Molecular Nutrition & Food Research
www.mnf-journal.com

Genetics and Epigenetics in Personalized Nutrition: Evidence, Expectations, and Experiences

Christina Holzapfel, Melanie Waldenberger, Stefan Lorkowski, Hannelore Daniel, the Working Group "Personalized Nutrition" of the German Nutrition Society*

With the presentation of the blueprint of the first human genome in 2001 and the advent of technologies for high-throughput genetic analysis, personalized nutrition (PN) becomes a new scientific field and the first commercial offerings of genotype-based nutrition advice emerge at the same time. Here, the state of evidence for the effect of genetic and epigenetic factors in the development of obesity, the metabolic syndrome, and resulting illnesses such as non-insulin-dependent diabetes mellitus and cardiovascular diseases is summarized. This study also critically value the concepts of PN that are built around the new genetic avenue from both the academic and a commercial perspective and their effectiveness in causing sustained changes in diet, lifestyle, and for improving health. Despite almost 20 years of research and commercial direct-to-consumer offerings, evidence for the success of gene-based dietary recommendations is still generally lacking. This calls for new concepts of future PN solutions that incorporate more phenotypic measures and provide a panel of instruments (e.g., self- and bio-monitoring tools, feedback systems, algorithms based on artificial intelligence) that increases compliance based on the individual´s physical and social environment and value system.

1. Introduction

The economic development and wealth of many nations are accompanied by sedentary lifestyles and increasing intakes of energy-dense food, which are key drivers of non-communicable diseases (NCDs). The pathogenesis usually starts with obesity frequently followed by metabolic syndrome (MS) which in turn often results in the development of non-insulin-dependent diabetes mellitus (NIDDM) and cardiovascular disease (CVD). Although driven by lifestyle, there is a strong poly-genetic background in the sequence of disease. Evidence for genetic susceptibility is obtained from cohort studies in populations of different ethnic backgrounds, genetically isolated populations and from studies in families, adoptees, or mono- and dizygotic twins. The earliest evidence for significantly genetic contributions to disease susceptibility was obtained in family studies and by investigating disease incidence in mono- and dizygotic twin cohorts.[1] Whereas initial twin studies on NIDDM prevalence, for example, overestimated heritability,[2] the largest twin-study conducted so far with almost 35 000 twin pairs of The Discordant Twin (DISCOTWIN) Consortium, estimated a heritability of NIDDM of 72% and argues thus for a strong genetic predisposition.[3] A similar heritability index was obtained for obesity in twins.[4] As twins usually grow up in the same environment and are exposed to common exogenous risk factors, analysis of twin pairs reared apart are of particular interest;[5] but even these studies—despite a rather low number of available twin pairs—demonstrated a

C. Holzapfel,
Institute for Nutritional Medicine
School of Medicine
Technical University of Munich
81675 Munich, Germany
E-mail: christina.holzapfel@tum.de

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/mnfr.202200077

DOI: 10.1002/mnfr.202200077

M. Waldenberger
Research Unit Molecular Epidemiology
Institute of Epidemiology
Helmholtz Zentrum Munich
German Research Center for Environmental Health
85764 Neuherberg, Germany

M. Waldenberger
German Center for Cardiovascular Research (DZHK)
Partner Site Munich Heart Alliance
85764 Munich, Germany

S. Lorkowski
Institute of Nutritional Sciences and Competence Cluster for Nutrition and Cardiovascular Health (nutriCARD) Halle-Jena-Leipzig
Friedrich Schiller University
07743 Jena, Germany

H. Daniel
Technical University of Munich
85354 Freising, Germany

significant heritability for an obese phenotype. Bouchard et al.[6] showed that overfeeding in monozygotic twins resulted in three times more variance in body weight gain between twin pairs than within twin pairs. Furthermore, a study with 540 adult Danish adoptees revealed a statistically significant association between body mass index (BMI) of adopted children and the BMI of their biological parents, whereas there was no statistically significant relation with BMI of their non-biological parents.[7] Studying the underlying causes of obesity revealed also a major influence of the intrauterine environment. In particular, fetal development with a low weight at birth is a major risk factor for the development of NIDDM and CVD in later stages of life.[2,8] In a Swedish study it has been observed that the odds ratio for hypertension in persons with a 500 g lower birth weight was 1.42 and this was independent of genetic factors.[2,8] These studies added major arguments to the concept that epigenetics may be also important in the health-disease trajectory.

Most cases of NIDDM emerge from an obese phenotype with an intermediate state characterized by insulin-resistance and other metabolic impairments associated with an increased risk for CVD and overall mortality.[9] Genetic variants associated with an obese phenotype are consequently also identified as susceptibility genes contributing to MS, NIDDM, and CVD in many populations. However there are also major modulators in the ethnic background as shown, for example, for Pacific Islanders,[10] with a considerably higher incidence of NIDDM than found in the USA or Europe. Also, certain isolated populations such as the Inuit in Greenland carry NIDDM-associated gene variants such as a nonsense p.Arg684Ter variant in the *TBC1 domain family member 4* (*TBC1D4*) gene not found in other geographic regions.[11]

NIDDM and CVD are prototypical diseases for the expression of a mismatch of an individual´s genome with its given environment to which social and behavioral factors as well contribute. In contrast to rare monogenetic diseases that follow Mendelian order with a distinct genotype–phenotype causality, such a correlation cannot be found for the polygenic causes of obesity, MS, and the diseases arising from them. It has to be mentioned, that the present work is focused on polygenetic NCDs and not on mono-genetic metabolic disorders such as, for example, phenylketonuria.

A key instrument for the analysis of the role of single nucleotide polymorphisms (SNPs) in populations are genome-wide associations studies (GWAS) based on the concept that a common disease has a common genetic portfolio as background. In polygenic diseases, susceptibility alleles that associate with disease risk usually have a modest or very small effect size but are generally more common in the population. The SNP rs9939609 in the *fat mass and obesity associated* (*FTO*) gene, for example, has a minor allele frequency (MAF) of 40–45% but a modest BMI effect of 0.35 kg m^{-2} per risk allele.[12] Here it becomes evident that the larger the population under study, the more variants can be found because the majority of variants possess very low odd ratios ranging from 1.10 to 1.25 per allele.[13] However, large cohorts also identify variants with strong effect sizes but of very low frequency.[14] For instance, a GWAS with almost 800 000 individuals identified genetic loci with a MAF of 1.6% and a BMI effect size of 0.04 kg m^{-2} per risk allele.[15] Since most identified gene variants have small effect sizes, carriers and non-carriers usually also have only slightly lower or higher risks than the average population making it difficult to identify the causal genetic loci. Combined effects of genetic variants (expressed, e.g., by polygenetic risk scores) can also be identified via GWAS. Overall disease risks thus depend on both, the number of risk variants of an individual and the specific risk associated with each genotype. In the past years, these approaches have been extended with whole genome sequencing efforts and this will likely increase the density of genetic information underlying the health-disease trajectory to unexpected levels.[16] At the same time, biomedical science almost daily reveals many more new genes and variants contributing to metabolic dysregulation and highlights important (and often unexpected) pathways that are involved in disease development or progression.

In contrast to the large number of susceptibility genes identified, personalized nutrition (PN) approaches usually integrate only a few selected genetic variants/genes into the intervention programs for changes in dietary intake and lifestyle and for reduction of disease risk (**Figure 1**). We here provide the current status of knowledge and value on the genetics underlying the most common NCD´s and assess the success of PN approaches providing genetic information.

1.1. Genetics of Obesity

In a meta-analysis based on GWAS, 941 genetic loci were identified or confirmed for their association with adiposity traits. As mentioned above, the effect of a single SNP is rather small and moreover, these SNPs in summary explain only around 6% of the BMI variation.[15] When the top gene variants that together confer a threefold increased risk for NIDDM are defined, they are as strong in prediction as a BMI of >30 kg m^{-2} alone.[17] However, they represent around 2.5% of the population whereas far more individuals fall into the >30 kg m^{-2} BMI group. Despite the enormous progress made on the genetic basis of obesity it has yet to pay off in view of its diagnostic and public health value.

The most studied obesity locus is the *FTO* gene, which was identified in 2007.[12] It has the strongest individual effect on body weight and it has been shown that homozygous carriers of the risk allele of SNP rs9939609 weigh up to 3 kg more than non-risk allele carriers.[12] Claussnitzer et al.[18] showed that the *FTO* SNP rs1421085 promotes the formation of white adipocytes over beige adipocytes, indicating that weight gain may not necessarily be the result of higher energy intake, but may be related to a reduced proportion of brown-adipose tissue that utilizes more energy than white fat cells. There is also evidence that the *FTO* risk allele associates with different intake levels of macronutrients and food energy.[19] In a study with 71 326 individuals of European ancestry A allele carriers of the SNP rs10163409 in the *FTO* gene showed a significantly positive association with carbohydrate intake ($\beta = 0.166$) expressed as percent energy derived from carbohydrates[20] and a meta-analysis revealed that persons reported a lower total daily energy intake of 6.46 kcal per *FTO* risk allele.[21] However, a weight loss study with 609 participants and interventions with either a low fat or a low carbohydrate diet revealed that there was no significant effect on weight loss after 12 months and this was also independent of the genetic variants in

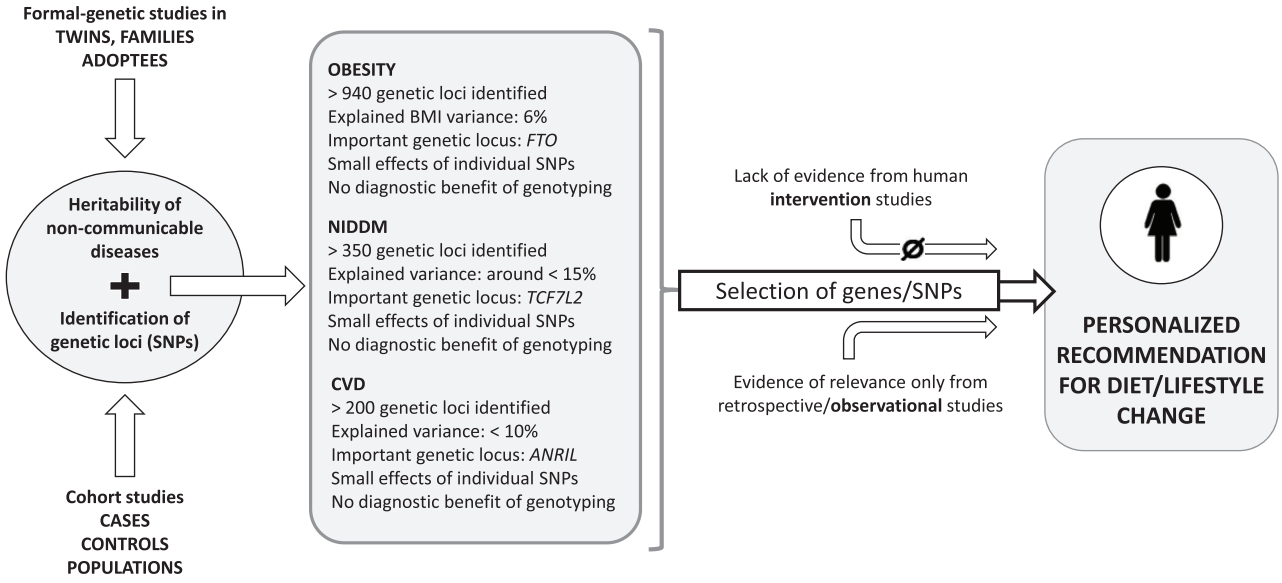

Figure 1. Approaches used to identify genetic variants, their effects on obesity, non-insulin dependent diabetes mellitus (NIDDM), cardiovascular disease (CVD), and the limitations to translate the findings from genotyping into current concepts of personalized nutrition; the term "explained variance" refers to the variance explained by genetic factors only; *ANRIL*, *CDKN2B antisense RNA 1*; *FTO*, *fat mass and obesity associated*; *SNP, single nucleotide polymorphism; TCF7L2, transcription factor 7-like 2.*

three genes known to be involved in metabolic and body weight control.[22]

1.2. Genetics of NIDDM

For NIDDM, a meta-analysis of 74 124 cases and 824 000 controls of European ancestry identified over 240 loci.[23] Many of those loci were also dominant in a large group of East Asian ancestry with more than 77 000 individuals diagnosed with NIDDM. A good correlation of the effect sizes across the loci and across the populations was found. The correlation of per-allele effect sizes between the two ancestries was 0.87 for 106 variants significantly associated with NIDDM.[24] Together, these two studies identified >300 loci associated with NIDDM. One striking gene is *transcription factor 7-like 2* (*TCF7L1*): it shows an odds ratio of 1.46 for NIDDM.[25] The *TCF7L2* gene encodes the transcription factor 7-like 2 protein that belongs to the high mobility group (HMG) box protein family that influences several biological pathways and plays a prominent role in Wnt signaling.[26] The SNP rs7903146 in the gene is the most significant genetic marker associated with NIDDM and is found across all studied ethnic groups with similar effect sizes.[27] The *TCF7L2* risk variant is not only the most prominent susceptibility allele for NIDDM, it also seems to confer resistance to sulfonylurea therapy but not to metformin,[28] whereas a lifestyle intervention with a low-calorie, low-fat diet, and with physical activity of moderate intensity was as effective in carriers as in non-carriers.[29] Despite the large number of loci identified, they collectively still explain less than 25% of the overall variance of NIDDM. That also holds true for the genetic basis of fasting glucose levels.[30] Therefore, classic measures of NIDDM risk such as family history, age, sex, BMI, and fasting plasma glucose still outperform the diagnostic value of single gene variants or polygenetic scores.[31,32] Moreover, risk models did not improve if genetic information was added to the traditional phenotypic parameters assessed.[31]

1.3. Genetics of CVD

Dietary factors make the largest contribution to overall CVD mortality.[33] Also obesity and NIDDM are risk factors for CVD.[9,34] It is thus conceivable that loci that have been identified as being associated with obesity and NIDDM are also part of the genetic landscape of CVD susceptibility. GWAS and related approaches have enlarged the number of loci underlying CVD markedly. For blood pressure, a recent analysis delivered more than 1000 loci that together explain less than 6% of the overall variance.[35] A closer look at the respective genes reveals that they are spread across the whole genome with some enrichment in expected pathways but also in numerous other pathways not at all known for links to blood pressure control. For instance, common to most studies identified genes underlying calcium signaling processes and hemostasis.[35] Despite the strong association with many lifestyle factors, gene variants that link dietary intake to hypertension or to the final stages of CVD are sparse.

Although a larger number of genetic loci has been found to be associated with cardiovascular risk factors such as blood pressure and plasma lipids, more than 200 genetic loci have thus far been identified that influence the risk of myocardial infarction and coronary artery disease.[36] The genetic susceptibility explains a small fraction of the overall heritability for myocardial infarction and coronary artery disease.

Next, not all patients with coronary atherosclerosis suffer from myocardial infarction although most patients with a myocardial infarction also have coronary atherosclerosis. In line with this, recent studies indicate that at least some of the processes contributing to the initiation or progression of atherosclerosis are

distinct from those genetic factors that predispose more strongly or specifically to plaque rupture and thrombosis.[36] One example is the *CDKN2B antisense RNA 1* (*ANRIL/CDKN2BAS*) locus that is one of the most strongly associated loci for the severity of coronary atherosclerosis but is not specifically associated with myocardial infarction.[37,38] In contrast, the ABO blood group system defining locus is associated with myocardial infarction among individuals with coronary atherosclerosis but is not necessarily associated with the presence of coronary artery disease itself.[37] A recent study revealed eight loci for myocardial infarction, of which six loci were more robustly associated with myocardial infarction than with coronary atherosclerosis without a cardiovascular event.[36] The locus encoding for the choline-like transporter 3 (*SLC44A3*) was confirmed in independent cohorts as associated with myocardial infarction in patients with coronary atherosclerosis, but not with coronary artery disease itself. Of note, no association of this locus was found with cardiovascular risk factors or any other biomarkers.[36] These examples illustrate the difficulties in deriving personalized dietary recommendations for the prevention of cardiovascular diseases and related complications.

1.4. Evidence for Epigenetic Effects

The term epigenetics refers to "heritable" phenotype changes that do not involve changes in the deoxyribonucleic acid (DNA) sequence.[39] Although epigenetic mechanisms, including modifications of DNA, histone proteins, and chromatin remodeling, do not alter the nucleotide sequence, they have a fundamental impact on genomic structure and function, including gene expression and cellular differentiation. Epigenetic modifications may therefore account for a significant fraction of the missing heritability in genetic studies. A main feature of epigenetic mechanisms is that they are reversible, cell-specific, and reflect genetic and environmental influences over the life course.[40]

The DNA methylation, a covalent addition of a methyl group to the C-5 position of the cytosine ring of DNA in the context of CG dinucleotides (CpG sites), is the most widely investigated epigenetic modification due to technological advances that allow its assessment at a large scale in epidemiologic studies.

An established link between diet and epigenetic mechanisms is the availability of the universal methyl donor S-adenosylmethionine (SAM) generated in one-carbon metabolism.[41] Enzymes such as methyltransferases require SAM to methylate DNA or histones.[42] The activity of enzymes within the one-carbon metabolism require folate, vitamin B_{12}, and vitamin B_6 as cofactors while betaine, choline, or methionine deliver the methyl groups.[43]

A systematic review compiling studies that reported associations between maternal diet during pregnancy and epigenetic changes (DNA methylation, micro ribonucleic acid (microRNA)) in placenta and in the offspring addressed also the current limitations like heterogeneity in response in samples (e.g., placenta, cord blood), sample size effects, gestational period, exposures (e.g., diet, exercise), or outcome measures.[44] Other studies demonstrated the role of dietary micronutrients during early life in altering gene expression and influencing health or disease later in life.[45,46]

In adults, large-scale analysis of DNA methylation in leukocytes, for example, identified differentially methylated CpG sites associated with folate or vitamin B_{12} intake.[47] A study of habitual diet quality, including the Mediterranean diet score and the Alternative Healthy Eating Index, reported an association with differential leukocyte DNA methylation levels of 30 CpG sites, most of which were also associated with adverse health outcomes.[48] In general, intervention studies investigating the effect of epigenetic mechanisms are sparse and usually have small sample sizes. For example, one study of 36 persons investigated whether an intervention over 5 years with a Mediterranean diet affected the methylome of peripheral blood cells, and identified differential methylated positions in genes related to inflammatory pathways.[49]

As shown in **Figure 2**, links between DNA methylation, obesity, the MS, and related cardiometabolic diseases have been established by several well-powered epigenome-wide association studies (EWAS).[50] In the case of obesity, the largest study to date, combining data from over 10 000 whole blood samples, identified 187 CpG sites as significantly associated with BMI and showed that obesity-associated DNA methylation sites predicted future NIDDM development.[51] A large number of obesity-associated CpG sites overlap with those identified in studies of other metabolic phenotypes like blood lipids or NIDDM.

EWAS of DNA methylation data using adipose tissue samples identified multiple additional CpG sites associated with obesity-related traits, including sites annotated to *FTO*.[52] Using data from 648 twins revealed that DNA methylation variation (34%) was highly heritable.[53] The CpG sites associated with BMI and waist circumference were reported to explain 29% and 26% of trait heritability, respectively,[54] and 18% of the inter-individual variation in BMI.[55] Using causal inference methods like Mendelian randomization, the majority of these adiposity-associated changes in DNA methylation were found to be consequence rather than cause.[51]

Numerous studies have analyzed DNA methylation in relation to glycemic traits and NIDDM, including studies in whole blood, adipose tissue, pancreatic islets, liver, and skeletal muscle.[56–61] Several differentially methylated CpG sites were identified to robustly predict incident NIDDM, either alone or combined in a methylation risk score.[62,63] EWAS conducted in studies using key tissues of NIDDM pathogenesis identified numerous CpG sites, among them several well-known candidates such as *TCF7L2*. These studies are typically small due to the limited sample availability, but of importance for a comprehensive insight into disease mechanisms. Their results support a role of epigenetics in the pathogenesis of NIDDM despite the modest effect sizes of individual CpG sites. Comprehensive analysis of histone modifications or chromatin structure in persons with NIDDM still represent an under-researched topic.[61,64]

The majority of EWAS of CVD to date have been conducted cross-sectional including retrospective events at a single timepoint.[65–68] While these studies provide molecular findings, changes in DNA methylation may here as well be the consequence of an acute event rather than the cause. Recent investigations have started to provide links between DNA methylation and incident CVD.[69,70] The largest study of incident events to date investigated the association between 11 461 leukocyte DNA methylation profiles and a variety of outcomes including

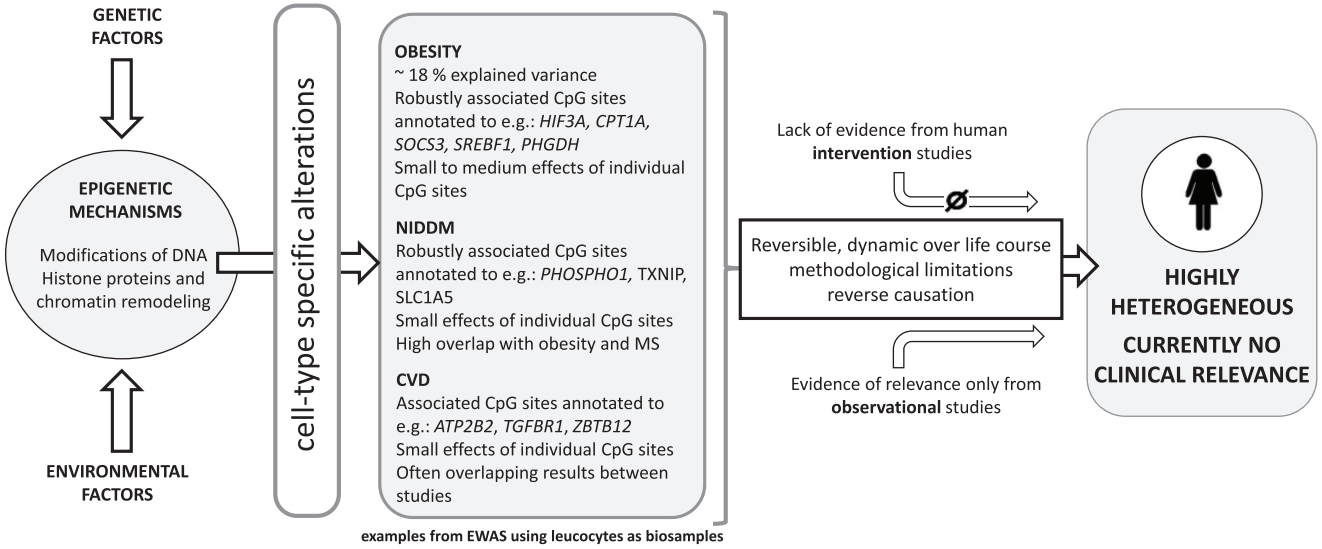

Figure 2. Associations between deoxyribonucleic acid (DNA) methylation and obesity, the metabolic syndrome (MS), non-insulin dependent diabetes mellitus (NIDDM), and cardiovascular disease (CVD) and the limitations to translate the findings from epigenome-wide association studies (EWAS) into current concepts of personalized nutrition; the term "explained variance" refers to the variance explained by epigenetic factors only; *ATP2B2, ATPase plasma membrane Ca2+ transporting 2; CPT1A, carnitine palmitoyltransferase 1A; HIF3A, hypoxia inducible factor 3 subunit alpha; PHGDH, phosphoglycerate dehydrogenase; PHOSPHO1, phosphoethanolamine/phosphocholine phosphatase 1; SLC1A5, solute carrier family 1 member 5; SOCS3, suppressor of cytokine signaling 3; SREBF1, sterol regulatory element binding transcription factor 1; TXNIP, thioredoxin interacting protein; TGFBR1, transforming growth factor beta receptor 1; ZBTB12, zinc finger and BTB domain containing 12.*

coronary insufficiency, angina, myocardial infarction, coronary revascularization, and cardiovascular mortality with a mean follow-up of 11.2 years.[71] The study identified 52 differentially methylated CpG sites.[71] Taken together, the results of EWAS on diet-dependent diseases are in an early stage and the effect sizes of individual CpG sites identified are small.

1.5. Genotype-Based Personalized Nutrition

A variety of diet intervention studies investigating the effects of common gene variants on diet–responses have been conducted already in the 1990s and revealed significant effect sizes.[72–75] One example is the effect of riboflavin intake in cardiovascular disease patients homozygous for the common 677C→T polymorphism in the *methylenetetrahydrofolate reductase (MTHFR*) gene. After 16 weeks of intervention with 1.6 mg riboflavin per day or with placebo it was found, that riboflavin intake reduced the mean blood pressure in persons homozygous for the studied polymorphism.[76] Another showcase-study investigated the effect of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplements on cardiometabolic factors dependent on the *apolipoprotein E* (*APOE*) genotype. Significant sex-genotype-treatment interactions were observed with the strongest effects on blood triacylglycerol lowering in men with a specific *APOE* genotype.[77]

In particular weight loss and the genetic variants that could affect weight management received academic and commercial interest.[78] Results from these kinds of studies provided the basis for most of the commercial offers that combine DNA analysis with dietary recommendations and occasionally also for the type of exercise that could help in weight loss. The first commercial offering of a DNA-based advice system for individual health management was by *Sciona* in 2003. What at that time caused intense discussions in the academic as well as in the public domain, was the disclosure of genetic information to a commercial company.[79] Meanwhile this is less often considered as problematic given the fact that genotyping, for example, to obtain information on ancestry is now more common practice. Numerous companies offer genotyping and either personalized products such as supplements or premixed muesli or provide personalized recommendations for a healthy diet or for weight loss. Similar to commercial tests of genetic variants, commercial offerings for DNA methylation profiling have recently emerged. For example, companies are offering the assessment of the individual´s biological age based on DNA methylation status at sets of CpG sites as a basis for managing longevity or for "rejuvenating" interventions.[80]

The largest academic human intervention study on PN to date is the Food4me study. As a pan-European activity with seven countries, applying the same methods and tools across centers, around 1600 healthy participants representative of the European population were recruited. The main goal was to assess whether personalized dietary advice is superior over generic advice in changing a person´s diet and lifestyle over a 6-month study period.[81] Moreover, it was designed as a proof-of-concept study with contact to the participants solely via internet and email, except for the delivery of DNA samples and dry blood spots that were collected by participants via defined procedures (per video tutorials) and shipped in for analysis. Dry blood spots were analyzed for some clinical chemistry markers but also for diet-dependent measures such as vitamin D3 levels or the n6:n3 fatty acid ratio. From 30 preselected SNPs that related to BMI, NIDDM, or dietary factors (e.g., *MTHFR* or *fatty acid desaturase*

1/2 risk variants) only five were communicated back to the participants in the context of the advice to change diet and lifestyle. The outcome measures assessed at month 3 and month 6 were changes in nutrient intakes, changes in the Healthy Eating Index (HEI) and changes in body mass, and BMI, respectively. Additionally, the Food4me study addressed other aspects such as ethical issues or comparative participant compliance depending on the country of origin.[79,82,83] Based on the HEI and other parameters reflecting a healthy diet, personalization was superior to generic advice but inclusion of blood markers and genetic risks in the communication delivered no significant beneficial effects.[84] That inclusion of genetic risks did not significantly affect changes in diet or lifestyle behaviors is in line with similar findings in other settings, although in smaller sized studies subtle positive effects, for example, on salt intake were found.[85] A systematic review of randomized controlled trials (RCTs) on effects of PN and tailored advice based on diet, phenotype, or genetic information revealed the same findings as in Food4me in that PN advice results in a greater improvement of dietary intake compared to generalized dietary advice.[86]

Other systematic reviews and meta-analyses consistently report that communicating genetic risks, such as for NIDDM or for CVDs alone neither increases motivation for lifestyle changes nor translates into proper changes in dietary intake or physical activity level.[87,88] A behavioral science study investigated whether the gained information on the individual genetic risk is associated with changes in gene-related physiology, behavior, and subjective experience. Most interestingly, genetic risk information changed, for example, cardiorespiratory physiology, satiety, and perceived fullness after food consumption. The authors concluded that genetic risk information can change an individual´s physiology and behavior without active intervention, which suggests placebo and nocebo effects of the genetic information provided.[89]

2. Discussion

This manuscript provides the current evidence status on the genetics underlaying the most common NCD´s and assess the success of PN approaches providing genetic information. The manuscript is focused on NCD's, where the evidence for genotype-based dietary recommendations is scarce. However, there is no doubt that genetically determined metabolic disorders such as, for example, phenylketonurea require a personalized approach in dietary management of the disease but such cases are not considered here.

Although PN does not require genetic testing as a mandatory assessment tool, almost all commercial offers and related services provide profiling of a limited number of gene variants. Identifying such variants from DNA samples isolated from saliva or buccal cells and collected by the customer for analysis is nowadays very easy and is done at low cost. According to a representative survey in Germany, 70% of participants thought that a genotype-based dietary recommendation is a reasonable measure for weight loss. Furthermore, about half of the survey participants believed that PN based on the genetic make-up of a person is an effective concept in general.[90]

Scientific evidence that the genetic make-up is associated with either distinct responses to diet or body weight or disease risk is derived from many observational studies and is used as a conceptual framework of almost all personalized genotype-based dietary recommendations. Despite enormous progress in identifying new gene variants underlying the health-disease trajectory, this is not yet reflected in PN approaches which are mainly based on a few genetic variants. There are studies assessing the association between genetic factors and the effect of dietary intervention,[76,77] but larger-sized human intervention studies with dietary recommendations based on a specific genotype of participants are currently unavailable.

What is new is that both academic and commercial PN settings now include microbiome data obtained via 16S RNA sequencing from stool samples. In addition, more sophisticated algorithms that take into account food intake data (information collected via 24 h dietary recall or via food frequency questionnaire), anthropometric information, vital parameters (e.g., blood pressure) as well as DNA and microbiome data have been developed. Some commercial offers also include the option of online recordings of interstitial glucose levels via blue-tooth-coupled sensors originally developed for diabetes management and used as a feedback loop indicator of changes in glucose homeostasis upon dietary changes. That real-time feedback may increase overall compliance, in particular when a softening of the glucose-profiles becomes visible. Most commercial PN offers that include glucose monitoring were generated based on findings reported by Zeevi et al.,[91] which, in addition to basic information on the participants, also included microbiome data from stool samples and an algorithm with predictive quality for the individual´s glycemic response to provided food items. But, it should be kept in mind that glycemic responses are not the ultimate measure of human health. Moreover, whether recording of glucose profiles changes food intake behavior in the long term remains to be shown.

A new quality of comprehensive phenotyping that led to new concepts of PN are the studies by the Personalized Responses to Dietary Composition Trial (PREDICT) consortium with thousands of participants and combined analyses of genotype, microbiome, and blood chemistry and defined breakfast and lunch challenges followed by recording of postprandial glucose and triglyceride profiles.[92] These studies identified that genetics next to meal composition was the most important determinant of glucose responses, whereas for triglyceride responses genetics had only a negligible influence. The wealth of data collected via these approaches will also form the basis for new algorithms and machine learning approaches with better predictive quality, which will be one of the pillars of future PN applications. For the time being, blood or interstitial glucose are the most frequently used continuously and easily measurable metabolic parameters included in PN approaches.

It needs to be emphasized that at least from experience in academic PN test studies, study participants generally appear to be more interested in diet and health than the average consumer and they are also usually well-educated, have proper income and show a high tech-affinity. They are thus likely not the group that may need and benefit most from PN offers—whether commercial or academic. Taken together, most, if not all PN concepts available these days use selected gene variants as input parameter in addition to anthropometric, physical activity, and food intake data to derive individualized recommendations. However, studies that assessed whether inclusion of genetic information in the recommendation had an effect on food choices, physical activity

levels, or weight development, did not reveal a real benefit to participants´ successes.[78]

3. Conclusion

Despite enormous efforts in research about gene–diet interaction, the recent conclusion of the Academy of Nutrition and Dietetics was "*..... that there are still relatively few RCTs to inform integration of genetic variation into the Nutrition Care Process.*"[93] This "non-clinical relevance" of genetic information for dietary advice is mainly due to the fact that genetic evidence is derived from epidemiological association studies and cannot be directly transferred to clinical practice. A further bottleneck is, that larger dietary intervention studies based on the genetic background of an individual are missing. It is evident, that procedures need to be developed and agreed upon in the scientific community to identify clinically and practically relevant gene variants among those hundreds of loci known to be associated with obesity, NIDDM, or CVD. These could then be incorporated into effective PN recommendations.

Based on the experience of the past 20 years it becomes obvious that future PN concepts need improved input and output variables. It is necessary to collect real world data on food intake, physical and social behavior which the "digital environment" enables as never before. Furthermore, it needs more comprehensive phenotyping and improved algorithms based on artificial intelligence to predict the effect on an individual´s diet on metabolic response and risk management. The research on PN would benefit from better integrating data sciences and multidisciplinary cooperation.

Acknowledgements

The authors thank the members of the Working Group "Personalized Nutrition" of the German Nutrition Society: Janine Bröder, Anette Buyken, Johanna Conrad, Paola A. Ferrario, Kurt Gedrich, Michael Leitzmann, Jakob Linseisen, Britta Renner, Margrit Richter, Marie-Christine Simon, Christian Sina, Bernhard Watzl, Jan Wirsam. C.H. leads the "Personalized nutrition and eHealth" (grant number: 01EA1709; *enable* publication number: 84) group within the *enable* cluster and S.L. is chairing the NutriCard cluster, both *funded by the* German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF). M.W. received funding from the German Federal Ministry of Education and Research (BMBF) within the framework of the EU Joint Programming Initiative "A Healthy Diet for a Healthy Life" (DIMENSION grant number 01EA1902A).

Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

C.H. and H.D. have written the manuscript, M.W. and S.L. contributed to the manuscript. All authors discussed the content and commented on the manuscript.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords

cardiovascular diseases, diabetes, methylation, obesity, single nucleotide polymorphism

Received: February 4, 2022
Revised: May 17, 2022
Published online:

[1] P. Poulsen, K. O. Kyvik, A. Vaag, H. Beck-Nielsen, *Diabetologia* **1999**, *42*, 139.
[2] A. Vaag, P. Poulsen, *Curr. Opin. Clin. Nutr. Metab. Care* **2007**, *10*, 591.
[3] G. Willemsen, K. J. Ward, C. G. Bell, K. Christensen, J. Bowden, C. Dalgard, J. R. Harris, J. Kaprio, R. Lyle, P. K. Magnusson, K. A. Mather, J. R. Ordonana, F. Perez-Riquelme, N. L. Pedersen, K. H. Pietilainen, P. S. Sachdev, D. I. Boomsma, T. Spector, *Twin Res. Hum. Genet.* **2015**, *18*, 762.
[4] D. B. Allison, J. Kaprio, M. Korkeila, M. Koskenvuo, M. C. Neale, K. Hayakawa, *Int. J. Obes. Relat. Metab. Disord.* **1996**, *20*, 501.
[5] N. L. Segal, Y. S. Montoya, E. N. Becker, *Twin Res. Hum. Genet.* **2018**, *21*, 295.
[6] C. Bouchard, A. Tremblay, *J. Nutr.* **1997**, *127*, 943S.
[7] A. J. Stunkard, T. I. Sorensen, C. Hanis, T. W. Teasdale, R. Chakraborty, W. J. Schull, F. Schulsinger, *N. Engl. J. Med.* **1986**, *314*, 193.
[8] N. Bergvall, A. Iliadou, S. Johansson, U. de Faire, M. S. Kramer, Y. Pawitan, N. L. Pedersen, P. Lichtenstein, S. Cnattingius, *Circulation* **2007**, *115*, 2931.
[9] J. S. Yun, S. H. Ko, *Metabolism* **2021**, *123*, 154838.
[10] A. J. Karter, D. Schillinger, A. S. Adams, H. H. Moffet, J. Liu, N. E. Adler, A. M. Kanaya, *Diabetes Care* **2013**, *36*, 574.
[11] I. Moltke, N. Grarup, M. E. Jorgensen, P. Bjerregaard, J. T. Treebak, M. Fumagalli, T. S. Korneliussen, M. A. Andersen, T. S. Nielsen, N. T. Krarup, A. P. Gjesing, J. R. Zierath, A. Linneberg, X. Wu, G. Sun, X. Jin, J. Al-Aama, J. Wang, K. Borch-Johnsen, O. Pedersen, R. Nielsen, A. Albrechtsen, T. Hansen, *Nature* **2014**, *512*, 190.
[12] T. M. Frayling, N. J. Timpson, M. N. Weedon, E. Zeggini, R. M. Freathy, C. M. Lindgren, J. R. Perry, K. S. Elliott, H. Lango, N. W. Rayner, B. Shields, L. W. Harries, J. C. Barrett, S. Ellard, C. J. Groves, B. Knight, A. M. Patch, A. R. Ness, S. Ebrahim, D. A. Lawlor, S. M. Ring, Y. Ben-Shlomo, M. R. Jarvelin, U. Sovio, A. J. Bennett, D. Melzer, L. Ferrucci, R. J. Loos, I. Barroso, N. J. Wareham, et al., *Science* **2007**, *316*, 889.
[13] A. P. Morris, *Curr. Opin. Genet. Dev.* **2018**, *50*, 41.
[14] C. Langenberg, L. A. Lotta, *Lancet* **2018**, *391*, 2463.
[15] L. Yengo, J. Sidorenko, K. E. Kemper, Z. Zheng, A. R. Wood, M. N. Weedon, T. M. Frayling, J. Hirschhorn, J. Yang, P. M. Visscher, G. Consortium, *Hum. Mol. Genet.* **2018**, *27*, 3641.
[16] C. Fuchsberger, J. Flannick, T. M. Teslovich, A. Mahajan, V. Agarwala, K. J. Gaulton, C. Ma, P. Fontanillas, L. Moutsianas, D. J. McCarthy, M. A. Rivas, J. R. B. Perry, X. Sim, T. W. Blackwell, N. R. Robertson, N. W. Rayner, P. Cingolani, A. E. Locke, J. F. Tajes, H. M. Highland, J. Dupuis, P. S. Chines, C. M. Lindgren, C. Hartl, A. U. Jackson, H. Chen, J. R. Huyghe, M. van de Bunt, R. D. Pearson, A. Kumar, et al., *Nature* **2016**, *536*, 41.
[17] J. B. Meigs, *Curr. Diab. Rep.* **2019**, *19*, 62.
[18] M. Claussnitzer, S. N. Dankel, K. H. Kim, G. Quon, W. Meuleman, C. Haugen, V. Glunk, I. S. Sousa, J. L. Beaudry, V. Puviindran, N. A. Abdennur, J. Liu, P. A. Svensson, Y. H. Hsu, D. J. Drucker, G. Mellgren, C. C. Hui, H. Hauner, M. Kellis, *N. Engl. J. Med.* **2015**, *373*, 895.
[19] T. Drabsch, C. Holzapfel, *Nutrients* **2019**, *11*, 617.
[20] A. Y. Chu, T. Workalemahu, N. P. Paynter, L. M. Rose, F. Giulianini, T. Tanaka, J. S. Ngwa, C. N. W. Group, Q. Qi, G. C. Curhan, E. B. Rimm,

D. J. Hunter, L. R. Pasquale, P. M. Ridker, F. B. Hu, D. I. Chasman, L. Qi, C. DietGen, *Hum. Mol. Genet.* **2013**, *22*, 1895.
[21] K. M. Livingstone, C. Celis-Morales, J. Lara, A. W. Ashor, J. A. Lovegrove, J. A. Martinez, W. H. Saris, M. Gibney, Y. Manios, I. Traczyk, C. A. Drevon, H. Daniel, E. R. Gibney, L. Brennan, J. Bouwman, K. A. Grimaldi, J. C. Mathers, *Obes Rev* **2015**, *16*, 666.
[22] C. D. Gardner, J. F. Trepanowski, L. C. Del Gobbo, M. E. Hauser, J. Rigdon, J. P. A. Ioannidis, M. Desai, A. C. King, *JAMA, J. Am. Med. Assoc.* **2018**, *319*, 667.
[23] A. Mahajan, D. Taliun, M. Thurner, N. R. Robertson, J. M. Torres, N. W. Rayner, A. J. Payne, V. Steinthorsdottir, R. A. Scott, N. Grarup, J. P. Cook, E. M. Schmidt, M. Wuttke, C. Sarnowski, R. Magi, J. Nano, C. Gieger, S. Trompet, C. Lecoeur, M. H. Preuss, B. P. Prins, X. Guo, L. F. Bielak, J. E. Below, D. W. Bowden, J. C. Chambers, Y. J. Kim, M. C. Y. Ng, L. E. Petty, X. Sim, *Nat. Genet.* **2018**, *50*, 1505.
[24] C. N. Spracklen, M. Horikoshi, Y. J. Kim, K. Lin, F. Bragg, S. Moon, K. Suzuki, C. H. T. Tam, Y. Tabara, S. H. Kwak, F. Takeuchi, J. Long, V. J. Y. Lim, J. F. Chai, C. H. Chen, M. Nakatochi, J. Yao, H. S. Choi, A. K. Iyengar, H. J. Perrin, S. M. Brotman, M. van de Bunt, A. L. Gloyn, J. E. Below, M. Boehnke, D. W. Bowden, J. C. Chambers, A. Mahajan, M. I. McCarthy, M. C. Y. Ng, et al., *Nature* **2020**, *582*, 240.
[25] S. Cauchi, Y. El Achhab, H. Choquet, C. Dina, F. Krempler, R. Weitgasser, C. Nejjari, W. Patsch, M. Chikri, D. Meyre, P. Froguel, *J. Mol. Med. (Berl)* **2007**, *85*, 777.
[26] T. Jin, L. Liu, *Mol. Endocrinol.* **2008**, *22*, 2383.
[27] A. R. Vaquero, N. E. Ferreira, S. V. Omae, M. V. Rodrigues, S. K. Teixeira, J. E. Krieger, A. C. Pereira, *Physiol. Genomics* **2012**, *44*, 903.
[28] E. R. Pearson, L. A. Donnelly, C. Kimber, A. Whitley, A. S. Doney, M. I. McCarthy, A. T. Hattersley, A. D. Morris, C. N. Palmer, *Diabetes* **2007**, *56*, 2178.
[29] J. C. Florez, K. A. Jablonski, N. Bayley, T. I. Pollin, P. I. de Bakker, A. R. Shuldiner, W. C. Knowler, D. M. Nathan, D. Altshuler, *G. Diabetes Prevention Program Research, N. Engl. J. Med.* **2006**, *355*, 241.
[30] J. Dupuis, C. Langenberg, I. Prokopenko, R. Saxena, N. Soranzo, A. U. Jackson, E. Wheeler, N. L. Glazer, N. Bouatia-Naji, A. L. Gloyn, C. M. Lindgren, R. Magi, A. P. Morris, J. Randall, T. Johnson, P. Elliott, D. Rybin, G. Thorleifsson, V. Steinthorsdottir, P. Henneman, H. Grallert, A. Dehghan, J. J. Hottenga, C. S. Franklin, P. Navarro, K. Song, A. Goel, J. R. Perry, J. M. Egan, T. Lajunen, et al., *Nat. Genet.* **2010**, *42*, 105.
[31] P. J. Talmud, A. D. Hingorani, J. A. Cooper, M. G. Marmot, E. J. Brunner, M. Kumari, M. Kivimaki, S. E. Humphries, *BMJ* **2010**, *340*, b4838.
[32] J. L. Vassy, M. F. Hivert, B. Porneala, M. Dauriz, J. C. Florez, J. Dupuis, D. S. Siscovick, M. Fornage, L. J. Rasmussen-Torvik, C. Bouchard, J. B. Meigs, *Diabetes* **2014**, *63*, 2172.
[33] A. Timmis, N. Townsend, C. P. Gale, A. Torbica, M. Lettino, S. E. Petersen, E. A. Mossialos, A. P. Maggioni, D. Kazakiewicz, H. T. May, D. De Smedt, M. Flather, L. Zuhlke, J. F. Beltrame, R. Huculeci, L. Tavazzi, G. Hindricks, J. Bax, B. Casadei, S. Achenbach, L. Wright, P. Vardas, C. European Society of European Society, *Eur. Heart J.* **2020**, *41*, 12.
[34] M. S. Kim, W. J. Kim, A. V. Khera, J. Y. Kim, D. K. Yon, S. W. Lee, J. I. Shin, H. H. Won, *Eur. Heart J.* **2021**, *42*, 3388.
[35] C. P. Cabrera, F. L. Ng, H. L. Nicholls, A. Gupta, M. R. Barnes, P. B. Munroe, M. J. Caulfield, *Hum. Mol. Genet.* **2019**, *28*, R151.
[36] J. A. Hartiala, Y. Han, Q. Jia, J. R. Hilser, P. Huang, J. Gukasyan, W. S. Schwartzman, Z. Cai, S. Biswas, D. A. Tregouet, N. L. Smith, I. Consortium, C. C. H. W. Group, G.-C. Consortium, M. Seldin, C. Pan, M. Mehrabian, A. J. Lusis, P. Bazeley, Y. V. Sun, C. Liu, A. A. Quyyumi, M. Scholz, J. Thiery, G. E. Delgado, M. E. Kleber, W. Marz, L. J. Howe, F. W. Asselbergs, M. van Vugt, et al., *Eur. Heart J.* **2021**, *42*, 919.
[37] M. P. Reilly, M. Li, J. He, J. F. Ferguson, I. M. Stylianou, N. N. Mehta, M. S. Burnett, J. M. Devaney, C. W. Knouff, J. R. Thompson, B. D. Horne, A. F. Stewart, T. L. Assimes, P. S. Wild, H. Allayee, P. L. Nitschke, R. S. Patel, C. Myocardial Infarction Genetics, C. Wellcome Trust Case Control, N. Martinelli, D. Girelli, A. A. Quyyumi, J. L. Anderson, J. Erdmann, A. S. Hall, H. Schunkert, T. Quertermous, S. Blankenberg, S. L. Hazen, R. Roberts, *Lancet* **2011**, *377*, 383.
[38] F. Beutner, D. Teupser, S. Gielen, L. M. Holdt, M. Scholz, E. Boudriot, G. Schuler, J. Thiery, *PLoS One* **2011**, *6*, e29070.
[39] C. Dupont, D. R. Armant, C. A. Brenner, *Semin. Reprod. Med.* **2009**, *27*, 351.
[40] J. S. Hawe, R. Wilson, K. T. Schmid, L. Zhou, L. N. Lakshmanan, B. C. Lehne, B. Kuhnel, W. R. Scott, M. Wielscher, Y. W. Yew, C. Baumbach, D. P. Lee, E. Marouli, M. Bernard, L. Pfeiffer, P. R. Matias-Garcia, M. I. Autio, S. Bourgeois, C. Herder, V. Karhunen, T. Meitinger, H. Prokisch, W. Rathmann, M. Roden, S. Sebert, J. Shin, K. Strauch, W. Zhang, W. L. W. Tan, S. M. Hauck, et al., *Nat. Genet.* **2022**, *54*, 18.
[41] G. S. Ducker, J. D. Rabinowitz, *Cell Metab.* **2017**, *25*, 27.
[42] M. G. Goll, T. H. Bestor, *Annu. Rev. Biochem.* **2005**, *74*, 481.
[43] S. Friso, S. Udali, D. De Santis, S. W. Choi, *Mol Aspects Med* **2017**, *54*, 28.
[44] L. Rasmussen, S. Knorr, C. S. Antoniussen, J. M. Bruun, P. G. Ovesen, J. Fuglsang, U. Kampmann, *Nutrients* **2021**, 13.
[45] A. Gabory, L. Attig, C. Junien, *Am. J. Clin. Nutr.* **2011**, *94*, 1943S.
[46] R. A. Bekdash, *Nutrients* **2021**, 13.
[47] P. R. Mandaviya, R. Joehanes, J. Brody, J. E. Castillo-Fernandez, K. F. Dekkers, A. N. Do, M. Graff, I. K. Hanninen, T. Tanaka, E. A. L. de Jonge, J. C. Kiefte-de Jong, D. M. Absher, S. Aslibekyan, Y. B. de Rijke, M. Fornage, D. G. Hernandez, M. A. Hurme, M. A. Ikram, P. F. Jacques, A. E. Justice, D. P. Kiel, R. N. Lemaitre, M. M. Mendelson, V. Mikkila, A. Z. Moore, T. Pallister, O. T. Raitakari, C. G. Schalkwijk, J. Sha, et al., *Am. J. Clin. Nutr.* **2019**, *110*, 437.
[48] J. Ma, C. M. Rebholz, K. V. E. Braun, L. M. Reynolds, S. Aslibekyan, R. Xia, N. G. Biligowda, T. Huan, C. Liu, M. M. Mendelson, R. Joehanes, E. A. Hu, M. Z. Vitolins, A. C. Wood, K. Lohman, C. Ochoa-Rosales, J. van Meurs, A. Uitterlinden, Y. Liu, M. A. Elhadad, M. Heier, M. Waldenberger, A. Peters, E. Colicino, E. A. Whitsel, A. Baldassari, S. A. Gharib, N. Sotoodehnia, J. A. Brody, C. M. Sitlani, et al., *Circ. Genom. Precis. Med.* **2020**, *13*, e002766.
[49] A. Arpon, J. I. Riezu-Boj, F. I. Milagro, A. Marti, C. Razquin, M. A. Martinez-Gonzalez, D. Corella, R. Estruch, R. Casas, M. Fito, E. Ros, J. Salas-Salvado, J. A. Martinez, *J. Physiol. Biochem.* **2016**, *73*, 445.
[50] C. Ling, T. Ronn, *Cell Metab.* **2019**, *29*, 1028.
[51] S. Wahl, A. Drong, B. Lehne, M. Loh, W. R. Scott, S. Kunze, P. C. Tsai, J. S. Ried, W. Zhang, Y. Yang, S. Tan, G. Fiorito, L. Franke, S. Guarrera, S. Kasela, J. Kriebel, R. C. Richmond, M. Adamo, U. Afzal, M. Ala-Korpela, B. Albetti, O. Ammerpohl, J. F. Apperley, M. Beekman, P. A. Bertazzi, S. L. Black, C. Blancher, M. J. Bonder, M. Brosch, M. Carstensen-Kirberg, et al., *Nature* **2017**, *541*, 81.
[52] T. Ronn, P. Volkov, L. Gillberg, M. Kokosar, A. Perfilyev, A. L. Jacobsen, S. W. Jorgensen, C. Brons, P. A. Jansson, K. F. Eriksson, O. Pedersen, T. Hansen, L. Groop, E. Stener-Victorin, A. Vaag, E. Nilsson, C. Ling, *Hum. Mol. Genet.* **2015**, *24*, 3792.
[53] E. Grundberg, E. Meduri, J. K. Sandling, A. K. Hedman, S. Keildson, A. Buil, S. Busche, W. Yuan, J. Nisbet, M. Sekowska, A. Wilk, A. Barrett, K. S. Small, B. Ge, M. Caron, S. Y. Shin, C. Multiple Tissue Human Expression Resource, M. Lathrop, E. T. Dermitzakis, M. I. McCarthy, T. D. Spector, J. T. Bell, P. Deloukas, *Am. J. Hum. Genet.* **2013**, *93*, 876.
[54] S. Sayols-Baixeras, I. Subirana, A. Fernandez-Sanles, M. Senti, C. Lluis-Ganella, J. Marrugat, R. Elosua, *Epigenetics* **2017**, *12*, 909.
[55] M. M. Mendelson, R. E. Marioni, R. Joehanes, C. Liu, A. K. Hedman, S. Aslibekyan, E. W. Demerath, W. Guan, D. Zhi, C. Yao, T. Huan, C. Willinger, B. Chen, P. Courchesne, M. Multhaup, M. R. Irvin, A. Cohain, E. E. Schadt, M. L. Grove, J. Bressler, K. North, J. Sundstrom, S. Gustafsson, S. Shah, A. F. McRae, S. E. Harris, J. Gibson, P. Redmond, J. Corley, L. Murphy, et al., *PLoS Med.* **2017**, *14*, e1002215.

[56] T. Dayeh, P. Volkov, S. Salo, E. Hall, E. Nilsson, A. H. Olsson, C. L. Kirkpatrick, C. B. Wollheim, L. Eliasson, T. Ronn, K. Bacos, C. Ling, *PLoS Genet.* **2014**, *10*, e1004160.
[57] B. Hidalgo, M. R. Irvin, J. Sha, D. Zhi, S. Aslibekyan, D. Absher, H. K. Tiwari, E. K. Kabagambe, J. M. Ordovas, D. K. Arnett, *Diabetes* **2014**, *63*, 801.
[58] A. Abderrahmani, L. Yengo, R. Caiazzo, M. Canouil, S. Cauchi, V. Raverdy, V. Plaisance, V. Pawlowski, S. Lobbens, J. Maillet, L. Rolland, R. Boutry, G. Queniat, M. Kwapich, M. Tenenbaum, J. Bricambert, S. Saussenthaler, E. Anthony, P. Jha, J. Derop, O. Sand, I. Rabearivelo, A. Leloire, M. Pigeyre, M. Daujat-Chavanieu, S. Gerbal-Chaloin, T. Dayeh, G. Lassailly, P. Mathurin, B. Staels, et al., *Diabetes* **2018**, *67*, 1310.
[59] R. Ribel-Madsen, M. F. Fraga, S. Jacobsen, J. Bork-Jensen, E. Lara, V. Calvanese, A. F. Fernandez, M. Friedrichsen, B. F. Vind, K. Hojlund, H. Beck-Nielsen, M. Esteller, A. Vaag, P. Poulsen, *PLoS One* **2012**, *7*, e51302.
[60] E. Nilsson, P. A. Jansson, A. Perfilyev, P. Volkov, M. Pedersen, M. K. Svensson, P. Poulsen, R. Ribel-Madsen, N. L. Pedersen, P. Almgren, J. Fadista, T. Ronn, B. Klarlund Pedersen, C. Scheele, A. Vaag, C. Ling, *Diabetes* **2014**, *63*, 2962.
[61] P. Volkov, K. Bacos, J. K. Ofori, J. L. Esguerra, L. Eliasson, T. Ronn, C. Ling, *Diabetes* **2017**, *66*, 1074.
[62] J. C. Chambers, M. Loh, B. Lehne, A. Drong, J. Kriebel, V. Motta, S. Wahl, H. R. Elliott, F. Rota, W. R. Scott, W. Zhang, S. T. Tan, G. Campanella, M. Chadeau-Hyam, L. Yengo, R. C. Richmond, M. Adamowicz-Brice, U. Afzal, K. Bozaoglu, Z. Y. Mok, H. K. Ng, F. Pattou, H. Prokisch, M. A. Rozario, L. Tarantini, J. Abbott, M. Ala-Korpela, B. Albetti, O. Ammerpohl, et al., *Lancet Diabetes Endocrinol.* **2015**, *3*, 526.
[63] A. Cardona, F. R. Day, J. R. B. Perry, M. Loh, A. Y. Chu, B. Lehne, D. S. Paul, L. A. Lotta, I. D. Stewart, N. D. Kerrison, R. A. Scott, K. T. Khaw, N. G. Forouhi, C. Langenberg, C. Liu, M. M. Mendelson, D. Levy, S. Beck, R. D. Leslie, J. Dupuis, J. B. Meigs, J. S. Kooner, J. Pihlajamaki, A. Vaag, A. Perfilyev, C. Ling, M. F. Hivert, J. C. Chambers, N. J. Wareham, K. K. Ong, *Diabetes* **2019**, *68*, 2315.
[64] F. Paneni, S. Costantino, R. Battista, L. Castello, G. Capretti, S. Chiandotto, G. Scavone, A. Villano, D. Pitocco, G. Lanza, M. Volpe, T. F. Luscher, F. Cosentino, *Circ. Cardiovasc. Genet.* **2015**, *8*, 150.
[65] J. Li, X. Zhu, K. Yu, H. Jiang, Y. Zhang, S. Deng, L. Cheng, X. Liu, J. Zhong, X. Zhang, M. He, W. Chen, J. Yuan, M. Gao, Y. Bai, X. Han, B. Liu, X. Luo, W. Mei, X. He, S. Sun, L. Zhang, H. Zeng, H. Sun, C. Liu, Y. Guo, B. Zhang, Z. Zhang, J. Huang, A. Pan, et al., *Circ. Res.* **2017**, *120*, 1754.
[66] D. Li, J. Yan, Y. Yuan, C. Wang, J. Wu, Q. Chen, J. Song, J. Wang, *Int. J. Mol. Med.* **2018**, *41*, 220.
[67] M. Rask-Andersen, D. Martinsson, M. Ahsan, S. Enroth, W. E. Ek, U. Gyllensten, A. Johansson, *Hum. Mol. Genet.* **2016**, *25*, 4739.
[68] C. K. Ward-Caviness, G. Agha, B. H. Chen, L. Pfeiffer, R. Wilson, P. Wolf, C. Gieger, J. Schwartz, P. S. Vokonas, L. Hou, A. C. Just, S. Bandinelli, D. G. Hernandez, A. B. Singleton, H. Prokisch, T. Meitinger, G. Kastenmuller, L. Ferrucci, A. A. Baccarelli, M. Waldenberger, A. Peters, *Clin. Epigenetics* **2018**, *10*, 161.
[69] Y. Xia, A. Brewer, J. T. Bell, *Clin. Epigenetics* **2021**, *13*, 186.
[70] K. E. Westerman, J. M. Ordovas, *Curr. Opin. Clin. Nutr. Metab. Care* **2020**, *23*, 236.
[71] G. Agha, M. M. Mendelson, C. K. Ward-Caviness, R. Joehanes, T. Huan, R. Gondalia, E. Salfati, J. A. Brody, G. Fiorito, J. Bressler, B. H. Chen, S. Ligthart, S. Guarrera, E. Colicino, A. C. Just, S. Wahl, C. Gieger, A. R. Vandiver, T. Tanaka, D. G. Hernandez, L. C. Pilling, A. B. Singleton, C. Sacerdote, V. Krogh, S. Panico, R. Tumino, Y. Li, G. Zhang, J. D. Stewart, J. S. Floyd, et al., *Circulation* **2019**, *140*, 645.
[72] M. Stumvoll, H. Haring, *Diabetes* **2002**, *51*, 2341.
[73] D. Altshuler, J. N. Hirschhorn, M. Klannemark, C. M. Lindgren, M. C. Vohl, J. Nemesh, C. R. Lane, S. F. Schaffner, S. Bolk, C. Brewer, T. Tuomi, D. Gaudet, T. J. Hudson, M. Daly, L. Groop, E. S. Lander, *Nat. Genet.* **2000**, *26*, 76.
[74] P. M. Ueland, S. Hustad, J. Schneede, H. Refsum, S. E. Vollset, *Trends Pharmacol. Sci.* **2001**, *22*, 195.
[75] A. M. Minihane, *Nutrients* **2016**, *8*, 123.
[76] G. Horigan, H. McNulty, M. Ward, J. J. Strain, J. Purvis, J. M. Scott, *J. Hypertens.* **2010**, *28*, 478.
[77] M. J. Caslake, E. A. Miles, B. M. Kofler, G. Lietz, P. Curtis, C. K. Armah, A. C. Kimber, J. P. Grew, L. Farrell, J. Stannard, F. L. Napper, A. Sala-Vila, A. L. West, J. C. Mathers, C. Packard, C. M. Williams, P. C. Calder, A. M. Minihane, *Am. J. Clin. Nutr.* **2008**, *88*, 618.
[78] S. Bayer, V. Winkler, H. Hauner, C. Holzapfel, *Nutrients* **2020**, *12*, 2891.
[79] U. Gorman, J. C. Mathers, K. A. Grimaldi, J. Ahlgren, K. Nordstrom, *Genes Nutr.* **2013**, *8*, 373.
[80] R. Noroozi, S. Ghafouri-Fard, A. Pisarek, J. Rudnicka, M. Spolnicka, W. Branicki, M. Taheri, E. Pospiech, *Ageing Res. Rev.* **2021**, *68*, 101314.
[81] C. F. Marsaux, C. Celis-Morales, R. Fallaize, A. L. Macready, S. Kolossa, C. Woolhead, C. B. O'Donovan, H. Forster, S. Navas-Carretero, R. San-Cristobal, C. P. Lambrinou, G. Moschonis, A. Surwillo, M. Godlewska, A. Goris, J. Hoonhout, C. A. Drevon, Y. Manios, I. Traczyk, M. C. Walsh, E. R. Gibney, L. Brennan, J. A. Martinez, J. A. Lovegrove, M. J. Gibney, H. Daniel, J. C. Mathers, W. H. Saris, *J Med Internet Res* **2015**, *17*, e231.
[82] R. Poinhos, I. A. van der Lans, A. Rankin, A. R. Fischer, B. Bunting, S. Kuznesof, B. Stewart-Knox, L. J. Frewer, *PLoS One* **2014**, *9*, e110614.
[83] A. Berezowska, A. R. Fischer, A. Ronteltap, I. A. van der Lans, H. C. van Trijp, *Genes Nutr.* **2015**, *10*, 42.
[84] C. Celis-Morales, K. M. Livingstone, C. F. Marsaux, A. L. Macready, R. Fallaize, C. B. O'Donovan, C. Woolhead, H. Forster, M. C. Walsh, S. Navas-Carretero, R. San-Cristobal, L. Tsirigoti, C. P. Lambrinou, C. Mavrogianni, G. Moschonis, S. Kolossa, J. Hallmann, M. Godlewska, A. Surwillo, I. Traczyk, C. A. Drevon, J. Bouwman, B. van Ommen, K. Grimaldi, L. D. Parnell, J. N. Matthews, Y. Manios, H. Daniel, J. A. Martinez, J. A. Lovegrove, et al., *Int. J. Epidemiol.* **2017**, *46*, 578.
[85] D. E. Nielsen, A. El-Sohemy, *PLoS One* **2014**, *9*, e112665.
[86] R. Jinnette, A. Narita, B. Manning, S. A. McNaughton, J. C. Mathers, K. M. Livingstone, *Adv. Nutr.* **2021**, *12*, 657.
[87] J. G. Godino, E. M. van Sluijs, T. M. Marteau, S. Sutton, S. J. Sharp, S. J. Griffin, *PLoS Med.* **2016**, *13*, e1002185.
[88] S. X. Li, Z. Ye, K. Whelan, H. Truby, *Br. J. Nutr.* **2016**, *116*, 924.
[89] B. P. Turnwald, J. P. Goyer, D. Z. Boles, A. Silder, S. L. Delp, A. J. Crum, *Nat. Hum. Behav.* **2019**, *3*, 48.
[90] S. Bayer, T. Drabsch, G. Schauberger, H. Hauner, C. Holzapfel, *Public Health Nutr.* **2021**, *24*, 1916.
[91] D. Zeevi, T. Korem, N. Zmora, D. Israeli, D. Rothschild, A. Weinberger, O. Ben-Yacov, D. Lador, T. Avnit-Sagi, M. Lotan-Pompan, J. Suez, J. A. Mahdi, E. Matot, G. Malka, N. Kosower, M. Rein, G. Zilberman-Schapira, L. Dohnalova, M. Pevsner-Fischer, R. Bikovsky, Z. Halpern, E. Elinav, E. Segal, *Cell* **2015**, *163*, 1079.
[92] S. E. Berry, A. M. Valdes, D. A. Drew, F. Asnicar, M. Mazidi, J. Wolf, J. Capdevila, G. Hadjigeorgiou, R. Davies, H. Al Khatib, C. Bonnett, S. Ganesh, E. Bakker, D. Hart, M. Mangino, J. Merino, I. Linenberg, P. Wyatt, J. M. Ordovas, C. D. Gardner, L. M. Delahanty, A. T. Chan, N. Segata, P. W. Franks, T. D. Spector, *Nat. Med.* **2020**, *26*, 964.
[93] A. Braakhuis, C. R. Monnard, A. Ellis, M. Rozga, *J. Acad. Nutr. Diet.* **2021**, *121*, 545.