less liver fat. The associations with visceral fat and liver fat remained present after adjustment for total body fat, indicating that the associations are indeed specific for visceral and liver fat rather than merely representing associations with overall adiposity. We observed that associations were not driven by one component in particular, but rather that all components seemed important.

Besides food items or food groups, excessive alcohol consumption is a well-known risk factor for liver fattening and liver disease. However, it was unknown whether moderate alcohol consumption is also associated with liver fat content, and energy-containing non-alcoholic beverages might also contribute to liver fat accumulation. In **Chapter 5** we report that each additional serving of alcoholic beverages per day was indeed associated with more liver fat. Light and moderate consumption were not associated with liver fat. Nevertheless, replacing one alcoholic serving with one non-alcoholic serving was associated with less liver fat. Isocaloric replacement (5 En%) of alcoholic beverages with sugar sweetened beverages was equally associated with liver fat, whereas substitution of 5 En% alcohol with 5 En% milk was associated with less liver fat.

In addition to dietary habits, physical activity is an important cornerstone in the prevention of obesity. Not only exercise, but also habitual, unstructured activity is essential. In **Chapter 6** we studied different objectively measured activity levels of physical activity (sedentary behaviour, light, moderate and vigorous activity) in relation to total body fat, visceral fat and liver fat. We observed that sedentary time was associated with more total body fat, visceral fat and liver fat, whereas moderate to vigorous physical activity was associated with less total body fat, visceral fat and liver fat. Replacing 30 minutes of sedentary time per day with moderate to vigorous physical activity was associated with less total body fat, visceral fat and liver fat. These associations with visceral fat and liver fat disappeared after additional adjustment for total body fat. It therefore seems that there is no extra effect on visceral fat and liver fat beyond effects via total body fat.

METHODOLOGICAL CONSIDERATIONS

Before we can causally interpret the findings described in this thesis, several methodological considerations need to be discussed. For **Chapters 3** to **6**, baseline measurements of the Netherlands Epidemiology of Obesity study were used. This study has been set up in 2008 to investigate pathways that lead to obesity-related diseases. A strength of this population based study is that the large study population has been extensively phenotyped, which allowed us to adjust for multiple confounding factors and to study possible sex differences. Moreover, physical activity has been measured

objectively, and direct imaging of visceral fat and liver fat has been performed. A limitation, however, is the observational and cross-sectional nature of the analyses performed on the baseline measurements. Residual confounding due to unmeasured lifestyle factors might be present despite our efforts to minimize confounding as much as possible. Moreover, the cross-sectional design and possible reverse causation precludes causal inference. In the following paragraphs we will discuss these and other limitations regarding the study design and data collection from the NEO study, and how we attempted to minimize the potential bias and confounding that might have resulted from those limitations.

Internal validity: bias and confounding by lifestyle

During the past year, a substantial amount of criticism on nutritional epidemiology has been expressed. Whereas results from nutritional epidemiological studies are often presented as causal ones, most risks or benefits associated with dietary habits are said to mainly reflect the magnitude of different types of bias and residual confounding, since most of the studies are of an observational nature [1]. Furthermore, most nutritional variables are correlated with each other and therefore associations between one specific dietary variable and health outcomes might not be specific, but rather represent associations between other dietary variables and health outcomes [1]. By combining multiple food items into food groups and also studying dietary quality as measured by the Dutch Healthy Diet Index, we have aimed to minimize this problem. Furthermore, when studying food groups, we also adjusted for a marker of a healthy diet in order to adjust for potential correlations between the food group under study and overall diet.

The study of an association between consumption of foods or food groups in relation to visceral fat or liver fat poses problems. In free-living populations, consumption of most nutrients and thereby food items is positively correlated with total caloric intake [2]. Increased consumption of a certain food item means that the total caloric intake also increases due to the caloric contribution of the macronutrients from that specific food item. Moreover, large persons, or those who are more physically active, on average consume more of everything and therefore even food items with very low to no caloric value are correlated with total energy intake [2]. If caloric intake is also associated with the outcome, for example total body fat, this may overestimate the association between the food item and the outcome. In order to control for this, an increase in consumption of a certain food item must be accompanied by a decrease in consumption of another food item to keep total caloric intake similar. This can be modelled using substitution analyses, by defining the contrast of which food item is to be replaced by the food item under study.

From origin, substitution analyses have been used to study and compare the effects of different macronutrients on multiple health outcomes in an isocaloric manner [3]. This statistical method has become increasingly used throughout the entire field of nutritional epidemiology, and also in the field of physical activity [4]. It entails a statistical technique to mimic a trial in which the dietary composition is altered, without changing the total caloric intake. In this thesis, we used substitution analyses to study replacement of dairy with other food groups, replacement of alcoholic by non-alcoholic beverages, and replacement of sedentary time with time spent on other types of physical activity. However, compared with the study of macronutrients, that of substitution of food groups or items leads to additional methodological considerations [5]. Firstly, the results are dependent on the reference group that is chosen. Although theoretically any two food groups could be chosen for substitution analysis, results will become meaningless without cautious considerations [5]. For instance, the replacement of a food group with detrimental health effects to a food group with even worse health effects will yield an association that appears beneficial, and results could be misleading. Therefore, it is advised that food items or groups used for substitution analysis should be part of a well-defined category and commonly consumed within the population under study. They should also be relevant for replacement, with desirably a fair inverse correlation [5]. Furthermore, substitution analyses with food items or food groups may amplify confounding [5]. In contrast to nutrients, which are mainly consumed to meet the body's energy requirements, consumption of food items or groups is strongly influenced by health-related behaviours. For example when meat is substituted with fish: consumption of meat may be more associated with unhealthy behaviour, whereas fish consumption with healthy behaviours. An analysis in which meat is substituted for fish may therefore not only represent an exchange of food products, but also indirectly an exchange of behaviours, and the net effect of the substitution is overestimated. This also holds true when using substitution analysis for physical activity. Adequate adjustment for lifestyle factors is therefore of great importance. Nonetheless, results of the substitution analyses described in this thesis may be overestimated despite our efforts to minimize confounding and need to be interpreted cautiously. It should be noted that even if we interpret the substitution analysis causally, which means that if individuals had replaced item A with item B, they would have had less, say, liver fat, this does not mean that substitution would lead to a reduction of liver fat.

Measurement error

Most large epidemiological cohort studies rely on self-reported body mass index or waist circumference as an indication of adiposity. In the NEO study, however, body weight and percent body fat were assessed by the Tanita foot-to-foot bio impedance balance system

(TBF-310, Tanita International Division, UK). Although it has been suggested that foot-to-foot BIA might give an overestimation of the amount of fat mass [6], a strong correlation (r = 0.84) has been shown between foot-to-foot and hand-to-foot BIA with regard to total body fat percentages [7]. Furthermore, a strong correlation (r = 0.89) was also found in a study comparing resistance measurements provided by foot-to-foot BIA with measurements from dual-energy X-ray absorptiometry and underwater weighing [8].

Additionally, a unique feature of the NEO study is that abdominal adipose tissue was assessed using imaging techniques in a random subsample of the total NEO population without contra-indications to MRI [9]. In total, abdominal adiposity was assessed in 2,580 participants using a turbo spin echo imaging protocol. At the level of the 5th lumbar vertebra 3 transverse images each with a slice thickness of 10 mm were obtained during a breath-hold [10]. Hepatic triglyceride content was assessed using proton MRS of the liver in the same subset of participants. However, the number of participants with technical failures for liver fat measurement was relatively high because only a limited time slot was available per participant and therefore it was not possible check the spectra during the measurement and repeat the measurement when technical failures were present. However, the failure rate was not related to age, sex, waist circumference, BMI, total body fat or amount of visceral fat [11]. Based on this information, we can conclude that the group in which the liver fat assessment was successful was a completely random subgroup of the total group of participants who underwent the proton MRS.

In **Chapters 3, 4 and 5** we used a food frequency questionnaire to estimate dietary habits. Although such questionnaires are suited for large epidemiological studies, they are notorious for their risk of bias, and estimates of intake may be subject to substantial error, which in turn may affect the interpretation of epidemiological studies [12-14]. Social desirability in the way respondents fill in items can result in an overestimation of intake of healthy foods, and an underestimation of intake of unhealthy foods [15]. Especially obese participants may underreport their total energy intake [16] and fatty foods or foods rich in carbohydrates [17], but no major differences were found between men and women [17]. Kipnis and colleagues have described two types of dietary measurement error that can occur when a food frequency questionnaire is used: intake-related bias, which represents the correlation between the error and true intake, and person-specific bias, which is independent of the true intake and reflects measurement error related to personal characteristics of the participant. The latter can be reduced considerably by energy adjustment, which is why we adjusted all our dietary models for total energy intake, but will nonetheless remain present to a certain extent. With respect to the three studies in this thesis using a food frequency questionnaire, it means that the associations between healthy dietary habits an adiposity measures are likely underestimations of reality [18].

Reverse causation

In **Chapters 3 to 6** we performed cross-sectional analyses to study the association between diet and physical activity and body fat distribution. These analyses were based on the baseline measurements of the NEO study, meaning that the exposure and the outcome variables were measured at the same time. This poses difficulties in the interpretation of results, as we cannot always tell with certainty which came first: the exposure, or the outcome. For example, people who are told by their general practitioner that they have an increased risk of having a myocardial infarction due to their current lifestyle, are more likely to change their lifestyle and develop healthier dietary habits than the general population. However, while their diet might be healthier due to these changes, they are still more likely to suffer from a myocardial infarction than the general population. When studying the association between dietary habits and the risk of myocardial infarction, it might therefore appear as if a healthier diet is associated with an increased risk of having a myocardial infarction.

In **Chapters 3, 4, 5 and 6** this would mean that participants with a higher body fat percentage, or more visceral fat or liver fat, might have altered their dietary habits or physical activity patterns as a result of their adiposity. A higher body fat percentage or more ectopic fat has been associated with cardiovascular disease and diabetes, and worrying about this increased risk might have resulted in a change of lifestyle. If reverse causation was present in our analyses, this would have led to an underestimation of the associations, as it would appear that a healthy diet or time spent performing physical activity is not associated with less total body fat or ectopic fat. For that reason, we have repeated our analyses described in these chapters after exclusion of participants with a history of cardiovascular disease and participants who had been diagnosed with type 2 diabetes, as they might have changed their dietary habits after being diagnosed. After exclusion of these participants, results remained similar. This suggests that reverse causation did not bias our associations to a large extent.

External validity

In the NEO study, we have included 5,000 participants with a BMI of 27 kg/m^2 or higher, and a reference group of 1,671 participants irrespective of their BMI. This reference group has a normal BMI distribution, similar to and thus representative of the general Dutch population [19]. Thus, although the majority of the participants has been selected based on their body weight and therefore possibly also other weight-related factors, this

is countered by weighting our analysis towards the BMI distribution of the reference population. After weighting, results represent characteristics and associations in the general population [19].

Furthermore, visceral fat and liver fat were assessed in a random subgroup of participants without contraindications (e.g. claustrophobia, metallic devices or a body circumference of more than 1.70 meter). As a result, on average participants who underwent an MRI/MRS measurement had a slightly lower BMI and were somewhat less likely to have a history of cardiovascular disease. Results described in this thesis are therefore applicable to the general, middle-aged Dutch population without contraindications for an MRI, and may not be representative for extremely obese persons with a body circumference of more than 1.70 meter.

POTENTIAL UNDERLYING MECHANISM

After a careful review of our results and the methodological considerations that come with them, it is interesting to think about an underlying mechanism. Based on the current literature, fructose consumption might be a potential underlying mechanism that explains several of our findings in relation to liver fat as described in this thesis.

In **Chapter 2** we showed that dietary macronutrient composition and the quality of those macronutrients affects liver fat content. Whereas there was no effect of total fat with carbohydrates, the type of fat did matter: consumption of saturated fat leads to an increased liver fat content as compared with unsaturated fat, which is in line with a previous review on macronutrient composition in relation to liver fat accumulation [20]. As not all included studies in our meta-analysis provided information on which type of fat was replaced with carbohydrates, we could not assess whether replacing saturated fat with carbohydrates affects liver fat differently than replacing unsaturated fat with carbohydrates. However, the three studies that found that a low-carbohydrate high-fat diets decreases liver fat as compared with a high-carbohydrate low-fat diet all used unsaturated fat for this comparison [21, 22]. Previous research has shown that consumption of carbohydrates is a major stimulus for hepatic de novo lipogenesis and might even contribute to non-alcoholic fatty liver disease to a greater extent than dietary fat [23].

The type of carbohydrates also plays a role in the effect on liver fat. Most carbohydrates that are consumed, will enter the blood as glucose. Glucose serves as an energy source for the body and can be used by all the cells in a human body. It has a high glycaemic index, meaning it increases the blood glucose level rapidly, and stimulates production of insulin directly. Glucose is transported into cells throughout the body by the glucose transport type-4 (GLUT-4), which is an insulin-dependent transporter. A second common carbohydrate, fructose, has a low glycaemic index and does not stimulate the secretion of insulin. It is almost entirely cleared by the liver and does not signal the brain when satiety is reached, leading to an increased food consumption. Moreover, fructose is transported into cells by the glucose transporter type-5 (GLUT-5), of which most cells only have low amounts, and it is poorly absorbed by the gastrointestinal tract. The metabolism of fructose, which takes place in the liver, stimulates lipogenesis and high consumption is therefore associated with an increased hepatic de novo lipogenesis, an increased concentration and secretion of triglycerides and also with a decrease in the clearance of very low density lipoprotein triglycerides. Several studies have shown that excessive dietary fructose consumption is associated with non-alcoholic fatty liver disease [24-26]. It must be noted that a high visceral fat volume can also promote further liver fat accumulation.

CONCLUSIONS AND IMPLICATIONS

In this thesis, we aimed at answering the question to what extent dietary habits and physical activity are associated with ectopic fat. The main conclusions of this thesis are that dietary macronutrient composition is likely to play a role in the accumulation of liver fat, and that diets high in saturated fat lead to more liver fat than diets high in unsaturated fat. Increased consumption of dietary protein at the expense of carbohydrates results in less liver fat. However, our study identified an important gap in the current knowledge, and we therefore recommend that more and larger randomized controlled dietary trials should be performed in which the source and type of macronutrients should be taken into account. More specifically, trials on the exchange between dietary protein and fat should be conducted, as evidence on this comparison was completely lacking. We furthermore showed that consumption of sweet snacks was associated with increased liver fat, and consumption of fruit and vegetables with less visceral fat. Additionally, a higher score on the Dutch Healthy Diet Index was associated with less total body fat, as well as less visceral and liver fat. Consumption of alcoholic and sugar sweetened beverages was associated with more liver fat, and replacement of alcoholic beverages with milk was associated with less liver fat. Replacement of alcohol with sugar sweetened beverages was associated with an equal amount of liver fat. Replacement of 30 minutes of sedentary time per day with moderate to vigorous physical activity was associated with less total body fat, visceral fat and liver fat. In the paragraph below we

will translate our findings to implications for clinical practice and to recommendations for future research.

Clinical implications

As described in the introduction of this thesis, body fat or body mass index is not a good indicator when it comes to the risk of cardiometabolic diseases. Rather, one should focus on the amount of ectopic fat as this proves to be a more pronounced risk factor for chronic diseases. In this thesis, we have shown that dietary habits and physical activity are associated with both visceral fat and liver fat. Even after additional adjustment for total body fat most associations remained present, indicating that most exposures we studied in this thesis are specifically associated with both visceral fat and liver fat. Future research should aim to study whether these associations are indeed, as we believe, causal, and whether changes in diet and physical activity indeed lead to beneficial changes in ectopic fat accumulation. Nevertheless, our findings are promising and hint towards the importance of considering diet as a whole, instead of separate components, which is in line with the current changes in dietary guidelines throughout the world.

Based on the results described in this thesis, we are able to make some recommendations with regard to diet and physical activity. Firstly, our results are in line with the recommendations made by the Netherlands Nutrition Center, which state that consumption of sweet snacks such as chocolate or cake should be limited and consumption of fruit and vegetables should be encouraged. In line with this recommendation, people should adhere to the 2015 Dutch Dietary Guidelines for a Healthy Diet, which entails following a dietary pattern that involves more plant-based and less animal-based foods. Consumption of carbohydrates should be limited and if possible replaced with dietary protein, and saturated fat should be replaced with unsaturated fat. Consumption of alcoholic beverages should be limited. What we have added to this, is that for those who wish to limit their alcohol consumption, it is recommended to not replace this with sugar sweetened beverages. Consuming a glass of milk, tea, coffee or water instead of a glass of alcohol appears to be better. Our results are also in line with the Dutch physical activity guidelines, which state that sufficient physical activity should be performed and sedentary time should be limited. Our results indicate that, preferably, sedentary behaviour should be replaced with moderate to vigorous physical activity rather than light physical activity.

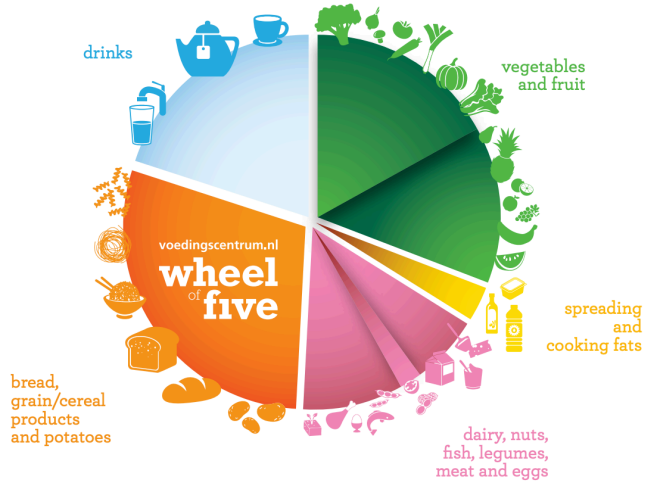

Figure 1. Dietary recommendations from the Netherlands Nutrition Center

FUTURE PERSPECTIVES

Although the results described in this thesis contribute to current knowledge on determinants of body fat distribution, they need to be confirmed in larger prospective studies, or in randomized controlled trials. Below we describe recommendations for future research in the field of nutritional epidemiology.

Mendelian randomization: the solution to confounding and reverse causation?

As described above, results from observational epidemiological studies might sometimes be confounded and not completely accurate, despite our best efforts to minimize confounding by improving the design and statistical analyses from the study. A potential solution for this problem is to perform a Mendelian randomization study. This type of study, based on Mendel's laws of inheritance, uses genetic variants that are associated with the exposure rather than the exposure itself [27]. Genes are randomly

assorted from parents to offspring, a process that occurs during the formation of gametes and conception. Inheritance of a certain genetic variant is therefore completely random and does not, for example, depend on lifestyle decisions made later on in life. This way, the association between the genetic variant and the disease resembles the association between an exposure and the disease, but it does not suffer from reverse causation or confounding to which a conventional observational study might be susceptible [27]. Whereas randomized trials can often only assess short term effects, a Mendelian randomization study is particularly useful for studying lifetime exposures, such as dietary intake. Several previous studies have therefore used this concept in order to study causal effects of lifestyle factors such as consumption of dairy, cruciferous vegetables and alcohol on varying health outcomes [28]. As such, alcohol consumption has been shown to be causally related to oesophageal cancer risk by the use of genetic data on the aldehyde dehydrogenase 2 family (ALDH2) gene in a Mendelian randomization study [29]. Moreover, consumption of dairy and cruciferous vegetables has been causally linked to cancer [30].

Following the research outlined in this thesis, Mendelian randomization studies could also be used to further investigate whether the associations we described are indeed causal. For example, a genome wide association study on inter-individual variation in dietary macronutrient intake in almost 300,000 participants has been conducted and has identified 96 genome-wide significant loci [31]. Such loci have also been reported in relation to dietary pattern scores, although the population was smaller [32]. These loci can be used to investigate to what extent macronutrient intake influences liver fat content. By using such genetic instruments, we would be able to study the effect of dietary habits on adiposity while limiting reverse causation and confounding by other lifestyle factors such as smoking, physical activity, stress, sleep habits or culture, provided a strong genetic scoring instrument is available and the number of participants is sufficient. Nevertheless, the analogy of Mendelian randomization with randomized controlled trials has strong implications for the design, reporting and interpretation, and therefore the use of this study design has several limitations to overcome in the future [33]. In the meantime, we have to rely on randomized controlled trials and observational studies to further explore the role of dietary habits and physical activity and visceral fat and liver fat.

Future of the NEO study

As described before, all research in this thesis has been performed in a cross-sectional setting and is based on the baseline measurements of all participants. The Netherlands Epidemiology of Obesity has been designed as a prospective cohort study and participants were included between 2008 and 2012. Since then, Dutch general practitioner databases have been used to collect information on incident diabetes, cardiovascular events or mortality. Moreover, it is planned that participants of the Netherlands Epidemiology of Obesity study will be invited to the study center for a second visit, during which multiple measurements and questionnaires will be taken and administered. Future research with these data will reveal whether changes in dietary intake or physical activity habits, the risk factors studied in this thesis, are also longitudinally associated with changes in visceral fat and liver fat, and the occurrence of cardiometabolic disease.

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