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Further development and application of the metabotyping concept

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List of abbreviations

AHEI	Alternative healthy eating index
BMI	Body mass index
CMD	Cardiometabolic diseases
CVD	Cardiovascular diseases
DASH	Dietary approaches to stop hypertension
DFI	Dietary fiber intervention
GGT	Gamma-glutamyltransferase
GOT	Glutamate-oxaloacetate transaminase
GPT	Glutamate-pyruvate transaminase
HbA1C	Glycated hemoglobin
HDLc	High-density lipoprotein cholesterol
hs-CRP	High-sensitive C-reactive protein
KORA	Cooperative health research in the region of Augsburg
LDLc	Low-density lipoprotein cholesterol
MDS	Mediterranean diet score
Non-HDLc	Non-high-density lipoprotein cholesterol
OGTT	Oral glucose tolerance test
PN	Personalized nutrition
T2D	Type 2 diabetes
TC	Total cholesterol

List of publications

1. Dahal C, Wawro N, Meisinger C, Breuninger TA, Thorand B, Rathmann W, Koenig W, Hauner H, Peters A, Linseisen J. Optimized metabotype definition based on a limited number of 4 standard clinical parameters in the population-based KORA study.
   DOI: https://doi.org/10.3390/life12101460

2. Dahal C, Wawro N, Meisinger C, Brandl B, Skurk T, Volkert D, Hauner H, Linseisen J. Evaluation of the metabotype concept after intervention with oral glucose tolerance test and dietary fiber-enriched food: An enable study. Nutrition, Metabolism & Cardiovascular Diseases.
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1. Contribution to the publications

1.1 Contribution to paper I

As a first author, the doctoral candidate performed the literature review, developed a statistical analysis plan, performed the data analysis, and interpreted the results autonomously. She also drafted the manuscript independently. Likewise, she also selected the targeted journal for the publication of the manuscript. She also responded to the concerns raised during the peer review process and did the required revisions. Besides, during the publication process, she did necessary correspondence with the representa- tives of the journal. During the entire course, she was supported and guided by her su- pervisor Prof. Dr. Jakob Linseisen.

1.2 Contribution to paper II

The doctoral candidate independently conducted the literature review and statistical analysis. Being a first author, she also interpreted the results and drafted the manuscript by herself. She was also responsible for identifying the targeted journal. Based on the reviewer's comments, she performed the necessary revisions to the manuscript. Her supervisor Prof. Dr. Jakob Linseisen guided her and gave her feedback during the whole process.

2. Introduction

2.1 The burden of cardiometabolic diseases

Cardiometabolic diseases (CMD) encompass a spectrum of diseases ranging from diabetes and other metabolic diseases to cardiovascular diseases (CVD) such as myocardial infarction and stroke (1). It is one of the major public health concerns and is a leading cause of death worldwide. Almost 17.9 million people died of CVD in 2019, which accounts for 32% of all global deaths (2). Likewise, in the same year, almost 463 million (9.63%) people worldwide had diabetes which is estimated to increase to 700 million (10.9%) by 2045 (3). In Germany, approximately 10.1 million people are projected to suffer from diabetes in 2030 (3). In addition to being a public health problem, CMD is also regarded as a global economic burden. Worldwide, diabetes accounted for USD 1.3 trillion in 2015 which is expected to rise to USD 2.1 trillion in 2030 (4). Similarly, according to European Heart Network's 2017 report, CVD is estimated to cost the EU economy € 210 billion a year (5).

Worldwide, over a billion people are suffering from metabolic diseases (6). According to World Health Organization 2020 fact sheets, obesity has tripled, hypertension has doubled since 1975, and diabetes has quadrupled since 1980 (7). In 2015, 603.7 million adults were affected by obesity (8). In Germany, 26% of adults were obese in 2016 (9). High body fat, especially central obesity, is associated with several metabolic diseases such as insulin resistance, hypertension, and dyslipidemia (10). Over two-thirds of the prevalence of hypertension is directly related to obesity (11). Globally, 22% of adults had raised blood pressure in 2015 (9). Hypertension doubles the relative risk of CVD and triplets the relative risk of type 2 diabetes (T2D) (11). It is regarded that metabolic diseases may overtake smoking as a leading risk factor for CVD in the future (12,13). Although there has been a substantial decrease in age-standardized morbidity and mortality from CVD in Europe over the past 40 years, there is a serious concern that a considerable increase in obesity and T2D might slow or even reverse the trend (5,14).

The increase in the elderly population will further increase the prevalence of metabolic diseases (10,15). The population aged 65 years and over is increasing. In 2019, one in 11 people worldwide, i.e. 9 % of the population was over 65. By 2050, this number is expected to increase to 16% (16). With increasing age, several physiological changes

occur in the body. One of the changes refers to the increase in intra-abdominal fat, which leads to insulin resistance, hypertension, and dyslipidemia (10).

Metabolic diseases also increase the risk of getting other severe diseases like cancers of different sites and infections (17–19). Recent studies have shown that individuals with CMD have a higher risk of getting COVID-19 and a more severe course of the disease and more vaccine breakthroughs (20,21). This situation has further emphasized the urgency of the best prevention and management of CMD. In recent years, there was an increased interest in research and the health care sector to prevent CMD. However, despite intense public health efforts (9), results are not very promising so far. Therefore, the development of a more robust and practical preventive approach that can be con- ducted at a large scale is necessary for the better prevention of CMD.

2.2 Role of diet in CMD

Diet is one of the major modifiable risk factor for CMD (22). Along with influencing the present health, diet also determines the future occurrence of chronic diseases (23). Several epidemiological studies have shown the relation between diet and the occurrence of CMD. For instance, the consumption of a high amount of sodium, and a low amount of fruits, vegetables, and potassium has been shown to increase the risk of hypertension (24). Similarly, an atherogenic diet that is rich in saturated fat elevates the blood cholesterol concentration, specifically LDL cholesterol (25) which can increase the risk of getting CVD. Similarly, a higher intake of refined carbohydrates is also linked with a higher risk of dyslipidemia (26). The consumption of foods with a high glycemic index (a measure of how much 50 g of carbohydrate from a specific food raises the blood glucose level) increases the risk of insulin resistance and obesity.

As people eat different combinations of food in daily life, diet quality indices or dietary pattern has been increasingly used in nutritional studies to explore the relationship between diet and disease occurrence. The dietary indices based on a combination of different nutritional components can provide a holistic approach than using the single nutrient approach (27). Several dietary indices and patterns have shown promising results in preventing CMD. According to a recent review, a higher adherence to the Mediterranean diet score (MDS) which is rich in fruits, vegetables, nuts, olive oil, and fatty fish, alters the type 2 diabetes (T2D) related mechanisms, like anti-inflammatory actions, glucagon-like peptide agonist compounds, and changes in gut microbiota (28). The American Heart Association also recommends the MDS for the primary prevention of CVD

(29). The Alternate Healthy Eating Index (AHEI) which was initially designed in 2002 (30) based on American Dietary Guidelines and later revised in 2012 as AHEI-2010 (31) has shown to be associated with a decreased risk of chronic diseases such as T2D and CVD (32). Similarly, the Dietary Approaches to Stop Hypertension (DASH) eating plan consisting of fruits, vegetables, and low-fat dairy reduces the risk of hypertension (24). A study comparing four different dietary patterns (MDI, Healthy Eating Index 2010, AHEI-2010, and DASH) showed that better dietary pattern scores were inversely associated with the incidence of T2D (33).

A study conducted in the US in 2017 showed that 45.4% of CMD-related deaths could be attributed to a suboptimal diet (34). Another study investigating the effects of dietary risk in 195 countries from 1990 to 2017 showed that globally one in five deaths was associated with dietary risk factors such as high intake of sodium, and low intake of whole grains, and fruits (35). Collectively, these data underpins the importance of diet in the reduction of the current as well as the future burden of CMD. The development of in- formed and evidence-based dietary recommendations can help millions of people at risk of metabolic and cardiovascular diseases.

2.3 Inter-individual variation in response to diet

Optimal nutrition is key to maintaining homeostasis, promoting health, and preventing diseases. The usual public health approach for preventing diet-related CMD is recommending a healthy diet and lifestyle (36). The underlying evidence for such dietary recommendations is obtained from epidemiological or large clinical studies where generalized nutritional advice is given at a population level (37). However, the evidence shows that there exists high interpersonal variability in response to the same food (19,38–42). Thus, people may have different metabolic reactions to specific dietary regimens. For instance, a study by Zeevi et al. (40) showed that people have different postprandial blood glucose responses even after consuming the same standard meals. Similarly, Berry et al. (41) also demonstrated inter-individual variability in postprandial triglyceride, insulin, and glucose following identical meals. Similar inter-individual differences were seen regarding hypertension response to salt intake (43) and absorption of Vitamin E (44).

The variation in response to diet can be explained by the interpersonal heterogeneity in the microbiome, genetics, epigenetics, and environmental factors which impact the individual's metabolism (19,45–47). This high variability illustrates that the use of generic

dietary advice, although practical, may not be very effective. For the optimal prevention of diet-related diseases, nutritional/dietary advice should move from the one size fits all concept to a more tailored/individualized approach. The growing understanding of inter-individual variation has led to the development of a new concept called personalized nutrition (PN) or precision nutrition (45). Although there is not a universally agreed-upon definition of PN, it is based on the idea of using the information of an individual to develop nutritional advice which would be more effective than generic advice (22,48).

PN has shown to be effective in improving dietary habits compared to the generalized population level advice (40,49–52), most likely due to increased motivation. The large randomized controlled trial study called Food4me investigated the influence of personalized versus generalized nutrition advice in changing the dietary behavior of people in seven different European countries (51). The study showed that after six months, the personalized advice group implemented better and sustained dietary behavior than the generic advice group. Likewise, the improvement in diet quality was seen among pregnant women when they received computer-based tailored dietary counseling compared to pregnant women who received generic dietary advice (52). Similarly, the study by Zeevi et al. (40) developed an algorithm to predict the individual postprandial blood glu- cose based on blood parameters, dietary habits, anthropometrics, physical activity, and gut microbiota (40). When the participants were assigned to blinded randomized con- trolled dietary intervention based on the algorithm, lowered post-meal glucose and con- sistent alterations to the gut microbiota were observed. These results exhibit the effec- tiveness of PN in improving the health of individuals and reducing the burden of CMD.

2.4 Metabotyping

Though providing dietary advice on an individual level is the epitome of the PN, we cannot ignore the fact that it requires an extensive amount of data and resources (22). For each intervention to be effective and influence the population's health, it has to be practical and scalable (53). Therefore, the concept of providing targeted dietary advice (targeted nutrition) (54) to groups of metabolically most similar individuals, also known as metabotype, is gaining momentum (46,55–57). A recent review by Zeisel (45) has also highlighted the fact that personalization at a stratified level is a more feasible and practical approach than personalization at an individual level. According to Toro-Martín et al., the process of stratifying people based on key characteristics makes the nutritional advice the same for all members of a stratum and thus can be considered as a personalized approach (58).

Metabotyping refers to the process of grouping similar individuals together into smaller subgroups based on their metabolic or phenotypic characteristics (46,57,59). These metabolic phenotypes, also known as metabotypes, are the results of genetic and environmental factors such as diet, lifestyle, and gut microbiome (53,60). The individual within the same metabotype subgroup has similar metabolic profiles compared to individuals in different metabotype subgroups. The grouping of metabolically similar individuals helps to identify subpopulations with differing risks for metabolic diseases and would allow the efficient use of preventive measures such as dietary and lifestyle intervention for the prevention of CMD, provided that differential effects were scientifically proven (**Figure 1**).

The development and use of the metabotype concept was rapidly increasing in recent years aiming to investigate the linkage between diets and different chronic diseases (22,46,56). Several markers of metabolic pathways are used to identify and define a metabotype concept (22,46,56). For instance, Tzeng et al. (61) used a metabotyping approach with 10 cardio-metabolic parameters to cluster the women sharing similar metabolic risk factors into similar subgroups. Similarly, Chua et al. (62) used 263 lipids in blood plasma and identified three distinct circadian metabolic phenotypes. Frazier-Wood et al. (63) also used a metabotyping approach to explore the relationship between the diameter of three lipoproteins and metabolic syndromes. Likewise, in our previous studies, we identified three distinct metabotype subgroups using 32 (64) and 16 (65) different biochemical and anthropometric parameters.

Few studies have also incorporated metabolomics for metabotyping purposes (66–70). For instance, Fiamoncini and colleagues (67) analyzed around 300 plasma metabolites to identify 2 metabotypes and evaluated their respective responses to mixed meal tolerance tests and dietary interventions aimed at weight loss. Similarly, Muniandy et al. (68) explored 111 plasma metabolites and identified two subgroups related to cardio-metabolic risk factors.

Metabotypes have also been defined based on differential responses to nutritional interventions and supplements (67,71–74). For example, Krishnan et al. (73) identified the three distinct subgroups based on the differential response to a low and high glycemic meal. Likewise, in a controlled cross-over intervention study Wang et al. (75) identified the distinct subgroups with differing carotenoid responses to carotenoid-rich beverages.

In the same way, Vázquez-Fresno and colleagues (74) identified four clusters with distinct clinical profiles using 69 biochemical and anthropometric parameters in response to red wine polyphenol intake.

Evidence shows that the application of metabotyping in epidemiological or longitudinal studies aids in identifying the metabolically similar groups that are related to diet-related diseases and cardio-metabolic risk factors (22,64,65,76). Likewise, the use of metabotyping in intervention studies can help in investigating the differential response to dietary interventions (71,72,74). For example, in our previous study where we investigated the association between diet and T2D, we found that the associations varied by different metabotype subgroups (65). The metabotype with healthy metabolic characteristics showed a higher risk of T2D when the consumption of meat was increased. Whereas, the risk of T2D among the unfavorable metabotype subgroup was positively associated with consumption of sugar-sweetened beverages and inversely associated with fruit in- take. Also, in another study, we could only identify the significant association between T2D and dietary indices (AHEI and MDS) in the unfavorable metabotype subgroup which was otherwise significant in the total study population (76). Likewise, an intervention study conducted by O'Sullivan showed that a significant effect of vitamin D (decrease in insulin, homeostatic model assessment scores, and CRP) was only seen after stratifying the study population into metabolic subgroups (72).

Furthermore, the metabotyping approach has also been used as a tool for developing personalized/targeted nutrition. The decision tree method was used in different studies (53,54,77) to develop targeted dietary advice at the metabotype subgroup level. The comparison of results from the decision tree with the individual-based approach delivered by dietitians showed very good agreement, i.e. the dietary advice matched in more than 80% of study participants.

As individuals at high risk of CMD are more motivated to change their health behavior (78), the use of targeted dietary advice based on metabotypes may help to effectively influence the population's dietary behavior. Moreover, metabotype can also aid in transferring the targeted nutrition into practice by helping clinicians to overcome the usual hurdles like lack of time, workload, and inadequate training (79,80) and provide dietary advice quickly (53,54).

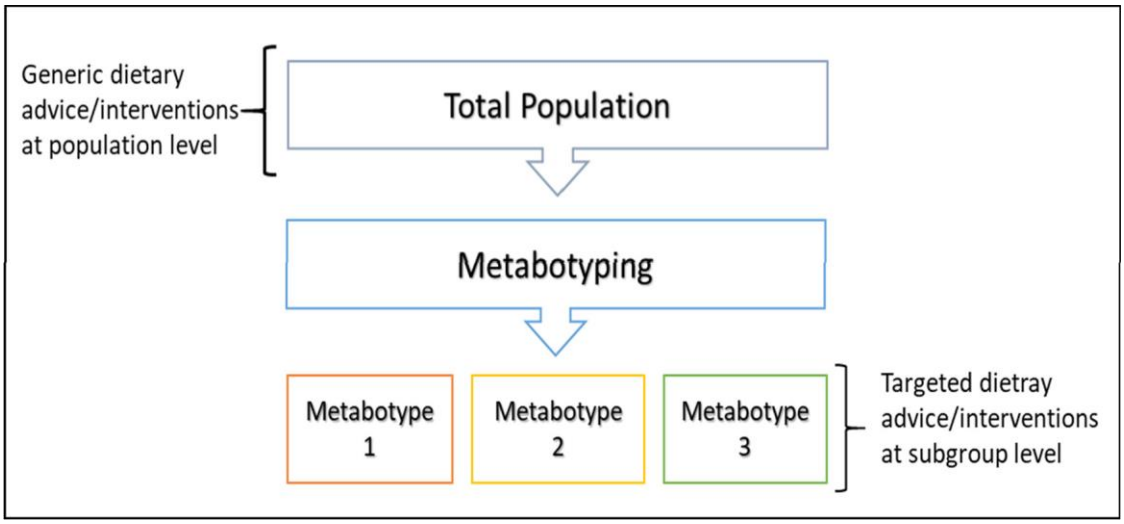

Figure 1: Flowchart representing a shift of dietary approach from population level to targeted subgroup level.

2.5 Scientific Challenges

Despite of known advantages of the metabotype concepts, the application of metabotyping in nutritional studies is still at an early stage. There exists no unique definition of metabotype nor a defined method to identify metabotype subgroups. Moreover, the selection criteria of parameters for metabotyping (clustering parameters) are usually arbitrary (22) or based on availability or expert opinions. Due to these significant limitations, studies have used different methods and several parameters from different metabolic pathways to define metabotypes (46,56). The use of parameters ranges from a few simple and affordable clinical parameters to very large and expensive omics data. This heterogeneity in definitions and methods has limited the use of the metabotyping concept in general research settings and primary care. For instance, the use of different metabotypes in different studies has made it difficult to make reasonable comparisons (22,46). Similarly, it has also reduced the reproducibility across the research groups which has further hindered the generalizability across different cohorts and populations.

Therefore, there is an urgent need to identify a valid metabotype definition based on a few easily accessible clinical parameters. The metabotyping parameters should be chosen based on valid statistical methods without disregarding the availability and clinical/nutritional relevance. Furthermore, these metabotypes should be evaluated using differential reactions to dietary factors and validated in different study populations to ensure

reproducibility and generalizability across populations. And most importantly metabotypes should be easily and quickly definable, affordable, and thus suitable for large-scale applications.

A unique definition of metabotypes would help to identify the metabolically similar subgroups that may benefit from tailored/personalized dietary interventions for optimal prevention of CMD at a population level.

2.6 Aims and objectives of the Dissertation

The current dissertation aims to address the scientific challenges and current gaps in the literature by developing a metabotype concept based on standard clinical parameters that identify metabolically homogenous groups which respond similarly to dietary interventions. For this purpose, the doctoral candidate has published two first-author manuscripts in international peer-reviewed journals.

The objective of the first publication was (i) selection of few and routinely available standard clinical parameters for metabotyping purposes and (ii) to identify the valid metabotype definition based on selected parameters in a population-based Cooperative Health Research in the Region of Augsburg (KORA) F4 study (81,82) and a seven-year follow-up KORA FF4 study (83). Likewise, the aim of the second publication was to evaluate the identified metabotypes by (i) assigning participants from *enable* cluster of nutrition research to metabotype subgroups identified in the KORA F4 study and (ii) examining if the different metabotypes subgroups react differently to dietary interventions like oral glucose tolerance test (OGTT) (84) and 12-week dietary fiber intervention (DFI) (85).

2.7 Description of the analyses and contribution to the problem at hand

The first publication identified two valid metabotype definitions for each disease group, cardiovascular diseases and metabolic diseases, based on four and five standard clinical parameters, respectively **(Table 1)**. For this purpose, we used the data from 3001 study participants of population-based KORA F4 and KORA FF4 studies. We selected six metabotyping parameters (**Table 1**) using the machine learning-based variable selection method called permutation variable importance which was further validated by sensitivity

analysis performed using two different methods called cross-validated permutation variable importance measure and gradient boosted feature selection. Based on the selected parameters 18 different metabotype models with three clusters each were created using the K-means clustering algorithm. Based on the distribution of the clustering parameters (triglyceride, glucose, uric acid, BMI, HDLc, and Non-HDLc), cluster 1 was regarded as the healthy cluster, cluster 2 was regarded as the intermediate cluster, and cluster 3 was regarded as the unfavorable cluster. Next, all models were compared based on the incidence of CMD in the unfavorable cluster (cluster 3). Model 7 had the highest incidence of any metabolic disease (defined as the presence of at least one of the metabolic diseases: hypertension, hyperuricemia, dyslipidemia, and T2D) and was regarded as the best model with respect to the development of metabolic diseases. Model 7 was comprised of only five metabolic parameters namely, glucose, BMI, uric acid, HDLc, and Non-HDLc. Similarly, model 17 consisting of only four parameters (triglyceride, glucose, HDLc, and Non-HDLc) showed the highest incidence of cardiovascular diseases (myo- cardial infarction, stroke) and was regarded as the best model with respect to cardiovas- cular diseases.

Both selected models, model 7 and model 17 were further evaluated using socio-demographic characteristics as well as an additional set of biochemical parameters that were not included in identifying metabotype groups. In both models, cluster 1 showed favorable socio-demographic characteristics such as the lowest age, the highest percentage of participants that are non-smokers, physically active, and have more than 12 years of education. Similarly, cluster 1 also had the lowest median concentrations of unfavorable biochemical parameters such as insulin, alkaline phosphatase, gamma-glutamyltransferase (GGT), glutamate-oxaloacetate transaminase (GOT), glutamate-pyruvate transaminase (GPT), glycated hemoglobin (HbA1c), and high-sensitive C-reactive protein (hs-CRP). In contrast, cluster 3 of both models showed unfavorable socio-demographic characteristics such as the highest median age, the highest percentage of heavy drinkers, and physically inactive participants. This subgroup also had the highest median concentrations of biochemical parameters. The characteristics of cluster 2 were in between cluster 1 and cluster 3.

Thus the homogenous characteristics within the clusters and distinct differences across the clusters proved that this work successfully identified a valid metabotype concept based on a few standard clinical parameters. The findings from this publication can be easily used in the general population on large scale for early identification of metabolically similar subgroups that may benefit from the preventive measures.

Table 1: Selected parameters and identified metabotype models in the first publication.

Selected parameters	Identified metabotype models
1. Triglyceride 2. Uric acid 3. BMI 4. HDLc 5. Glucose 6. Non-HDLc	Metabolic disease model 1. Glucose 2. HDLc 3. Non-HDLc 4. Uric acid 5. BMI
	Cardiovascular disease model 1. Glucose 2. HDLc 3. Non-HDLc 4. Triglyceride

BMI: body mass index; HDLc: high-density lipoprotein; LDLc: low-density lipoprotein; Non-HDLc: non-high-density lipoprotein.

The second publication evaluated the metabotype definition identified in the first publication. For this metabotypes identified in the KORA study were assigned to 356 participants of two sub-studies (OGTT sub-study and 12-week DFI sub-study) of the *enable* cohorts. It was done by minimizing the Euclidean distance of the z-standardized clustering parameters of the KORA study to the respective z-standardized cluster centers of the same parameters of the *enable* study. Next, the differential reaction of participants across the metabotype subgroups to OGTT and DFI was investigated by using linear mixed models and multivariate linear regression models. The participants of the OGTT sub-study were provided with an oral glucose bolus (75 g) and blood glucose values were determined in blood samples drawn at baseline (before OGTT) and 30, 60, 90, 120, 180, and 240 minutes. In the case of the DFI sub-study, intervention participants were provided with dietary fiber-enriched food for 12 weeks with the aim of increasing intake of dietary fiber by 10 grams per day.

Similar to the results of the KORA studies, the participants of the enable cohorts assigned to clusters 1, 2, and 3 showed favorable, intermediate, and unfavorable metabolic characteristics, respectively. Regarding the differential reaction to OGTT, participants in different metabotype subgroups showed significantly different reactions even when adjusted for age, sex, and physical activity. The unfavorable cluster (cluster 3) revealed the strongest reaction in serum glucose values at all measured time points whereas the favorable cluster (cluster 1) had the lowest reaction. Also, according to the results of the linear regression models, the baseline glucose-adjusted area under the curve (AUC) of cluster 3 participants was significantly higher compared to participants

in clusters 1 and 2. Similar results were seen when the analyses were stratified by age groups, i.e. in middle-agers (40-65 years) and older adults (75-85 years). In the case of the dietary fiber intervention study, differential reactions between metabotype subgroups were measured in terms of the change in metabolic parameters (**Table 2**) before (visit 1) and after 12 weeks of intervention (visit 3). No significant difference in metabolic parameters was seen across the metabotype subgroups in linear regression adjusted for age, sex, and physical activity. This might have been due to a low number of participants in cluster 3 which is the major limitation of this study. Nevertheless, by the end of the 12-week intervention, participants in cluster 3 exhibited the highest mean reduction in metabolic parameters like insulin, TC, LDLc, Non-HDLc, and systolic and diastolic pressure.

The results from the second publication further verified the validity and transferability as well as the generalizability of the metabotype definition identified in the first publication. Furthermore, it supported the use of the identified metabotypes to explore the inter-individual variation in diet. Thus, these findings present a metabotype concept as a promising tool to identify the subgroups that can benefit from targeted dietary interventions as a measure to prevent CMD at a population level.

Table 2: Outcome parameters included in second publication.

Outcome parameters in OGTT sub-study	Outcome parameters in DFI sub-study
Fixed effects 1. Glucose values 2. Time of measurements (Baseline, 30 minutes, 60 minutes, 90 minutes, and 120 minutes) Random effects 1. Participants	1. Glucose 2. Insulin 3. Total cholesterol 4. LDLc 5. HDLc 6. Non-HDLc 7. Triglyceride 8. Systolic BP 9. Diastolic BP 10. hs-CRP

HDLc: high-density lipoprotein; LDLc: low-density lipoprotein; Non-HDLc: non-high-density lipoprotein; hs-CRP: high sensitive C-reactive protein.

3. Summary

Cardiometabolic diseases (CMD) are major challenges for public health and lead to a substantial economic burden globally. Diet is regarded as one of the main modifiable risk factors for CMD. However, growing evidence suggests that people react differently to the same diet. This idea of inter-individual variation in response to diet has given rise to the concept of personalized nutrition. In contrast to the current practice of giving the same dietary advice to an entire population, personalized nutrition aims to provide tar- geted dietary advice at a group or individual level. One such approach is grouping metabolically similar individuals (metabotyping) into smaller subgroups called metabotypes. This concept is based on the notion that individuals within a subgroup show a high metabolic similarity compared to the other subgroups and are expected to react similarly to dietary interventions.

Based on earlier scientific work, the current dissertation aimed (i) to identify a valid metabotype definition using few and routinely available standard clinical parameters and (ii) to replicate the identified metabotype concept in an independent study and to test for differential response of the metabotype subgroups to dietary interventions, i.e. to an oral glucose tolerance test (OGTT), and a 12-week dietary fiber intervention (DFI).

In the first part of the work, we used data from 3001 adults from the Cooperative Health Research in the Region of Augsburg (KORA) F4 cohort. We identified the optimal set of parameters using the permutation variable importance method and validated it with two other similar feature selection methods. Using unique combinations of the set of identified parameters, namely triglyceride, glucose, uric acid, HDL cholesterol, Non-HDL cholesterol, and BMI, different metabotype models were created with three clusters each by K-means clustering. Based on the distribution of clustering parameters, the obtained clusters were regarded as the healthy cluster (cluster 1), intermediate cluster (cluster 2), and unfavorable cluster (cluster 3). The models were compared based on the cumulative incidence of CMD as assessed in a seven-year follow-up study (KORA FF4).

Based on the highest incidence of metabolic disease in cluster 3, model 7 was selected as the best model for metabolic diseases that consisted of only five parameters, namely glucose, uric acid, BMI, HDLc, and Non-HDLc. Similarly, based on the highest incidence of cardiovascular disease in cluster 3, model 17 consisting of only four parameters (glucose, triglyceride, HDLc, and Non-HDLc) was selected as the best model for cardiovascular disease. In both selected models, participants in cluster 3 had the most unfavorable median values of available metabolic parameters. Likewise, individuals in cluster 3 were older, were more likely to have received less than 10 years of education, and were more

frequently physically inactive. In contrast participants in cluster 1 exhibited favorable metabolic as well as socio-demographic characteristics. Characteristics of cluster 2 were in between clusters 1 and 3. The homogenous characteristics within the cluster and distinct differences across the clusters prove that valid metabotypes were identified based on a few and easily accessible clinical parameters.

In the second part of the work, we assigned 365 participants of two *enable* sub-studies, the oral glucose tolerance test (OGTT), and the 12-week dietary fiber intervention (DFI), to metabotypes as identified in KORA by minimizing the Euclidean distances to the cluster centers of z-standardized clustering parameters. In the OGTT study, volunteers were provided with an oral 75 g glucose bolus and blood glucose values were determined in blood samples drawn at baseline (before OGTT) and 30, 60, 90, 120, 180, and 240 minutes thereafter. In the DFI sub-study, participants were provided with dietary fiber-enriched foods for 12 weeks leading to an average increase in dietary fiber intake of 10 grams/day. The changes in metabolic markers were determined in blood samples collected at baseline and the end of the intervention phase.

The linear mixed model revealed that participants in the unfavorable cluster 3 had a significantly higher blood glucose reaction after glucose bolus at all measured time points. The analysis of the area under the curve (AUC) confirmed these results. In the DFI study, no statistically significant differences in metabolic parameters by metabotype subgroups could be obtained. However, a few participants in the unfavorable cluster 3 (n=6) showed the highest mean reduction in metabolic parameters, like serum insulin, cholesterol parameters (TC, LDLc, and Non-HDLc), and systolic and diastolic blood pres- sure. Taken together, the results of the two interventions indicate that participants as- signed to the three metabotyping react differently to dietary intervention, and thus may benefit from targeted dietary advice. Furthermore, the successful replication of metabo- types demonstrated that the identified metabotypes are easily transferable and general- izable to different populations.

The optimized metabotyping concept as developed and tested in these studies can promote the use of metabotyping on a large scale, leading to targeted and effective advice for the primary prevention of CMD.

4. Zusammenfassung (deutsch)

Kardiometabolische Erkrankungen (CMD) stellen eine große Herausforderung für die öffentliche Gesundheit dar und führen weltweit zu einer erheblichen wirtschaftlichen Belastung. Die Ernährung gilt als einer der wichtigsten modifizierbaren Risikofaktoren für CMD. Es gibt jedoch zunehmend Hinweise darauf, dass Menschen unterschiedlich auf dieselbe Ernährung reagieren. Diese Idee der interindividuellen Unterschiede in der Reaktion auf die Ernährung hat das Konzept der personalisierten Ernährung hervorgebracht. Im Gegensatz zur derzeitigen Praxis, der ganzen Bevölkerung dieselben Ernährungsempfehlungen zu geben, zielt die personalisierte Ernährung darauf ab, gezielte Ernährungsempfehlungen auf Gruppen- oder Individualebene zu geben. Ein solcher Ansatz besteht darin, stoffwechselmäßig ähnliche Personen in homogene Untergruppen, so genannte Metabotypen, einzuteilen. Diesem Konzept liegt die Vorstellung zugrunde, dass Personen innerhalb einer Untergruppe im Vergleich zu den anderen Untergruppen eine große Ähnlichkeit im Stoffwechsel aufweisen und voraussichtlich ähnlich auf Ernährungsmaßnahmen reagieren werden.

Auf der Grundlage früherer wissenschaftlicher Arbeiten zielte die aktuelle Doktorarbeit darauf ab, (i) eine gültige Metabotyp-Definition anhand weniger und routinemäßig verfügbarer klinischer Standardparameter zu ermitteln und (ii) das ermittelte Metabotyp-Konzept in einer unabhängigen Studie zu replizieren und die unterschiedliche Reaktion der Metabotyp-Untergruppen auf Ernährungsinterventionen zu testen, d. h. auf einen oralen Glukosetoleranztest (OGTT) und eine 12-wöchige Ballaststoffintervention (DFI).

Im ersten Teil der Arbeit wurden Daten von 3001 Erwachsenen aus der Kooperativen Gesundheitsforschung in der Region Augsburg (KORA) F4 verwendet. Die Auswahl der wichtigsten Parameter erfolgte mithilfe der Permutation Variable Importance-Methode und wurde mit zwei anderen ähnlichen Methoden zur Feature-Auswahl bestätigt. Für unterschiedliche Kombinationen der identifizierten Parameter, nämlich Triglyceride, Glukose, Harnsäure, HDL-Cholesterin, Non-HDL-Cholesterin und BMI, wurden verschiedene Metabotyp-Modelle mit jeweils drei Clustern mittels der K-means-Cluster clustering erstellt. Auf der Grundlage der Verteilung der Clusterparameter wurden die erhaltenen Cluster als gesunde Cluster (Cluster 1), mittlere Cluster (Cluster 2) und unvorteilhafte Cluster (Cluster 3) betrachtet. Die Modelle wurden auf der Grundlage der kumulativen Inzidenz von CMD über 7 Jahre (erfasst in der KORA FF4-Studie) verglichen.

Aufgrund der höchsten Inzidenz von Stoffwechselerkrankungen in Cluster 3 wurde Modell 7 als Modell für Stoffwechselerkrankung ausgewählt, das aus nur fünf Stoffwechsel-

parametern besteht, nämlich Glukose, Harnsäure, BMI, HDLc und Non-HDLc. In ähnlicher Weise wurde aufgrund der höchsten Inzidenz kardiovaskulärer Erkrankungen in Cluster 3 das Modell 17 mit nur vier Parametern (Glukose, Triglyzeride, HDLc und Non-HDLc) als Modell für kardiovaskuläre Erkrankungen ausgewählt. In beiden ausgewählten Modellen hatten die Teilnehmer in Cluster 3 die unvorteilhaftesten Medianwerte der verfügbaren Stoffwechselparameter. Ebenso waren die Personen in Cluster 3 älter, hatten häufiger einen Bildungsabschluss von weniger als 10 Jahren und waren häufiger körperlich inaktiv. Im Gegensatz dazu wiesen die Teilnehmer in Cluster 1 sowohl günstige metabolische als auch soziodemographische Merkmale auf. Die Merkmale von Cluster 2 lagen zwischen denen von Cluster 1 und 3. Die Homogenität der Merkmale innerhalb der Cluster und die deutlichen Unterschiede zwischen den Clustern beweisen, dass gültige Metabotypen auf der Grundlage einiger weniger und leicht zugänglicher klinischer Parameter identifiziert werden konnten.

Im zweiten Teil der Arbeit ordneten wir 365 TeilnehmerInnen in zwei Interventionsstudien, dem oralen Glukosetoleranztest (OGTT) und der 12-wöchigen Ballaststoffintervention (DFI), den in KORA identifizierten Metatbotypen zu, indem wir die euklidischen Abstände zu den Zentren der z-standardisierten Clustering-Parameter minimierten. In der OGTT-Studie erhielten die Probanden einen oralen Glukosebolus von 75 g und die Blutzuckerwerte wurden in Blutproben bestimmt, die zu Beginn (vor der OGTT) und 30, 60, 90, 120, 180 und 240 Minuten danach entnommen wurden. In der DFI-Teilstudie erhielten die Teilnehmer 12 Wochen lang mit Ballaststoffen angereicherte Lebensmittel, was zu einer durchschnittlichen Erhöhung der Ballaststoffaufnahme um 10 Gramm/Tag führte. Die Veränderungen der Stoffwechselmarker wurden in Blutproben bestimmt, die zu Beginn und am Ende der Interventionsphase entnommen wurden.

Das Linear Mixed Modell ergab, dass die Teilnehmer im unvorteilhaften Cluster 3 (im Vergleich zu Cluster 1 und 2) zu allen gemessenen Zeitpunkten eine signifikant höhere Blutglukosereaktion nach Glukosebolus aufwiesen. Die Analyse der Fläche unter der Glukosekurve (Area Under the Curve, AUC) bestätigte diese Ergebnisse. In der DFI-Studie konnten keine statistisch signifikanten Unterschiede in den Stoffwechselparametern zwischen den Metabotyp-Untergruppen festgestellt werden. Allerdings zeigten einige wenige Teilnehmer im unvorteilhaften Cluster 3 (n=6) die höchste mittlere Reduktion einiger Stoffwechselparameter, wie Seruminsulin, Cholesterinparameter (TC, LDLc und Non-HDLc) sowie des systolischen und diastolischen Blutdrucks. Zusammengenommen deuten die Ergebnisse der beiden Interventionen darauf hin, dass die Teilnehmer, die den drei Stoffwechseltypen zugeordnet wurden, unterschiedlich auf die Ernäh-

rungsintervention reagieren und somit von einer gezielten Ernährungsberatung profitieren können. Darüber hinaus hat die erfolgreiche Replikation der Metabotypen gezeigt, dass die identifizierten Metabotypen leicht auf andere Bevölkerungsgruppen übertragbar sind.

Das Metabotypkonzept zeichnet sich somit zusehends als vielversprechende Methode zur Stratifizierung der Bevölkerung in metabolisch homogene Gruppen ab, um eine gezielte und effektive Intervention zur Prävention von cardio-metabolischen Krankheiten druchzuführen.

5. Paper I

Dahal C, Wawro N, Meisinger C, Breuninger TA, Thorand B, Rathmann W, Koenig W, Hauner H, Peters A, Linseisen J. Optimized metabotype definition based on a limited number of 4 standard clinical parameters in the population- based KORA study.

DOI: https://doi.org/10.3390/life12101460

6. Paper II

Dahal C, Wawro N, Meisinger C, Brandl B, Skurk T, Volkert D, Hauner H, Lin- seisen J. Evaluation of the metabotype concept after intervention with oral glucose tolerance test and dietary fiber-enriched food: An enable study. Nutrition, Metabolism & Cardiovascular Diseases.
DOI: https://doi.org/10.1016/j.numecd.2022.06.007

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