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The effect of genetic, metabolic and anthropometric factors on energy expenditure and dietary intake

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“the apparently modest effect of common variation on most human diseases […] probably reflects the efficiency of natural selection” (*David B. Goldstein*)

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Abstract

Obesity is one of the main challenges in health care and leads to impaired insulin sensitivity (IS) and thus to an increased risk for type 2 diabetes mellitus. Reasons for the development of obesity, such as a positive energy balance caused by physical inactivity, an altered energy metabolism, or a reduced activity of the sympathetic nervous system, are discussed. Therefore, the associations between genetic, metabolic or anthropometric parameters and energy expenditure and dietary intake were examined in this thesis. A systematic review of articles investigating the associations between single nucleotide polymorphisms (SNPs) and energy, carbohydrate and fat intakes was carried out as a first step. Associations between genetic and metabolic factors and resting metabolic rate (RMR) were subsequently studied. Thereby, the effect of C-reactive protein (CRP) on the association between RMR and IS was investigated in a cohort study. Due to the association between brown adipose tissue (BAT) and RMR, magnetic resonance imaging (MRI) was performed in a subgroup of persons participating in the cohort study to evaluate the quantification of the proton density fat fraction (PDFF) as a rough marker of BAT. Potential associations between SNPs and energy expenditure (EE) are studied in another systematic literature search.

The first systematic review identified 39 articles with inconsistent findings for the association between SNPs and dietary intake. Furthermore, no significant evidence for the mediator role of CRP within the association between RMR and IS was found in the cohort study. Regarding the results of the subgroup MRI analyses, the supraclavicular PDFF was significantly smaller than gluteal PDFF. Moreover, significant associations were found between PDFF and anthropometric markers. Results of the second systematic review did not provide evidence for consistent associations between SNPs and EE. In summary, there is no consistent evidence for correlations between SNPs and energy, carbohydrate and fat intakes or SNPs and EE. Furthermore, in the young and healthy cohort, no evidence could be found for CRP as mediator within the RMR-IS association. However, this result may be limited by the low specificity of CRP as an inflammatory marker. The significant results of the PDFF subgroup analyses suggest that PDFF serves as a surrogate marker for BAT, which may improve the future characterization of obesity. However, further studies are needed to develop personalized gene based dietary recommendations and to improve obesity prevention by validating related parameters.

Zusammenfassung

Adipositas ist eines der Hauptthemen im Gesundheitswesen und führt unter anderem zu einer beeinträchtigten Insulinsensitivität (IS) und damit zu einem erhöhten Risiko für Typ-2-Diabetes mellitus. Gründe für die Entstehung der Adipositas, wie eine positive Energiebilanz, verursacht durch eine körperliche Inaktivität, einem veränderten Energiestoffwechsel oder einer reduzierten Aktivität des sympathischen Nervensystems, werden diskutiert. Daher war es das Ziel dieser Dissertation, die Zusammenhänge zwischen genetischen, metabolischen oder anthropometrischen Parametern und dem Energieverbrauch und der Nahrungsaufnahme zu untersuchen. Eine systematische Übersichtsarbeit, zu Assoziationen zwischen Einzel-Nukleotid-Polymorphismen (SNPs) und der Energie-, Kohlenhydrat- und Fettzufuhr, wurde durchgeführt. Assoziationen zwischen genetischen und metabolischen Faktoren und dem Ruheumsatz (RMR) wurden betrachtet. Zunächst wurde der Effekt des C-reaktiven Proteins (CRP) auf die Assoziation zwischen RMR und IS in einer Kohortenstudie untersucht. Aufgrund der Assoziation zwischen braunem Fettgewebe (BAT) und dem RMR, wurde eine Magnetresonanztomographie (MRT) zur Quantifizierung der Protonendichte-Fettfraktion (PDFF) als grober Marker von BAT in einer Untergruppe der Kohortenstudie durchgeführt. Der Zusammenhang zwischen SNPs und dem Energieverbrauch, wurde in einer systematischen Literaturrecherche erörtert. Die erste systematische Übersichtsarbeit identifizierte 39 Artikel mit inkonsistenten Ergebnissen zur Assoziation zwischen SNPs und der Energiezufuhr. Zudem wurde keine signifikante Evidenz für die Mediatorrolle des CRP innerhalb der Assoziation zwischen RMR und IS in der Kohortenstudie gefunden. Was die Ergebnisse der Subgruppen-MRT-Analysen betrifft, so war die supraklavikuläre PDFF signifikant niedriger als die gluteale PDFF. Es wurden signifikante Assoziationen zwischen der PDFF und anthropometrischen Markern gefunden. Die Ergebnisse der Übersichtsarbeit gaben keine konsistenten Hinweise für signifikante Assoziationen zwischen SNPs und dem Energieverbrauch. Zusammenfassend lässt sich sagen, dass es keine Hinweise für signifikante Zusammenhänge zwischen publizierten SNPs und Energiezufuhr beziehungsweise -verbrauch gibt. Des Weiteren konnte in der jungen, gesunden Kohorte keine Evidenz für CRP als Mediator in der RMR-IS-Assoziation gefunden werden. Das Ergebnis könnte jedoch durch die geringe Spezifität von CRP als Entzündungsmarker eingeschränkt sein. Die signifikanten Ergebnisse der MRT-Analysen deuten darauf hin, dass PDFF als grober Marker für BAT geeignet ist, was die zukünftige Charakterisierung der Adipositas verbessern könnte. Es sind weitere Studien erforderlich, um personalisierte genbasierte Ernährungsempfehlungen zu erarbeiten und die Prävention von Adipositas durch die Validierung damit verbundener Parameter zu verbessern.

Abbreviations

ADRB3	beta 3 adrenergic
AT	adipose tissue
BAT	brown adipose tissue
BDNF	brain-derived neurotrophic factor
BIA	bioimpedance analysis
BMI	body mass index
CCK	cholecystokinin
CO_2	carbon dioxide
DNA	deoxyribonucleic acid
EE	energy expenditure
FFM	fat-free mass
FM	fat mass
FTO	fat mass and obesity associated
GWAS	genome-wide association study
H_2	deuterium
HOMA-IR	homeostasis model assessment for insulin resistance
(hs-)CRP	(high sensitive) C-reactive protein
IS	insulin sensitivity
LD	linkage disequilibrium
MC4R	melanocortin-4 receptor
MRI	magnetic resonance imaging
MSOT	multi-spectral optoacoustic tomography
O^{18}	oxygen-18
PDFF	proton-density fat fraction

PET-CT	positron-emission tomography and computed tomography
PICOS	participants, intervention, comparator, outcomes, study design
PPARG	peroxisome-proliferator-activated receptor gamma
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RMR	resting metabolic rate
RQ	respiratory quotient
SAT	subcutaneous adipose tissue
SEC16B	sec16 homolog b
SNP	single nucleotide polymorphism
SNS	sympathetic nervous system
SOP	standard operating procedure
T2DM	type 2 diabetes mellitus
TEE	total energy expenditure
TMEM18	transmembrane protein 18
UCP1/2/3	uncoupling protein 1/2/3
VAT	visceral adipose tissue
VCO_2	volume carbon dioxide production
VO_2	volume oxygen consumption
WAT	white adipose tissue
WC	waist circumference
WHO	World Health Organization

1 Introduction

1.1 Overweight and Obesity – A worldwide health problem

Worldwide, obesity is one of the major challenges in health care and is referred to as a worldwide health problem (NCD Risk Factor Collaboration, 2016). According to the World Health Organization (WHO), globally in 2014, 39% of all adults were overweight (Body mass index (BMI) ≥ 25.0 kilogram/meter² (kg/m²)), and 13% were obese (BMI ≥ 30.0 kg/m²) (WHO, 2014). Since 1980, the obesity prevalence increased and has more than doubled (Afshin et al., 2017; Gregg, & Shaw, 2017). Various factors are involved in the development of obesity. From a biological point of view, the major cause is attributed to a long-term positive energy balance explained by a sedentary lifestyle and an increased and energy-rich food consumption (World Health Organization, 2000).

Consequently, obesity can lead to metabolic disorders such as an increased risk for metabolic syndrome, an impaired insulin sensitivity (IS) and an impairment of glycemic control and thus to type 2 diabetes mellitus (T2DM), cardiovascular disease, sleep apnea, or inflammatory disorders (Dixon, 2010; Hossain et al., 2007; Hubert et al., 1983; NHLBI, 1998; Singh et al., 2013; Wormser et al., 2011). Obesity is mainly defined by BMI. According to the WHO and the National Institute of Health, normal weight is represented by a BMI of 18.5 - 24.9 kg/m², overweight by a BMI of 25.0 – 29.9 kg/m² and obesity by a BMI equal to or greater than 30.0 kg/m². Waist circumference (WC) is another factor defining obesity (NHLBI, 1998). According to the European guidelines of obesity, a WC over 88 cm for women or over 102 cm for men indicates abdominal obesity (Yumuk et al., 2015).

Some studies showed that the variability of BMI within a population might be explained by environmental, biological but also by genetic factors (Swinburn et al., 2011). For this reason, research intensively focuses on potential associations between biological mechanisms such as energy metabolism and genetic factors, and aims to identify causal genetic variants.

1.2 Genetic susceptibility of obesity

Two genetic forms of obesity can be distinguished: monogenic and polygenic obesity (Apalasamy, & Mohamed, 2015). The rare monogenic form is explained by a mutation in one single gene which is responsible for the development of obesity (S Farooqi, & O'Rahilly, 2006). For instance, a mutation within the leptin gene that leads to extreme obesity in childhood is the most popular monogenic form (Montague et al., 1997). The most common form is the polygenic obesity, where the interaction of many genes and the obesogenic

environment play a major role. For this reason, many candidate genes were studied for potential associations with obesity.

1.2.1 Identification of single obesity-related genetic factors

Up to date, there are indications that various genetic factors, especially single nucleotide polymorphisms (SNPs), are involved in the development of obesity (Maes et al., 1997). The first studies which assumed a genetic background of obesity have been conducted in adopted children and twins (Stunkard et al., 1986; Wardle et al., 2008). Only associations between body weight of adopted children and body weight of their biological parents were observed (Stunkard et al., 1986). During an overfeeding experiment in twin studies, the difference of body weight changes between and within twin pairs was investigated. Within twin pairs weight changes were more similar than between twin pairs (Bouchard, & Tremblay, 1997). In hypothesis-driven candidate gene studies on unrelated individuals, an association between specific genetic loci and body weight was examined. One example for a candidate gene, is the leptin locus, which was mainly studied due to its monogenic obesity coincidence (Mammes et al., 1998). Furthermore, uncoupling protein genes, which code for uncoupling proteins playing a major role in energy metabolism, and the beta 3 adrenergic (*ADRB3*) gene, which is ascribed to lipolysis and fat storage, were studied for associations with body weight (Fumeron et al., 1996). A significantly negative association between uncoupling protein 1 (*UCP1*) gene and body weight and no significant association between the *ADRB3* locus and weight change have been described. In addition, the peroxisome-proliferator-activated receptor gamma (*PPARG*) locus was described for significantly negative associations with BMI and improved IS (Deeb et al., 1998).

1.2.2 Genome-wide association studies and the fat mass and obesity associated locus

Beside the hypothesis-driven candidate gene studies, hypothesis-free genome-wide association studies (GWAS) revolutionized the research field of obesity. In this type of studies, in which high-resolution deoxyribonucleic acid (DNA) chips are used, there is no focus on biologically plausible gene variants.

To date, GWAS identified more than 100 loci which are linked to body weight or body weight regulation traits such as energy metabolism (Hägg et al., 2015; Locke et al., 2015; Thorleifsson et al., 2009; Willer et al., 2009). Altogether, the effect size of SNPs on anthropometric factors is rather small. The genetic factors identified by GWAS explain 2.7% of the variance in BMI (Locke et al., 2015). The five genetic loci with the strongest per allele effect on body weight were: the fat mass and obesity associated (*FTO*) gene, the

transmembrane protein 18 (*TMEM18*) gene, the melanocortin-4 receptor (*MC4R*) gene, the SEC16 homolog B (*SEC16B*) gene and the brain-derived neurotrophic factor (*BDNF*) gene (Speliotes et al., 2010) (Figure 1).

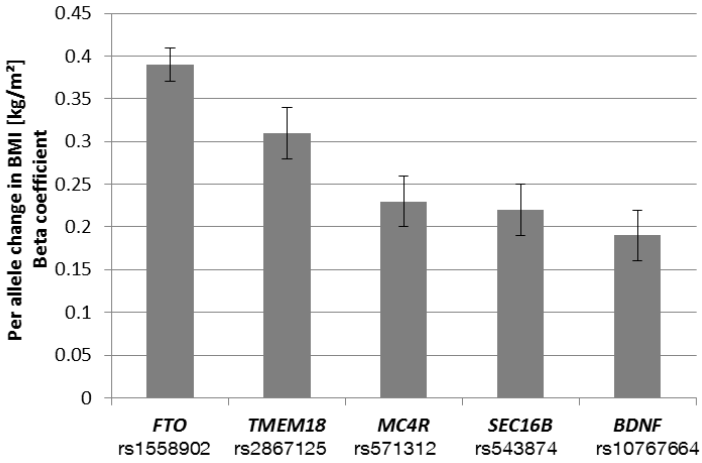

Figure 1: The five genetic loci with the strongest per allele effect on BMI from GWAS. Data presenting beta coefficients ± standard errors (Speliotes et al., 2010). *BDNF*, brain-derived neurotrophic factor; BMI, Body Mass Index; *FTO*, fat mass and obesity associated gene; GWAS, genome-wide association study; *MC4R*, melanocortin-4 receptor gene; *SEC16B*, SEC16 homolog B gene; *TMEM18*, transmembrane protein 18 gene.

Up to now and among all identified genes, SNPs at the *FTO* locus has the strongest per risk allele effect on BMI. For instance, the *FTO* SNP rs1558902 has an effect size of 0.39 kg/m² per risk allele (Speliotes et al., 2010). In 2007, a GWAS originally focused on T2DM found an association between the *FTO* SNP rs9939609 and a significantly increased BMI (Frayling et al., 2007). In adults, homozygous carriers of the risk allele weigh up to three kilograms more than homozygous carriers of the non-risk allele. The association between *FTO* SNPs and body weight was confirmed by a further study of French individuals (Dina et al., 2007), but not in a study of African Americans (Scuteri et al., 2007). Therefore, an ethnicity-dependent effect might be assumed. The *FTO* gene belongs to the $Fe2^{+}$ and 2-oxoglutarate (2-OG)-dependent dioxygenase family (Gerken et al., 2007) which is involved in cellular processes such as DNA repair, fatty acid metabolism, and posttranslational modifications (Ozer, & Bruick, 2007). Dina et al. assumed that the role of the *FTO* gene in body weight regulation may be based on the expression in the hypothalamic-pituitary-adrenalin axis (Dina et al., 2007). Further studies showed that the *FTO* locus plays a role in body weight, food intake and growth retardation in mice and thus assumed a broader biological function of the *FTO* locus (Yeo, & O'Rahilly, 2012). In 2015, Claussnitzer et al. identified the SNP rs1421085 as the main causal variant within the *FTO* locus (Claussnitzer et al., 2015). The risk allele of the *FTO* SNP rs1421085 promotes the expression of iroquois homeobox 3 and 5 in the early differentiation of adipocytes. This leads to a shift from browning to whitening and thus to a

change from energy-dissolving beige adipocytes to energy-storing white adipocytes resulting in an increased lipid storage.

The *TMEM18* gene is expressed throughout the body, but mainly in the hypothalamus, which is known to be involved in energy metabolism and food intake (Willer et al., 2009). In studies on mice and Drosophila melanogaster, *TMEM18* was assumed to affect body weight regulation, food intake and obesity development (Larder et al., 2017; Wiemerslage et al., 2016). Speliotes et al. described a BMI change of 0.31 kg/m² per risk allele (Figure 1) and thus 0.15% of the BMI variance could be explained (Speliotes et al., 2010).

Within the *MC4R* locus a per risk allele effect of 0.23 kg/m² on BMI (Figure 1) was described and thus further 0.10% of BMI variance might be explained (Speliotes et al., 2010). The MC4R is a G-protein receptor which is expressed in the hypothalamus and is known to be associated with food regulation (Cone, 2005). Aden et al. showed that due to the expression of the *MC4R* in the hypothalamus, signaling of this receptor in the brain stem influences meal size (Adan et al., 2006). Mutations of this gene lead to an early onset of obesity, impaired gluconeogenesis and hyperinsulinemia in mice (Huszar et al., 1997), and to obesity in humans (Hinney et al., 2013; Vaisse et al., 1998). A *MC4R* deficiency leads to the most common form of monogenic obesity (IS Farooqi et al., 2003). Loos et al. replicated the significantly positive association between the *MC4R* SNP rs17782313 and BMI (Loos et al., 2008).

The SEC16B plays a major role in the organization of intracellular proteins from the endoplasmic reticulum to the Golgi apparatus and in the biogenesis of peroxisomes (Budnik et al., 2011; Yonekawa et al., 2011). A significant association between *SEC16B* SNPs and an increased BMI or body weight has been shown (Locke et al., 2015; Thorleifsson et al., 2009). Speliotes et al. described a per risk allele change in BMI of 0.22 kg/m² (Figure 1) and further 0.07% of BMI variance could be explained (Speliotes et al., 2010).

BDNF is mostly expressed in the brain and is therefore involved in neuronal regulatory pathways of appetite and energy balance (Unger et al., 2007). In mice studies, deficiencies in the *BDNF* locus lead to hyperphagia and excessive weight gain after a high-fat diet (Xu et al., 2003). In humans, *BDNF* is involved in body weight regulation. In addition, haplotypes within the gene were shown to be associated with eating behavior (Mercader et al., 2007). As shown in Figure 1, Speliotes et al. described a per risk allele change in BMI of 0.19 kg/m² for *BDNF* SNPs (Speliotes et al., 2010).

1.3 Energy balance – determined by energy intake and expenditure

Aside the genetic background, obesity is caused by a long-term energy imbalance between energy intake and energy expenditure (EE). Especially reduced fat oxidation, energy metabolism, less spontaneous physical activity or reduced activity of the sympathetic nervous system (SNS) are factors for weight gain (Galgani, & Ravussin, 2008). In order to understand these complex mechanisms, associations between genetic, metabolic or anthropometric parameters and energy intake and expenditure are examined.

1.3.1 Energy intake

1.3.1.1 Hormones and energy intake

From a biological view, energy intake is regulated by internal and external factors that directly affect brain or other organs. These factors are mainly hormones that act on organs involved in the storage of nutrients such as blood, liver or adipose tissue (AT) (Woods, & D'Alessio, 2008). The best-known hormones are cholecystokinin (CCK), insulin, leptin and ghrelin. The hormone CCK serves as a satiety hormone, which is secreted in the gastrointestinal tract after ingestion of fat- or protein-containing food and activates sensory nerves in the duodenum. The secretion of CCK affects various gastrointestinal functions, such as gastric emptying and gastric acid release, or stimulation of the pancreas and the gallbladder (Raybould, 2007). Two further hormones which are mainly involved in food regulation are insulin and leptin. The secretion of insulin and leptin is dependent on the amount of body fat mass (FM) which is why they are also called adiposity signals. Studies have shown that insulin is secreted in basal amounts and after a meal in an oscillating manner. However, the balance between basal and meal-induced insulin levels is strongly correlated with FM (Polonsky et al., 1988; Rosenbaum et al., 1996). The other hormone, Leptin, is released from the AT, reflects the nutritional status, has similar functions to insulin, and is considered as a satiety signal (Lam, & Ravussin, 2016). Leptin regulates neuropeptide expression in the hypothalamic arcuate nucleus which in turn transmits further synaptic impulses influencing the catabolic and anabolic pathways (Crowley, 2008). Another regulator of food intake and body weight is the stomach-derived peptide ghrelin. Ghrelin is mainly secreted by the gastrointestinal tract after food intake and affects intestinal activity, blood circulation and hormones inside and outside the blood-brain barrier. The effect of ghrelin, especially in the hypothalamus, contributes to the control of food intake and subsequently to glucose, lipid and energy metabolism (Wiedmer et al., 2007). There are also other molecules, such as the peptide tyrosine-tyrosine, enterostatin, glucagon-like peptide-

1, or amylin which play an important role in weight regulation and food intake, but are not described here (Woods, & D'Alessio, 2008).

1.3.1.2 Genetic factors and energy intake

Another aspect is the possible effect of genetic factors on dietary intake. Various studies investigated potential associations between genetic factors and food intake with inconsistent findings (Corella et al., 2009; Labayen et al., 2016; Merino et al., 2018; Merritt et al., 2018). In a study on children, Cecil et al. described a significantly positive association between the *FTO* SNP rs9939609 and energy intake (Cecil et al., 2008). In contrast, in the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) cross-sectional study, energy intake was similar across *FTO* genotypes (Labayen et al., 2016). In large genome-wide meta-analyses, significant associations between the *FTO* SNP rs1421085 and increased protein intake were shown (Chu et al., 2013; Tanaka et al., 2013). In the same analyses, a significantly positive association between the fibroblast growth factor 21 gene and carbohydrate intake have been described. Beside the association between genetic factors and macronutrient intake, a significant interaction between genetic factors and the intake of sugar-sweetened beverages on body weight has been described (Qi et al., 2012). However, these epidemiological studies could not demonstrate consistent associations between genetic factors and dietary intake, and replication of the results was lacking.

Intervention studies investigated the interaction of genetic factors and specific meals on body weight. In the European Diet, Obesity and Genes (DiOGenes) study, gene-diet interactions on weight change were focused. However, no SNP-diet interactions on body weight were identified (LH Larsen et al., 2012; SC Larsen et al., 2016). The Nutrient-Gene Interactions in Human Obesity (NUGENOB) trial investigated the effects of a panel of SNPs on dietary induced weight change and aimed to figure out whether these effects are dependent on the fat or carbohydrate content in an energy-restricted diet (Sorensen et al., 2006). Results could not show evidence for a SNP-diet interaction on the clinical outcome. The recently published Diet Intervention Examining The Factors Interacting with Treatment Success (DIETFITS) randomized clinical trial examined whether a genotype pattern plays a role in the success of body weight change. Participants received a healthy low carb or low fat diet. Results indicated a similar weight change in both diet groups. The weight loss after twelve months was independent of the genetic setting of a person (Gardner et al., 2018).

In the clinical intervention study, Food4Me, participants received a personalized dietary recommendation based on the information of their phenotypic and genetic profile. In comparison to the control group, which has received standardized dietary

recommendations, the intervention groups had a higher weight change. However, in these intervention groups, no clinical evidence of a positive effect of a gene based dietary recommendation on body weight change was shown (Celis-Morales et al., 2017b). Another prospective study investigated the effect of a gene based diet on weight change. The participants were assigned to a standard therapy or a specific diet based on the results of a commercially available genetic test. Again, results were similar between groups and independent of the gene based dietary recommendation (Frankwich et al., 2015).

Up to date, the genetic loci used for gene based dietary recommendations are mainly based on biological plausibility as well as on findings from epidemiological studies. These epidemiological studies and further intervention studies could not show significant evidence for the gene-diet interactions as well as the effect of gene based dietary recommendations. Therefore, it might be assumed that a personalized dietary recommendation is still in a premature state and the information on the genetic profile is, up to date, clinically irrelevant.

1.3.2 Energy expenditure

In addition to energy intake, studies on the regulation of EE and its influencing factors can contribute to further explanations of biological mechanisms and the development of obesity.

1.3.2.1 Components of EE

The total energy expenditure (TEE) consists of three components (Figure 2):

- the basal or resting metabolic rate (RMR)
- the thermic effect of food
- the caloric needs by physical activity

Thereby, RMR accounts for 60-70% of TEE and is further divided into sleep metabolism and additional EE of awakening without physical activity (Goran, 2000; Ravussin, & Bogardus, 1992). The analysis of RMR is a fundamental marker for obesity treatment and provides information on the general EE of a person, as energy cost by physical activity is variable and differs between sedentary and active individuals (Levine, 2004). RMR is defined as the minimum energy requirement of the human body to obtain essential functions of the body at complete rest such as pulmonary and cardiovascular functions, metabolism, brain and central nerve processes as well as the electrolyte gradients and maintenance of body temperature (Poehlman et al., 1997).

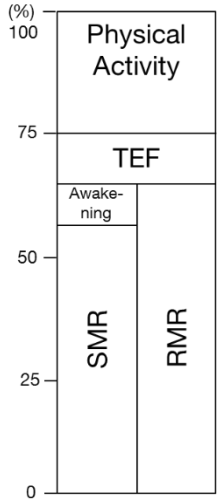

Figure 2: Components of EE according to Lam and Ravussin (Lam, & Ravussin, 2017). RMR takes 60-70% of TEE. Thereby, RMR is divided into SMR and the energy required for awakening. TEF accounts for 10% of TEE. Further EE is ascribed to physical activity.
EE, energy expenditure; RMR, resting metabolic rate; SMR, sleeping metabolic rate; TEE, total energy expenditure; TEF, thermic effect of food.

1.3.2.2 Measurement methods

EE can be determined by different methods. The simplest method, most commonly used in clinical practice, is to calculate EE using different equations. The best known equation is that of Harris and Benedict (Harris, & Benedict, 1918) or that of Mifflin (Mifflin et al., 1990). New equations distinguish between different BMI groups in order to be able to provide more precise information on EE (Muller et al., 2004). Nevertheless, the exactness of calculated RMR is uncertain, especially for women with a higher BMI (Marra et al., 2017).

Another promising method is the double labeled water method. The TEE is determined using deuterium (H_2) and labelled oxygen-18 (O^{18}). The methodology refers to the uptake of labeled H_2 and O^{18}, and the dilution of these isotopes in the body. By the difference of the elimination rate, the carbon dioxide (CO_2) production can be calculated and thus EE can be determined. This method has a high accuracy, but is very cost-intensive and requires sophisticated equipment (Goran, 2000; Pinheiro Volp et al., 2011).

Another method is direct calorimetry which analyzes heat emitted by the body, water emitted by respiration and skin, and the gas exchange with the environment. Absorbed water can be registered by thermal-sensors or thermometers. However, for this complex method an isolated chamber is required and the measurements usually take 24h to determine TEE (Blasco Redondo, 2015).

In most studies, EE is determined by indirect calorimetry. This non-invasive and precise method allows the determination of RMR and the breakdown of which energy substrates are metabolized at the time of measurement. The analysis of RMR is based on indirect measurement of heat released when energy substrates are oxidized which is assessed via a respiratory gas analysis over a certain period of time (Lam, & Ravussin, 2016; Pinheiro Volp et al., 2011).

An extended indirect calorimetry is the whole-room respiratory chamber. These chambers enable a continuous measurement of TEE over several days and give the test persons a relatively large number of possibilities for movement. In addition, interactions between fed and fasted states can be observed (Lam, & Ravussin, 2016).

Due to its relatively low cost and high accuracy, non-invasive indirect calorimetry is an indispensable tool that provides insights into the mechanisms by which energy homeostasis is regulated (Lam, & Ravussin, 2017).

1.3.2.3 Variability of RMR

In clinical practice, RMR is used to calculate the energy needs of individuals. However, there is a high variability of the RMR, which can lead to incorrect calculations and thus to incorrect recommendations. Ravussin and Bogardus have shown that RMR is highly variable between individuals (Ravussin, & Bogardus, 1992), but also the intra-individual differences were described (Ravussin et al., 1986).

Variability explained by technical factors

Technical devices influence RMR variability (Blond et al., 2011; Cooper et al., 2009). Beside inter-device variation also intra-device differences exist as has been shown by Ashcraft et al. (Ashcraft, & Frankenfield, 2015). Moreover, the technical differences and the variability due to the measurement method together explain about 4% of the variance in RMR.

Variability explained by environmental factors

Environmental factors such as temperature (van Ooijen et al., 2004), CO_2 content of the air, light, and noise (Compher et al., 2006), are suggested to affect RMR. For this reason, standardized data collection and the use of a standard operating procedure (SOP) are indispensable.

Variability explained by metabolic factors

Beside the technical effects, time dependent differences which were shown between measurements in the morning compared to the afternoon (Haugen et al., 2003), or metabolic factors such as hormones and proteins, play a crucial role in the variability of RMR. As obesity, impaired IS and T2DM are characterized by a low-grade chronic inflammation (Donath, & Shoelson, 2011; Wellen, & Hotamisligil, 2005), studies have shown that inflammatory markers, such as C-reactive protein (CRP) are associated with an increased RMR in severely ill individuals (Hickmann et al., 2014; Utaka et al., 2005). Increased RMR in obese individuals and particularly in persons with T2DM is explained by energy-intensive gluconeogenesis. Piaggi et al. could show that EE is positively associated with fasting plasma glucose levels (Piaggi et al., 2015). Further studies investigated associations

between RMR and IS, mostly measured by the homeostasis model assessment for insulin resistance (HOMA-IR) (Alawad et al., 2013; Bogardus et al., 1986; Bosy-Westphal et al., 2008; Fontvieille et al., 1992; Weyer et al., 1999). Beside this, impaired IS was also shown to be associated with a higher rate of a respiratory quotient (RQ) (Carstens et al., 2013). However, the biological mechanisms behind and the interplay between inflammation, EE, obesity or T2DM, remain unclear. Moreover, increased activity of the SNS including increased heart rate (Saad et al., 1991), body temperature (Munn, 2006), and hormones especially from the thyroid system (Kim, 2008), lead to a higher RMR. The variability of RMR is also dependent on the menstrual cycle of women. Solomon et al. could show a biphasic variation of a decreasing RMR with start of menstruation followed by an increase (Solomon et al., 1982), whereas Henry et al. could not confirm this regularity (Henry et al., 2003). Further investigations in a large cohort are needed for additional information of the mechanisms behind.

Variability explained by anthropometric factors

Many studies have shown that age, sex and body composition have the strongest influence on RMR (Fukagawa et al., 1990; Geisler et al., 2016; Johnstone et al., 2005; Ravussin, & Bogardus, 1989; Webb, 1981). Thereby women have a significant lower RMR than men which might be explained by a higher amount of FM in women. Concerning the ageing effect, RMR decreases 1-2% per life decade which is explained by a reduction of muscle mass and thus fat-free mass (FFM) (Ravussin, & Bogardus, 1989). Other confounders such as physical activity have not yet been fully clarified as some studies could show an increase through exercise and others do not (Speakman, & Selman, 2003).

Body composition and therefore in particular the FFM explains 60-80% of RMR variability (Johnstone et al., 2005). Some studies, therefore, investigated associations between RMR and body composition, especially FM and FFM. Fat distribution and FM have been described for effects on RMR, even if FM has a smaller effect than the metabolically more active FFM (Nelson et al., 1992). However, the metabolic activity of FM explains further 6% of RMR variability (Johnstone et al., 2005). Concerning the fat distribution, Weststrate et al. described a higher RMR in abdominally obese women compared to women with a more gluteal-femoral fat accumulation (Weststrate et al., 1990). Similar results were shown for an association between abdominal fat and RMR (Buffington et al., 1995; Okura et al., 2003).

Thereby, types of FM have to be distinguished between white AT (WAT), beige or “brite” adipocytes, and brown AT (BAT) (Rosen, & Spiegelman, 2014; Wankhade et al., 2016). The largest proportion of the FM is accounted to WAT which is mainly characterized by

unilocular lipid droplets, few mitochondria and by the storage of energy in form of fat accumulation. Beige adipocytes are infiltrated in WAT, have more mitochondria and consist of multilocular lipid droplets. Brown adipocytes are mostly intrascapular, rich in mitochondria, consist of multilocular lipid droplets, are highly vascularized and produce energy in form of heat (Cinti et al., 2001; Lidell et al., 2013; Wankhade et al., 2016). Furthermore, brown adipocytes activate uncoupling proteins which lead to heat generation (Enerback, 2010; Lahesmaa et al., 2014). In several studies, human BAT was discovered in the supraclavicular region of adults (Cypess et al., 2009) and was identified for a thermoregulatory function which responds to a cold environment via increased sympathetic nerve activity (Enerback, 2010). A study by Gerngross et al. could show that the highest mean value of active BAT in patients was 308.1 mL which might be a target for metabolic diseases in future (Gerngross et al., 2017). So far, BAT was identified by using positron-emission tomography and computed tomography (PET-CT) (Cypess et al., 2009; van der Lans et al., 2013; Yoneshiro et al., 2011). Due to the ionizing radiation and need of intravenous injections, alternative imaging methods such as magnetic resonance imaging (MRI) measurements based on chemical shift encoding-based fat quantification techniques have been established. These techniques are non-invasive, free of ionizing radiation, without the need for intravenous injection and clearly show BAT even if inactive (Cypess et al., 2009; Deng et al., 2018; Franssens et al., 2016; Gifford et al., 2016). One imaging possibility of the inactive BAT is the proton-density fat fraction (PDFF), which is defined as the proportion of proton density in fat tissue over the sum of water and fat signal intensities (Reeder et al., 2012). However, up to date little is known about this technique. Further studies investigating the association between PDFF, anthropometric markers and RMR in adults are needed.

Variability explained by genetic factors

As previously mentioned, 60-80% of the variability of RMR can be explained by body composition (Johnstone et al., 2005). The remaining unexplained 30% might be attributed to genetic factors (Bosy-Westphal et al., 2008). A genetic effect on RMR was detected in twin studies (Bouchard et al., 1989; Fontaine et al., 1985; Hewitt et al., 1991). Furthermore, heritability of RMR was described for different ethnicities (Cai et al., 2008; Wang et al., 2010). Based on these findings, associations between candidate genes and RMR were studied in different samples. After the publication of an association between the *FTO* SNP rs1421085 and fat storage, a correlation between the *FTO* locus and RMR was hypothesized. In the Quebec Family Study, the *FTO* SNPs rs17817449 and rs1421085 were significantly associated with RMR (Do et al., 2008). In children, this effect has been confirmed (Cecil et al., 2008). A study on Swedish men observed a significantly higher RMR

for risk allele carriers of the *FTO* SNP rs9939609, but significance disappeared after adjustment for FFM (Berentzen et al., 2008). Nevertheless, Speakman et al. summarized findings of different kind of studies which investigated the impact of the *FTO* gene on energy metabolism and assumed that due to inconsistencies, *FTO* SNPs might not be associated with EE (Speakman, 2015). Beside the *FTO* locus, further candidate gene studies could show significant associations between other gene loci and EE. For instance, in a cohort study, a significantly lower RMR was shown for *ADRB3* homozygous risk allele carriers compared to homozygous non-risk allele carriers even after adjustment for FFM (Walston et al., 2003). In addition, associations were found for SNPs at the fatty-acid binding protein 2 locus and a lower RMR (Takakura et al., 2005). Even if some studies could show a significant association, significance disappeared mostly after adjustments for body composition such as FFM. Due to the inconsistent findings, a systematic overview of current knowledge should be provided as basis for future investigations.

2 Aim of the thesis

Due to the limited and inconsistent findings of current research, associations between genetic, metabolic and anthropometric factors and energy metabolism were investigated. Figure 3 shows the hypotheses which have been evaluated.

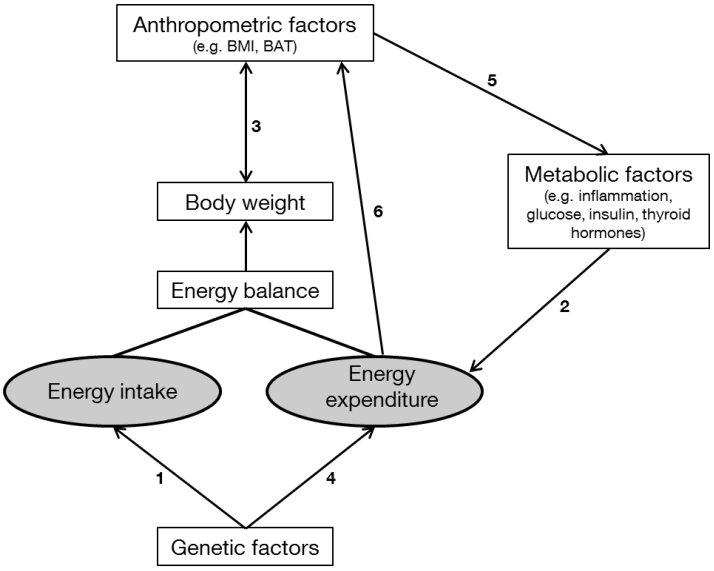

Figure 3: Schematic view of hypotheses investigated in this thesis. 1) Investigation of an association between genetic factors and energy intake. 2) Investigation of relations between metabolic factors such as inflammatory markers, IS and EE. 3) Investigation of PDFF as marker for BAT. 4) Investigation of an association between genetic factors and EE. 5) Investigation of an association between BAT measured by PDFF and thyroid hormones. 6) Investigation of an association between PDFF and EE. BAT, brown adipose tissue; EE, energy expenditure; *FTO*, fat mass and obesity associated; PDFF, proton density fat fraction.

To investigate the aforementioned factors, several projects will be performed. Systematic reviews on the associations between SNPs and energy, carbohydrate and fat intakes (Figure 3-1) as well as on the association between SNPs and EE (Figure 3-4) will be carried out. These reviews aim to give an overview on the effect of genetic factors on energy metabolism in order to generate hypotheses for future studies. Furthermore, this thesis aimed to investigate the effect of metabolic factors on body weight. Therefore, the effect of CRP, an inflammatory marker, on the association between IS and RMR will be evaluated in a cohort study (Figure 3-2). In addition to the metabolic factors, FM and especially BAT are suggested to play a role in energy metabolism and weight regulation. This question will be answered first of all, by the evaluation of the PDFF quantification as a marker for the detection of BAT which might provide information on better characterization of AT. Furthermore, associations between PDFF and anthropometric factors such as BMI or WC (Figure 3-3) as well as metabolic factors such as thyroid hormones (Figure 3-5) are hypothesized. Another question which will be addressed in the present work is the assumption that BAT is correlated with EE. Therefore, the association between PDFF and RMR will be investigated in a subgroup of persons participating in the cohort study (Figure 3-6).

3 Methods

3.1 Design and methodology of the analysis of energy intake

For the investigation of potential associations between genetic factors and dietary intake a systematic review was performed to describe studies which investigated associations between SNPs and energy, carbohydrate and fat intakes. The systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009) and was performed according to the systematic reviewing methodology (Higgins, & Green, 2011). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42015025738, Appendix A1).

3.1.1 Selection criteria and search strategy for the review on SNPs and dietary intake

For inclusion, references published between 1994 and September 2017 and in English or German language were considered (Appendix A1). In the following, the aspects of the PICOS (participants, intervention or exposure, comparator, outcomes, study design) criteria are described (O'Connor, 2008):

Participants: Studies with participants equal or older than 18 years, of all BMI categories and without specific comorbidities were eligible for inclusion. Studies reporting analyses on pregnant or breastfeeding women were excluded, to increase the comparability of the results to the general population.

Exposure: Instead of intervention, the exposure has been taken into account. The carriage of the risk allele of any SNP was selected as exposure.

Comparator: Results of non-risk allele carriers were considered as comparators.

Outcome: For specification of the outcome dietary intake studies analyzing the association between SNPs and energy, carbohydrate of fat intakes were eligible.

Study design: Observational, randomized-controlled and non-randomized intervention studies were included.

The systematic literature search was conducted in four online databases: Cochrane Library, Web of Science, PubMed, and Embase. In accordance with the syntax rules of the respective database, truncations and plural forms were used. Whenever applicable, filters were used for “humans only” studies. The following search terms were employed: “genetic

variant", "gene variant", "genotype", "single nucleotide polymorphism", "SNP", "*FTO*", "*FABP*", "*PPARG*", "*ADRB*", "*APOA2*", and "*APOA5*". The keywords were selected based on biological functions of the loci as well as existing direct-to-consumer gene based tests for personalized dietary recommendations. All identified publications were exported into the reference management software EndNote X7 (Thomson Reuters, New York City, USA). Duplicates were reviewed and removed. Two reviewer screened titles, abstracts and full-texts independently for the aforementioned inclusion criteria. Any disagreement concerning eligibility of publications was resolved by discussion or by including a third reviewer. Reasons for exclusions during the screening process were documented. In order to ensure the completeness of relevant studies, reference lists were searched by hand for relevant publications not detected by the initial search.

3.1.2 Data extraction and synthesis for the review on SNPs and dietary intake

Data of eligible articles including study design, participants, outcome, sample size, statistics, information on SNPs and energy or macronutrient intake were exported to a pretested Excel spreadsheet. Estimate sizes or p-values of the associations between SNPs and energy, carbohydrate or fat intakes were documented and summarized in a tabular form as described in detail elsewhere (Drabsch et al., 2018a). Due to the high heterogeneity of studies included into the systematic review, no quality assessment was performed.

3.2 Design and methodology of the analysis of EE

Concerning the research on EE, measured by indirect calorimetry, a cohort study was carried out in which genetic, metabolic and anthropometric effects on the EE were investigated. Additionally, in a subgroup of the cohort a non-invasive imaging method of PDFF quantification as a biomarker for the differentiation of BAT and WAT in the supraclavicular fossa was examined. Furthermore, genetic effect on EE have been examined by a second systematic review.

3.2.1 Cohort study

This study is a cohort observational study to investigate various determinants of the RMR in adults. Between October 2013 and December 2017, around 1,000 adults were recruited at two equally equipped study sites of the Else-Kroener Fresenius Center for Nutritional Medicine in Munich and Freising-Weihenstephan, Germany. In order to ensure a standardized and comparable assessment of data, a cross-locational SOP was adapted for all measurements. An identification code was used for each participant to anonymize personal data. Written informed consent (Appendix A2) was obtained at the beginning of the measurements and all study protocols were in agreement with the ethical guidelines and were approved by the ethical committee of the Technical University of Munich, Germany (Number 2719/10 S). Participants were further invited for MRI measurements at the department of diagnostic and interventional radiology of the University Hospital Klinikum rechts der Isar in Munich (Appendix A3). All examinations were carried out according to SOPs.

The primary endpoint of the study was RMR measured by indirect calorimetry. The aim of the study was to analyze various factors associated with RMR. Following factors were assessed:

- clinical factors (fasting plasma-equivalent glucose, fasting insulin, high sensitive CRP (hs-CRP) levels)
- anthropometric measurements (weight, height, FM, FFM, BAT, WAT)

3.2.1.1 Inclusion criteria of participants

Volunteers were recruited via intra-university mailing distribution, announcements at the Technical University of Munich, via internet platforms, or by distributing flyers for example at events. Participants were eligible for inclusion if age was equal to or greater than 18 years and if BMI was equal to or greater than 18.5 kg/m^2. Participants showing a history of severe diseases, having a surgery within the last three months, showed an acute physical

impairment, or reported intake of medications affecting the sympathetic nervous system (i.e. beta blockers), were excluded. Furthermore pregnant or breastfeeding women were not considered for inclusion. For subanalyses further conditions, concerning glucose metabolism and blood pressure described in detail elsewhere (Drabsch et al., 2018b), were considered for exclusion.

3.2.1.2 Indirect calorimetry

For the assessment of the RMR an indirect calorimetry was conducted according to the SOP by using a ventilated canopy hood and the breath-by breath system (Quark RMR, Suite Version 10.0e, Cosmed s.r.l., Rome, Italy). The principle of indirect calorimetry is based on the measurement of oxygen consumption (VO_2) and CO_2 production (VCO_2) during substrate oxidation (Figure 4). The RQ is calculated as the quotient of VCO_2 and VO_2, provides information about the current metabolism and varies between 0.6 and 1.1. A RQ of 0.85 reflects a 50% fat or carbohydrate burning. The lower the RQ, the higher is the fat oxidation (Schadewaldt et al., 2013). Values for the RMR are calculated based on the equation of Weir et al. (Weir, 1990):

$$\text{RMR}\ \frac{kcal}{d} = \left[\left(3.941 \text{ x } VO_2 \frac{ml}{min}\right) + \left(1.106 \text{ x } VCO_2 \frac{ml}{min}\right)\right] \text{ x } 1.44$$

The ventilated canopy hood is continuously flooded with room air and diluted via a canopy blower which generates a continuous draft of air for the analysis of inspiration of O_2 and expiration of CO_2 (Figure 4).

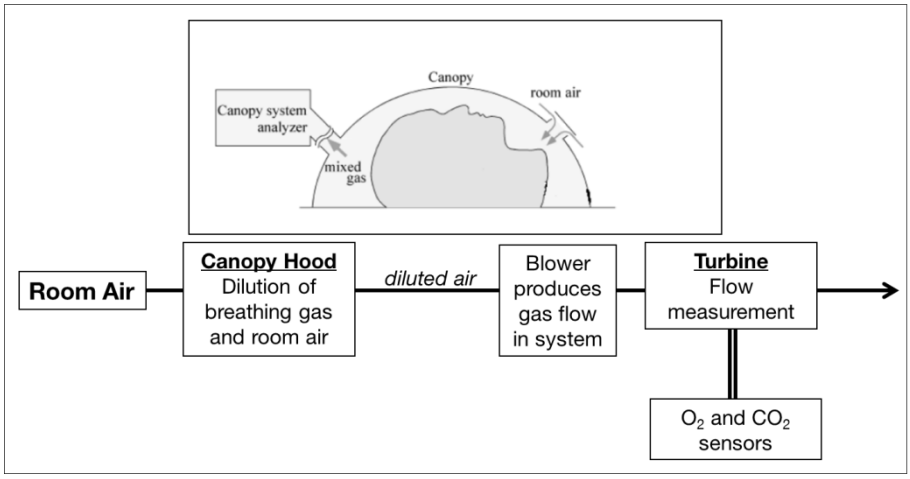

Figure 4: The principle of indirect calorimetry (according to Cosmed s.r.l., Rome, Italy). O_2, oxygen; CO_2, carbon dioxide.

Volunteers were studied according to the SOP after an overnight fast and after refraining from smoking for a minimum of 12h and physical activity for a minimum of 24 hours before RMR assessment, respectively. The initial five minutes were used as acclimatization phase

and for the adjustment of the fraction of expired carbon dioxide to 1.0%, as recommended by the manufacturer. After this acclimatization time, RMR was measured for 30 minutes. Participants have to stay fully awake and motionless during the measurement. To obtain the respiratory rate per minute, the breaths of the study participants, based on the movements of the thorax, were counted for 30 seconds during the RMR measurement and then multiplied by two. When variances of VO_2 and VCO_2 differed equal to or greater than 10.0%, recalculations of the RMR were performed by choosing a four-minute window within the 30 minute which is not statistically different to the mean RMR measured in a 30 minute measurement (Fullmer et al., 2015). Individuals, for whom values could not have been corrected for VO_2 and VCO_2 variances below 10.0%, were excluded from the analyses.

3.2.1.3 Medical history, lifestyle and anthropometric measurements

A standardized self-developed questionnaire was used for data collection. Information on date of birth, age, gender, and nationality were queried. In addition, weight changes in the last three months, health status and history of surgery, medication, smoking, physical activity, and eating habits, were recorded. For the assessment of the physical activity behavior, a four-level graded scale was used (Strobl et al., 2014). Body height was measured in a standing position using a stadiometer (Seca, Hamburg, Germany). In accordance to the SOP, bioimpedance analysis (BIA) was performed to determine body weight, FM and FFM (Tanita, BC 418 MA, Tokyo, Japan). Measurements were carried out with empty bladder, barefoot and in light clothing, whereby 1.0 kg were subtracted automatically for clothes.

3.2.1.4 Clinical parameters

In accordance with the American Heart Association (Pickering et al., 2005) blood pressure and heart rate were obtained. In addition, body temperature was analyzed by using an ear thermometer (ThermoScan 5, Braun GmbH, Lausanne, Switzerland). Fasting whole blood samples were obtained from the participants. Fasting plasma-equivalent glucose levels were analyzed by HemoCue® Glucose 201^+ System with plasma conversion (HemoCue AB, Ängelholm, Sweden). Serum was obtained from whole blood samples stored half an hour at room temperature before centrifugation at 3,000 rpm at 4°C for ten minutes. Serum samples were used for the measurement of hs-CRP levels by turbidimetry (ADVIA 2400, Siemens Healthcare GmbH, Erlangen, Germany) and for fasting insulin levels by chemiluminescence immunoassay (Immulite 2000, Siemens Healthcare GmbH, Erlangen, Germany). In accordance with the equation by Matthews et al., HOMA-IR was calculated (Matthews et al., 1985).

3.2.1.5 Abdominal subcutaneous and visceral fat volumes and PDFF by MRI

In a subgroup, MRI measurements of the supraclavicular and abdominal region were performed. Beside the volumes of subcutaneous and visceral AT (SAT and VAT), WC was measured. Detailed information on the methods is described elsewhere (Franz et al., 2018). For 10 minutes of the quantification scans, participants had to stay in a supine position with feet first and arms beside the body. Dixon technique was used for water and fat separated images. Data was analyzed by using Matlab (MathWorks). The determination of voxels of interests required manual identification for quantification of PDFF by drawing a region of interest. Finally, average PDFF values of each region were calculated.

3.2.1.6 Data management and statistical analyses

Data of the study was collected in an Excel spreadsheet. All datasets were prepared and proofed for plausibility according to good clinical practice. After removing implausible datasets, statistical analyses were performed as described elsewhere (Drabsch et al., 2018b; Franz et al., 2018). For these analyses, common statistical methods such as descriptive analyses, linear regressions and significance tests were carried out. Models were unadjusted or adjusted for potential confounders (e.g. FFM, age, sex, BMI, weight, smoking, or physical activity). In case of non-normally distribution of variables, log-transformation (e.g. HOMA-IR) or calculation of ratios (e.g. VAT/height) was performed.

3.2.2 A systematic review on the association between SNPs and EE

In accordance with the systematic review on the association between SNPs and dietary intake, a further literature search for the association between SNPs and EE was conducted based on the PRISMA statements (Moher et al., 2009) and the guidelines for systematic reviews (Higgins, & Green, 2011). The systematic review is registered in PROSPERO (registration number: CRD42018099482, Appendix A4).

3.2.2.1 Selection criteria and search strategy for the review on SNPs and EE

Articles published until June 2018, in English or German language were included. The following PICOS criteria were applied (O'Connor, 2008):

Participants: Studies on humans without specific conditions such as pregnancy, bariatric surgery or severe diseases, were eligible for inclusion to increase the comparability to the general population.

Exposure: Instead of the intervention, the exposure has been taken into account. The number of risk alleles of any SNP and EE, measured by indirect calorimetry, was exposed to be reviewed.

Comparator: Results of non-risk allele carriers were considered as comparators.

Outcome: Findings on the association between SNPs and EE were eligible.

Study design: Only observational studies were considered for inclusion.

The search strategy was applied in accordance with the review focused on associations between SNPs and dietary intake (Chapter 3.1), including the same databases, filters, if applicable, and syntax rules. The search terms included two blocks which were combined with the Boolean Operator "and". First, keywords for EE were included such as "resting energy expenditure", "resting metabolic rate", "basal metabolic rate", "resting energy requirement", "energy expenditure", "REE", "RMR", "BMR", and "RER". Second, genetic search terms were applied such as "genetic", "genetic variant", "gene variant", "polymorphism", "SNP", "single nucleotide polymorphism", "gene locus", "genotype", "gene", "genome-wide", "genomewide", "risk allele", "*FTO"*, and "fat mass and obesity associated". The *FTO* locus was included as the gene to date has the strongest effect on body weight (chapter 1.2.2). The reference management software EndNote X7 (Thomson Reuters, New York City, USA) was used for the export of data. After removing of duplicates, titles, abstracts and full-text articles were independently screened for eligibility, by two reviewers. Disagreements were resolved by a third reviewer. Finally, reference lists of included articles were screened by hand for relevant publications not detected by the search.

3.2.2.2 Data extraction, synthesis and quality assessment

Data extraction was performed according to the PROSPERO sheet (Appendix A4). For the interpretation of results, LD of SNPs was calculated by using a web-based tool based on the genotype for the CEU population (Barrett et al., 2005; Johnson et al., 2008) or by using the tools from *Ensembl* based on the European Molecular Biology Laboratory's European Bioinformatics Institute. All eligible articles underwent further quality assessment. Therefore, the online available *Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies* (National Heart, Blood and Lung Institute, Bethesda, USA) was used. The questions of the quality assessment tool are related to the description of the methodology, outcomes and dropout rate. The single studies are classified as good, fair or poor. The quality assessment was carried out by two independent reviewers.

4 Results

Results and publications related to the aims and hypotheses of this thesis are briefly summarized in the following.

4.1 Systematic review for associations between SNPs and energy intake

Associations between single nucleotide polymorphisms and total energy, carbohydrate and fat intakes: A systematic review

Theresa Drabsch, Jennifer Gatzemeier, Lisa Pfadenhauer, Hans Hauner, and Christina Holzapfel

Advances in Nutrition 2018; 9:425–453; Open Access article available from: https://academic.oup.com/advances/article/9/4/425/5055951

Summary of results: After the systematic search in four electronic databases for articles investigating associations between SNPs and energy, carbohydrate and fat intakes, in total, 12,552 articles were identified. After deletion of duplicates and screening of articles, 39 eligible articles describing 86 independent loci were included in the systematic review. Detailed study information is presented in a tabular form and the most frequently described loci are discussed in detail. One of the most investigated gene locus is the *FTO* gene. For the *FTO* locus, 13 studies and four meta-analyses investigated the relationship between SNPs and dietary intake. However, the results are inconsistent. Some studies showed a significantly negative association between A-risk allele carriers of the *FTO* SNP rs9939609 and energy intake, while others showed an association between this SNP and a higher energy intake. Similar results were found for the intake of carbohydrates without a clear direction of the association. With regard to fat intake, a significantly positive association has been shown between three *FTO* SNPs, which are in high LD, and fat intake. However, this finding is contradicted by a meta-analysis showing a lower fat intake in risk allele carriers of the *FTO* SNP rs9939609. The second most investigated genetic locus is the *MC4R* gene. A few studies could show a significantly positive association for the *MC4R* SNP rs17782313 and energy intake. However, this result was not confirmed by the other studies investigating associations between *MC4R* SNPs and energy intake. Results for associations between *MC4R* SNPs and carbohydrate or fat intakes were mostly not significant. Inconsistent findings were reported for all other published gene loci included into this systematic review. In conclusion, the data identified through this systematic literature search is quite heterogeneous which complicates the comparison of articles and conclusion of results. In

general, no consistent clinical relevant evidence has been shown for the association between SNPs and total energy, carbohydrate and fat intakes.

Personal contribution: **Theresa Drabsch** established and proofed the search strategy, performed the systematic review as primary reviewer, prepared tables and figures, and wrote the manuscript.

4.2 Effects of metabolic factors on EE

Associations between C-reactive protein, insulin sensitivity and resting metabolic rate in adults: a mediator analysis

Theresa Drabsch*, Christina Holzapfel*, Lynne Stecher, Julia Petzold, Thomas Skurk, and Hans Hauner; *authors shared the first authorship of this work
Frontiers in Endocrinology 2018; 9:556 Open Access article available from: https://www.frontiersin.org/articles/10.3389/fendo.2018.00556/full

Summary of results: In a sample of 782 adults (66.1% females) with a mean age of 32.4 ± 12.0 years the mediator role of the inflammatory status, represented by circulating CRP levels, within the association between RMR and IS was evaluated. Based on the values of fasting insulin and fasting plasma-equivalent glucose, HOMA-IR was calculated to represent IS. The mean BMI was 24.6 ± 5.2 kg/m² (women: 24.4 ± 5.6 kg/m²; men: 24.9 ± 4.3 kg/m²). Regression analyses indicated a significant association between RMR and HOMA-IR (ß = 39.3 ± 7.3 kcal/d; $p \leq 0.001$), and between RMR and CRP (ß = 25.8 ±4.1 kcal/d; $p \leq 0.001$), as well as between HOMA-IR and CRP (ß = 0.5 ± 0.1; $p \leq 0.001$). Additionally, subanalyses according to sex and BMI categories were performed. This included a comparison of persons having a normal weight (BMI < 25.0 kg/m²) with persons having a BMI equal to or greater than 25.0 kg/m². The association between RMR and HOMA-IR remained significant only in the group of persons with overweight or obesity (ß = 50.5 ± 11.6 kcal/d, $p \leq 0.001$). Results of the mediator analysis did not show significant evidence for a potential role of CRP as mediator within the association between RMR and HOMA-IR. In conclusion, the already known associations between RMR and HOMA-IR as well as RMR and CRP have been replicated. However, the finding concerning the mediator role of CRP within the HOMA-IR–RMR association of the study may be limited by the healthy young cohort and the low specificity of CRP. In addition, other methods for the determination of IS such as oral glucose tolerance test or the hemoglobin A1c level were not used.

Personal contribution: **Theresa Drabsch** was in charge of the measurements, processed the experimental data and conducted the statistical analysis. **Theresa Drabsch** designed the research question for the article together with co-authors and wrote the manuscript.

4.3 Effects of anthropometric markers on PDFF as a rough marker for BAT

Association of proton density fat fraction in adipose tissue with imaging-based and anthropometric obesity markers in adults

Daniela Franz, Dominik Weidlich, Fiedemann Freitag, Christina Holzapfel, **Theresa Drabsch**, Thomas Baum, Holger Eggers, Andreas Witte, Ernst J Rummeny, Hans Hauner, and Dimitros C Karampinos

International Journal of Obesity (Lond) 2018; 42(2):175-182; Open Access article available from: https://www.nature.com/articles/ijo2017194

Summary of results: MRI is one method which allows the identification of BAT even in an inactive status and without ionizing radiation by using chemical-shift-based fat quantification techniques. The PDFF quantification may represent a non-invasive technique for the investigation of fat fractions in multiple organs and BAT. In a subgroup of the cohort study, 61 participants (72% women) with a median age of 29.3 years were scanned via MRI measurements at the neck and abdomen. The mean supraclavicular PDFF of 75.3 ± 4.7% was significantly lower ($p < 0.0001$) than the mean gluteal PDFF of 89.7 ± 2.9%. Furthermore, a significantly positive association was analyzed between PDFFs and VAT (supraclavicular: $r = 0.73$, $p < 0.001$; gluteal: $r = 0.70$, $p < 0.001$) as well as between PDFFs and SAT volumes (supraclavicular: $r = 0.69$, $p < 0.001$; gluteal: $r = 0.60$, $p < 0.001$). With regard to anthropometric measures, significantly positive associations were found between PDFFs and BMI (supraclavicular: $r = 0.71$, $p < 0.001$; gluteal: $r = 0.47$, $p = 0.002$) as well as between PDFFs and WC (supraclavicular: $r = 0.70$, $p < 0.001$; gluteal: $r = 0.45$, $p = 0.003$). These significantly positive associations suggest PDFF as a rough marker for the imaging of BAT which may improve the characterization and risk stratification for the obese phenotype as well as the selection of appropriate treatment strategies for obesity.

Personal contribution: **Theresa Drabsch** was responsible for the recruitment of participants, for data collection and measurement of anthropometric data. In addition, **Theresa Drabsch** revised the manuscript and commented on the publication as a co-author.

4.4 Systematic review for associations between SNPs and EE

The association between single nucleotide polymorphisms (SNPs) and energy expenditure (EE) in humans: a systematic review of observational studies

Theresa Drabsch et al.

Article in preparation.

Summary of preliminary results: Research showed inconsistent impact of genetic factors on EE. Therefore, a systematic review of observational, human studies investigating the association between SNPs and EE was conducted by two independent reviewers. In Figure 5 the preliminary flow chart is shown.

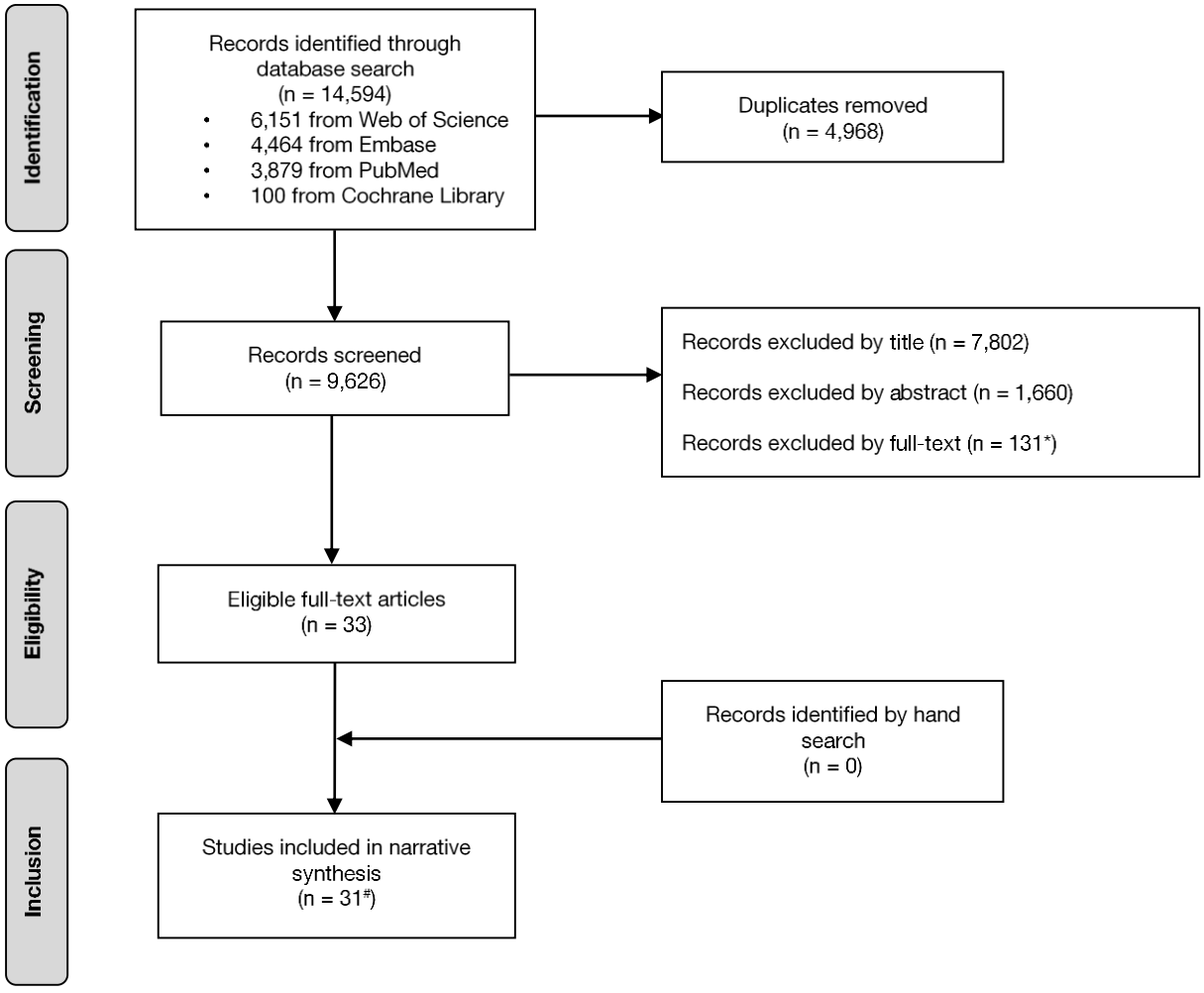

Figure 5: Flow chart of the systematic review according to PRISMA (Moher et al., 2009). *One full-text article not available. #Two GWAS identified by literature search not included into the narrative synthesis; GWAS: genome-wide association study.

In total, 14,594 articles were identified through database search. A total of 31 studies including 24 independent loci were included into the narrative synthesis. The studies were published between 1996 and 2018 and sample sizes varied between 62 and 1,246

individuals. More than half of the studies (n = 20) investigated associations between SNPs and EE in Caucasians, but also studies on other ethnicities such as Asians or African Americans were identified. In six articles, the associations between SNPs and EE were examined in children only. Most studies investigated an association between the *UCP1*, uncoupling protein 2 and 3 (*UCP2, UCP3*), the *FTO*, the *ADRB3*, or the *MC4R* loci and EE. These loci are mainly known from candidate gene studies. Two SNPs at the *UCP2* locus were investigated, whereby only one cohort study showed significant associations between the TT genotype of the *UCP2* SNP rs660339 and a higher RMR compared to the other genotypes. Further four studies on the same SNP could not show significant associations. Results of two SNPs at the *FTO* locus which are in high LD showed contradictory directions of associations. In one study, women carrying the A risk allele of the *FTO* SNP rs9939069 had significantly lower RMR values than non-risk allele carriers. In contrast, the CC genotype of the *FTO* SNP rs1421085 (r^2 to rs9939609 is 0.92) showed a significantly positive association with RMR. In a Swedish study, significance between a higher RMR and the *FTO* SNP rs9939609 disappeared after adjustment for FFM.
In conclusion, preliminary results could not show any significant clinical evidence for associations between SNPs and EE. The systematic review is limited by studies with rather small sample sizes. Six articles examined the results in collectives of less than 100 persons. A replication of associations between SNPs of identified loci and EE in larger cohorts or in GWAS is recommended to gain further information.

Personal contribution: **Theresa Drabsch** established and proofed the search strategy, performed the systematic review as primary reviewer, prepared tables and figures, and is writing the manuscript.

5 Discussion

The purpose of the present thesis was the investigation of potential effects of genetic, metabolic and anthropometric factors on energy intake and expenditure. These effects were analyzed in different projects which include a systemic review to describe the association between SNPs and energy intake as well as a systematic review for associations between SNPs and EE. Furthermore, the mediator role of circulating CRP on the association between RMR and IS was analyzed. Other tasks included the evaluation of the PDFF measurement as a rough parameter for BAT in adults as well as the investigation of an association between PDFF and thyroid hormones or RMR.

5.1 Genetic factors and energy metabolism

Association between SNPs and energy intake

A systematic literature search with the focus on associations between SNPs and energy, carbohydrate and fat intakes was performed (Drabsch et al., 2018a). In 39 articles, 176 independent SNPs were analyzed for associations with macronutrient intake and showed inconsistent effects. The most investigated SNPs were found at the *FTO* and the *MC4R* loci. In the present review, a significant association was described for risk allele carriers of the *FTO* SNPs rs9939609 and rs8050136, but studies reported a higher as well as a lower total energy intake (Lear et al., 2011; Livingstone et al., 2015; Oyeyemi et al., 2017; Qi et al., 2014; Rukh et al., 2013; Speakman et al., 2008; Steemburgo et al., 2013). Due to the relation between the *FTO* gene and BMI (Frayling et al., 2007), an association with a higher energy intake was assumed. However, the unexpected result of a higher energy intake might be explained by a potential underreporting of energy intake by *FTO* risk allele carriers (Sonestedt et al., 2009). Moreover, in a large GWAS on 18,773 European-ancestry individuals, no significant effect of the *FTO* gene and energy intake was detected (Jiang et al., 2018). With regard to carbohydrate and fat intake, contradictory results of studies were found in the systematic review. In another recently published GWAS which included 91,114 European ancestry participants from 24 epidemiologic cohorts, no genome-wide significant association between the *FTO* SNP rs1421085 with neither carbohydrate nor fat intake was observed (Merino et al., 2018).

The second most identified genetic locus was the *MC4R*. In eleven articles, associations between *MC4R* SNPs and energy intake were investigated. However, the results are similar to those for the *FTO* gene and no uniform direction of association was shown. Only few

studies described significant associations between the *MC4R* SNPs rs17782313 or rs571312 and a higher total energy, and a lower carbohydrate intake, respectively. No association with fat intake was found. As aforementioned (chapter 1.2.2), MC4R is involved in satiation and appetite regulation and might affect meal sizes through neuronal signals in the hypothalamus (Adan et al., 2006; Cone, 2005). Therefore, the assumption about a link between *MC4R* SNPs and dietary intake seems biologically plausible. Nevertheless, comparing the results of the systematic review with the recently published GWAS, Jiang et al. could not show a significant effect of the *MC4R* gene on daily energy intake. In the GWAS of Merino et al., the *MC4R* SNPs were even not detected for associations between SNPs and dietary intake (Jiang et al., 2018; Merino et al., 2018).

Associations between SNPs and EE

Due to the inconsistent results and based on the fact that energy metabolism is not only determined by energy intake but also by EE, a possible relation between SNPs and EE was assumed. Therefore, a systematic review investigating associations between SNPs and EE was performed. In total, 31 articles on observational studies were included in the systematic review. The two most investigated SNPs were at the *UCP2* and *FTO* gene locus. In a study on 150 European-ancestry, no significant association between the *FTO* SNP rs9939609 and EE was shown (Speakman et al., 2008). Comparing this result with the findings of the recent GWAS by Jiang et al., no significant associations between the *FTO* gene and EE have been shown either (Jiang et al., 2018). Notwithstanding, it has to be mentioned that EE analyzed in the GWAS was calculated on the basis of anthropometric data and not, as in Speakman et al., measured by using indirect calorimetry. Studies investigating other genetic loci for an association with EE could show significant, but inconsistent findings (Csernus et al., 2015; Walston et al., 2003). For instance, Csernus et al. investigated associations between SNPs at the *UCP1/2/3*, *PPARG* and *ADRB3* loci and EE in Hungarian children with overweight or obesity. They mostly described non-significant findings except for the *UCP3* TT genotype which is significantly negative associated with EE compared to the CC and CT genotype (Csernus et al., 2015). Nevertheless, preliminary results of the present systematic review could not provide any significant and consistent evidence for associations between SNPs and EE.

The main limitation of the two systematic reviews is the heterogeneity between the studies. The studies differ in terms of design, ethnicity or even specific collectives, such as children or persons with overweight or obesity. Due to the high heterogeneity concerning different study designs, no quality assessment for the review on associations between SNPs and

energy intake was applied. Contradictory, the second review investigating associations between SNPs and EE included only observational study thus a quality assessment was applicable. However, half of all eligible articles could only be rated with "fair", two of them even with "poor" quality. The main reasons for this can be mostly explained by a lack of adjustments of the association analyses, an imprecise implementation of the methodology, and missing information regarding the methodology, statistics or even the population itself. A further limitation of the reviews is that only SNPs were examined. Further investigation of rare genetic variants or exome analyses might give further information on the genetic effect on human energy metabolism. Nevertheless, compared to other reviews, the major strength was that not only one specific locus such as the *FTO* gene was included but all identified and published gene loci were described. Another limitation for the review on dietary intake is the exclusion of studies with associations between SNPs and protein intake. Reasons for the exclusion were that protein intake is not directly addressed in the treatment and prevention guidelines for obesity (Jensen et al., 2014; Wirth et al., 2014). However, the interest in protein intake is increasing since results of a 2-year randomized intervention trial, the Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) study, observed greater weight changes if risk allele carriers of the *FTO* SNP rs1558902 were recommended for a high-protein diet (X Zhang et al., 2012). In addition, these results were confirmed by de Luis et al. (de Luis et al., 2015). However, in a cross-sectional study, a significant interaction between the same *FTO* SNP rs1558902 and protein intake on BMI was described only in East Asians, but results were non-significant in Caucasian and South Asian individuals (Merritt et al., 2018). Results of GWAS could show significantly positive associations between the SNP rs77694286 at the DNA Damage Regulated Autophagy Modulator 1 gene as well as the *FTO* SNP rs1421085 and protein intake (Merino et al., 2018). Hence, a higher dietary protein intake might be associated with some genetic variants and may interact on BMI changes. Therefore, analyses on associations between SNPs and protein intake should be considered for further investigations.

It might be hypothesized, that not a single SNP has an effect on food intake, but the interaction of several SNPs. Nevertheless, the reviews are of added value for future investigations, as biologically plausible genes could not provide any significant association with energy intake or EE. Furthermore, it becomes apparent that even larger GWAS could not show significant associations between the biologically plausible genes and energy metabolism. Due to inconsistencies of findings and the lack of scientific evidence for the

genetic effect on dietary intake, further studies should not only include observational but also interventional studies or even gene-diet interaction approaches.

To date and in view of the studies included in the reviews, the associations between genetic factors and energy metabolism have been investigated mainly in epidemiological studies. However, the topic of genetics and nutrition, also with the endpoint of weight change, has already been investigated in intervention studies. There are studies in which people were randomized to different diets and the genetic effect was investigated retrospectively. For instance, 609 participants of the DIETFITS intervention study were randomly assigned to a healthy low carb or low fat diet. Based on three SNPs, a genotype pattern was generated and grouped to be sensitive to fat, to carbohydrate or neither of them. However, after 12 months of intervention, weight loss was similar between groups and independent of genetic pattern (Gardner et al., 2018). Similar results have been described in the large cohort studies NUGENOB and DiOGenes (chapter 1.3.1).
In contrast to this type of trials, in the Food4Me study the genotype was directly integrated into the dietary recommendation. The Food4Me trial aimed to investigate the effect of a gene based dietary recommendation on weight loss in a large European intervention study of 1,269 individuals (Celis-Morales et al., 2017a; Celis-Morales et al., 2017b). In that study, subjects were divided into four groups. In the first group dietary recommendations were based on standard dietary guidelines. Participants of the second group received dietary recommendations based on their eating preferences and energy consumption. The third group achieved personalized dietary recommendations additionally based on phenotypic data. The last group additionally received recommendations based on their eating habits and their dietary intake, their phenotypic as well as their genotypic data. All participants showed reductions of body weight and WC. However, risk allele carriers of the *FTO* gene showed non-significantly different but slightly greater reductions of body weight and WC which might be explained by a greater motivation and changes of dietary habits in the gene based intervention group.

In summary, considering the present results, no gene based dietary recommendation based on the common biologically plausible gene loci can be given. Findings of epidemiological studies and GWAS did not provide causal evidence for associations between SNPs and energy intake supported by the results of intervention studies. However, several companies offer direct-to-consumer genetic tests to provide a gene based dietary recommendation and thus promising weight loss. As has also been shown by the studies identified in the review, up to now there is no scientific evidence for such direct-to-consumer tests. These findings

also support the opinion of professional associations. The German Society for Human Genetics rejects the use of genetic tests (Reis, 2011) and the American Society for Dietetics and Nutrition (Academy of Nutrition and Dietetics, ADA) clearly rejects gene based dietary recommendations (Camp, & Trujillo, 2014).
Beside the genetic effect on energy metabolism, it has to be considered that food choice and the regulation of dietary intake is rather complex. Innovative approaches should also include new aspects concerning the individual response to dietary intake. In an Israeli experimental study the individual response of test meals on blood glucose levels was described (Zeevi et al., 2015). Study participants received identical meals, but the glucose response was significantly different from person to person. This response might be used as predictor for personalized dietary recommendations. Another study of the same research group showed that the glycemic reaction to different types of bread is person-related and associated with a different microbial reaction (Korem et al., 2017).

Up to date, most studies focused on one specific aspect of the human metabolism such as genetic or metabolic factors or even the microbiome. It seems increasingly relevant to conduct larger interdisciplinary studies that summarize all potential influencing factors as big data. With regard to nutrition research, funding institutions have also picked up the need for such landmark studies. In Germany, for example, the Federal Ministry of Education and Research funds four clusters of nutrition research as well as four related junior research groups. The so-called *enable* cluster (http://www.enable-cluster.de) is located in the region of Munich. In the junior research group Personalized Nutrition & e-health (PeNut), conducted as part of the *enable* cluster, an interdisciplinary approach is integrated with regard to a personalized dietary recommendation for the prevention and treatment of obesity. Within this group, the lifestyle intervention study (LION) is established. A total of 254 subjects with obesity will be randomized to four different intervention groups for weight loss maintenance. In a first deep phenotyping step, anthropometric, clinical and lifestyle data will be collected. In parallel, meal challenges are carried out, including stool and blood analyses. A weight reduction of participants is to be achieved in an eight-week formula diet phase. In the following, the participants will be randomized into different intervention groups. They will receive nutritional recommendations by a smartphone application or a newsletter, as well as either a low carb or a low fat dietary recommendation. During this phase, further data on the individual response to the respective diet will be collected. The study will provide information on the extent to which various genetic, metabolic and anthropometric factors play a role in weight regulation.

5.2 Metabolic and anthropometric factors and energy metabolism

Beside genetic factors, also metabolic and anthropometric factors have to be considered for associations with energy metabolism. One aspect, which has been investigated in the present thesis, is a mediator role of CRP, as inflammatory marker, within the association between impaired IS, measured by HOMA-IR, and increased RMR (Drabsch et al., 2018b). However, the analysis could not confirm a mediator role of CRP within the HOMA-IR–RMR association. This non-significant finding might be explained by the young and healthy investigated collective. Most of the participants had a CRP level of 0.02 mg/dL, which was also the lowest value which could be determined by the laboratory. Therefore, the range of CRP levels within the investigated cohort was limited. In addition, CRP levels were only measured once, but especially due to its low specificity, two-point measurements are recommended (Pearson et al., 2003). Anyhow, CRP might be assumed as a crude marker in this study as the positive correlation between BMI and CRP can be traced back to the significant associations between inflammatory markers and FM (Mohan et al., 2005) or weight (Aronson et al., 2004). Analysis of associations between further metabolic factors such as interleukins or cytokines on EE is needed including different values of inflammatory markers and an in depth analysis of IS to obtain further information on the biological background of EE.

Beside metabolic and genetic factors, anthropometry plays a crucial role in energy metabolism. Examples for anthropometric parameters are FM, fat distribution and WAT or BAT which influence RMR.

Activation of BAT leads to thermogenesis and therefore to an enhanced energy production in form of heat. Various studies have shown a significant association between RMR and BAT if activated by cold exposure (van der Lans et al., 2013; Yoneshiro et al., 2013). Usually, activated BAT was visualized by PET-CT scans. However, other imaging methods were validated for the imaging of BAT even if inactive. In the study by Franssens et al., significant associations between fat fractions, measured by MRI, in the supraclavicular region of adults and SAT have been described (Franssens et al., 2016). This finding was confirmed in the current work as supraclavicular PDFF was significantly lower than gluteal in the investigated cohort (Franz et al., 2018). On the one hand, this association indicates a difference in cellular properties, since it is assumed that the supraclavicular fossa consists of brown or beige fat cells (Gifford et al., 2016). On the other hand, the difference between supraclavicular and gluteal PDFF could also be explained by white fat cell size, vascularization and contamination of other cell types such as muscles. However, the

presence of BAT is further supported, as a significantly positive association was found for PDFF and anthropometric obesity markers (Franz et al., 2018). In addition, in the study by Franz et al. a stronger association between anthropometric parameters and PDFF for participants older than 30 years might reflect the decline of BAT by age. Furthermore, other studies have shown a significant relation between BAT and BMI (Saito et al., 2009), which in turn would confirm the presence of BAT in the supraclavicular PDFF, since an association was also found in the current work (Franz et al., 2018). Initial results from studies investigating BAT as a possible therapeutic target for the prevention of obesity are promising. In particular, they aimed to change BAT activity to counteract energy imbalances (Vijgen, & van Marken Lichtenbelt, 2013). The measurement of PDFF is cost-effective and not time-consuming which makes it relevant as a marker for the detection of BAT.

The role of PDFF as marker for the presence of BAT might be further explained by associations between PDFF and RMR which has been considered in subanalyses (data not shown). A significantly positive association was found for supraclavicular PDFF and RMR without adjustment for age, sex or FFM. However, significance disappeared after adjustment for potential confounders such as FFM. In RMR-studies, models were always corrected for FFM. However, it has to be taken into account that FFM was determined by BIA measurement and might already include the amount of BAT. It remains unclear if the adjustment for FFM is necessary in the present study. Initially, a negative association between supraclavicular PDFF and RMR was expected due to the presence of BAT. The finding of a positive association might possibly be explained by the BMI rather than by the amount of BAT. Due to this and an age-dependent effect on PDFF in women, which has been analyzed in a recently published subanalysis of the here investigated cohort (Burian et al., 2018), further subanalyses are necessary.

In order to bring more light on the understanding of EE, a subanalysis was conducted to analyze whether there is an association between thyroid hormones, as metabolic factors, which are known to have an effect on RMR (Johnstone et al., 2005), and BAT. However, preliminary results of the analysis could not show significant associations between thyroid hormones and supraclavicular PDFF (data not shown). This finding confirmed a study of Graves' disease-caused hyperthyroid patients describing no association between high circulating thyroid hormone levels and BAT (Q Zhang et al., 2014). Additionally, in a study by Brendle et al. no association between BAT and thyroid stimulating hormone levels has been shown (Brendle et al., 2018). In contrast, another study in thyroid cancer patients could show associations between hypothyroidism and an increased BAT activity (Lapa et al.,

2015). In the current cohort, participants showing a thyroid-dysfunction or patients not adjusted by medications were excluded. Therefore, it must be taken into account that the preliminary results of the study refer to a rather healthy collective.

Results of the analyses could not show evidence for associations between genetic, metabolic and anthropometric factors on RMR or BAT. Therefore, another aspect which should be considered is that an association between PDFF and RMR might only be seen when BAT is activated by stimulation such as cold exposure. One example has been presented in a recently published study where BAT thermogenesis has been stimulated by cold exposure but also by carbohydrate intake (U Din et al., 2018). Concerning the association between BAT and dietary intake another study, published by a German research group, could show that secretin, a hormone, which is involved in food regulation, stimulated BAT activity in mice (Li et al., 2018). Furthermore, Li et al. could show that a secretin injection could reduce food intake in short-term. It is assumed that secretin and the activity of BAT might lead to alteration of hunger signal in the brain which alters eating behavior.

Beside the PDFF quantification as a marker for BAT, a promising method might be the multi-spectral optoacoustic tomography (MSOT), which was investigated in a German study (Reber et al., 2018). Results showed that during activation of BAT, MSOT can differentiate BAT from WAT in mice. In conclusion, the MSOT method seems to be promising as it achieved precise spectral measurements of metabolic signals and allows comparison between water and fat. Both, MRI fat fraction and MSOT may provide deeper insight into human body fat and could therefore more precisely examine the impact of genetic, metabolic and anthropometric factors on BAT and on EE, respectively.

6 Conclusion

The present work investigated the effect of genetic, metabolic and anthropometric factors on energy metabolism. However, this highlighted only a few pieces of a complex puzzle.

In this thesis, standardized scientific methods such as systematic reviews, innovative approaches like the PDFF quantification by MRI measurements and a statistical mediator analysis were used. The identification of significant as well as of non-significant results is of added value for future studies and the scientific community, but does not account for clinical implementation. Findings of the present work provide indications, albeit inconsistent, for an effect of genetic, metabolic and anthropometric factors on energy metabolism. However, the remaining uncertainty about the biological mechanisms of body weight regulation is still an issue that needs to be discussed.

The long-term aim is to provide tailored dietary recommendations for weight management under the consideration of genetic, metabolic or anthropometric parameters. Therefore, future intervention studies including a variety of factors should figure out clinical evidence. Long-term intervention studies are needed for the investigation of not only body composition, health status and energy metabolism, but also of challenge-induced changes of body weight metabolism. These studies may provide a deeper insight into the relationships between the individual components of the energy balance and their effects on the human body. The human body must be understood as a network in which genetic, metabolic and anthropometric factors work together. The biological mechanisms behind the development of obesity are far more complicated, as obesity might not be a homogeneous entity. For future perspectives, personalized dietary recommendations based on genetic information, metabolic and anthropometric factors or even on information of the microbiome are promising for innovative approaches for the prevention and treatment of obesity.

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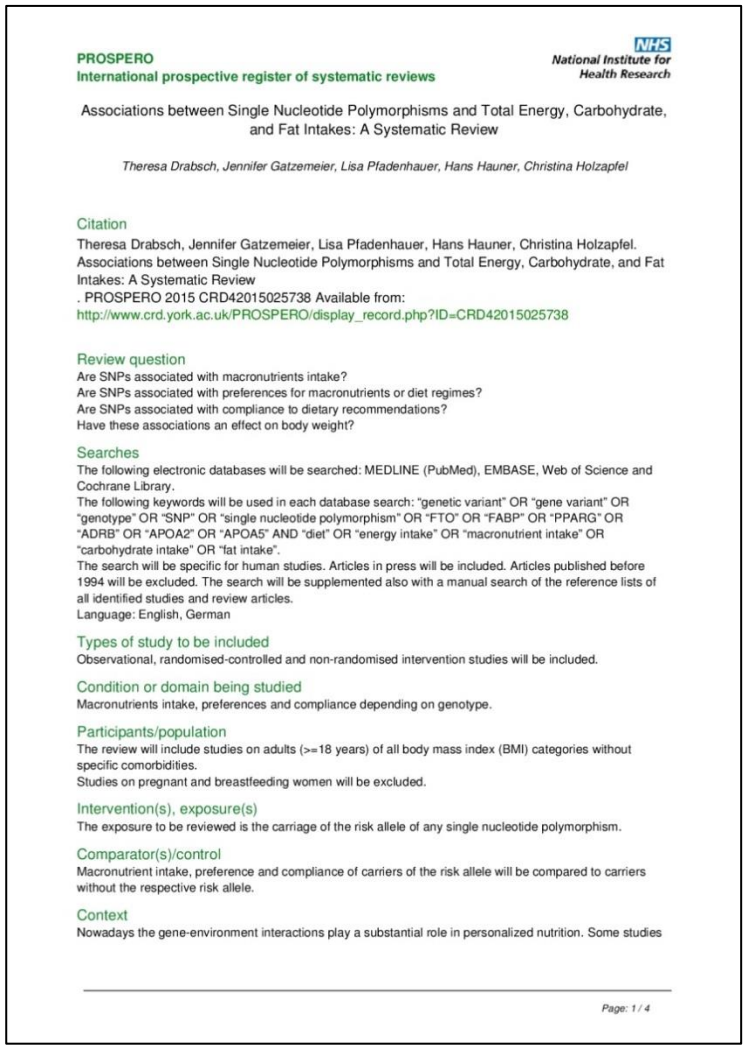
Appendix

A1 – Prospero registration of the review on associations between SNPs and dietary intake



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Associations between Single Nucleotide Polymorphisms and Total Energy, Carbohydrate, and Fat Intakes: A Systematic Review

Theresa Drabsch, Jennifer Gatzemeier, Lisa Pfadenhauer, Hans Hauner, Christina Holzapfel

Citation

Theresa Drabsch, Jennifer Gatzemeier, Lisa Pfadenhauer, Hans Hauner, Christina Holzapfel. Associations between Single Nucleotide Polymorphisms and Total Energy, Carbohydrate, and Fat Intakes: A Systematic Review
. PROSPERO 2015 CRD42015025738 Available from:
http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42015025738

Review question

Are SNPs associated with macronutrients intake?
Are SNPs associated with preferences for macronutrients or diet regimes?
Are SNPs associated with compliance to dietary recommendations?
Have these associations an effect on body weight?

Searches

The following electronic databases will be searched: MEDLINE (PubMed), EMBASE, Web of Science and Cochrane Library.
The following keywords will be used in each database search: "genetic variant" OR "gene variant" OR "genotype" OR "SNP" OR "single nucleotide polymorphism" OR "FTO" OR "FABP" OR "PPARG" OR "ADRB" OR "APOA2" OR "APOA5" AND "diet" OR "energy intake" OR "macronutrient intake" OR "carbohydrate intake" OR "fat intake".
The search will be specific for human studies. Articles in press will be included. Articles published before 1994 will be excluded. The search will be supplemented also with a manual search of the reference lists of all identified studies and review articles.
Language: English, German

Types of study to be included

Observational, randomised-controlled and non-randomised intervention studies will be included.

Condition or domain being studied

Macronutrients intake, preferences and compliance depending on genotype.

Participants/population

The review will include studies on adults (>=18 years) of all body mass index (BMI) categories without specific comorbidities.
Studies on pregnant and breastfeeding women will be excluded.

Intervention(s), exposure(s)

The exposure to be reviewed is the carriage of the risk allele of any single nucleotide polymorphism.

Comparator(s)/control

Macronutrient intake, preference and compliance of carriers of the risk allele will be compared to carriers without the respective risk allele.

Context

Nowadays the gene-environment interactions play a substantial role in personalized nutrition. Some studies

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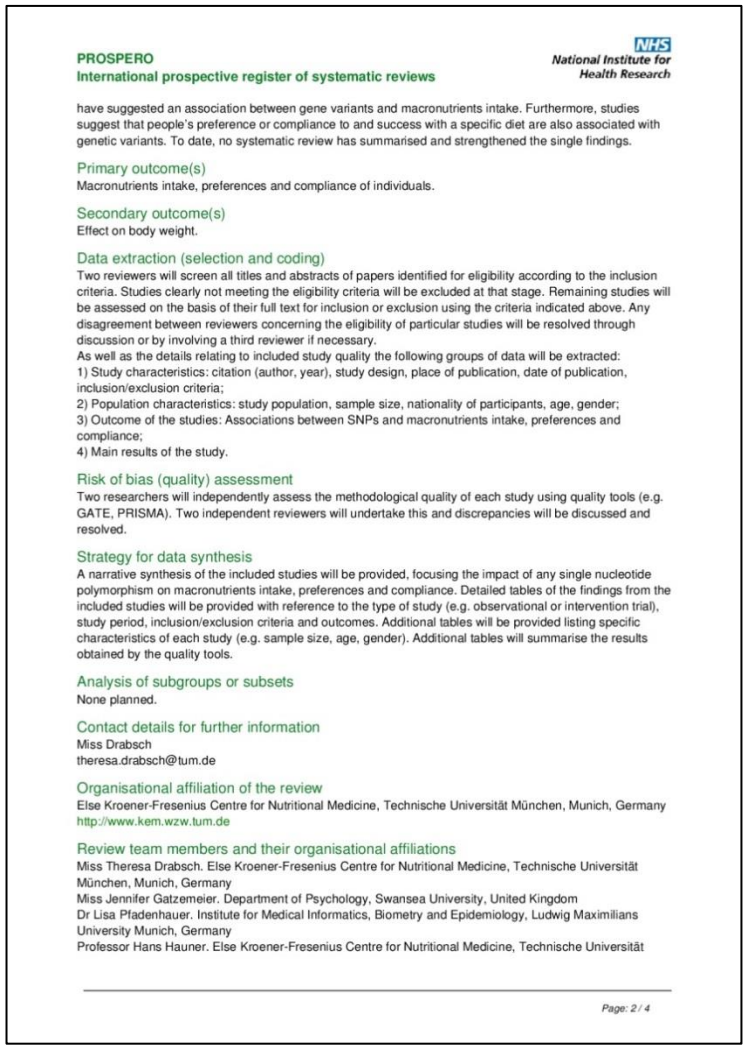

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have suggested an association between gene variants and macronutrients intake. Furthermore, studies suggest that people's preference or compliance to and success with a specific diet are also associated with genetic variants. To date, no systematic review has summarised and strengthened the single findings.

Primary outcome(s)

Macronutrients intake, preferences and compliance of individuals.

Secondary outcome(s)

Effect on body weight.

Data extraction (selection and coding)

Two reviewers will screen all titles and abstracts of papers identified for eligibility according to the inclusion criteria. Studies clearly not meeting the eligibility criteria will be excluded at that stage. Remaining studies will be assessed on the basis of their full text for inclusion or exclusion using the criteria indicated above. Any disagreement between reviewers concerning the eligibility of particular studies will be resolved through discussion or by involving a third reviewer if necessary.
As well as the details relating to included study quality the following groups of data will be extracted:
1) Study characteristics: citation (author, year), study design, place of publication, date of publication, inclusion/exclusion criteria;
2) Population characteristics: study population, sample size, nationality of participants, age, gender;
3) Outcome of the studies: Associations between SNPs and macronutrients intake, preferences and compliance;
4) Main results of the study.

Risk of bias (quality) assessment

Two researchers will independently assess the methodological quality of each study using quality tools (e.g. GATE, PRISMA). Two independent reviewers will undertake this and discrepancies will be discussed and resolved.

Strategy for data synthesis

A narrative synthesis of the included studies will be provided, focusing the impact of any single nucleotide polymorphism on macronutrients intake, preferences and compliance. Detailed tables of the findings from the included studies will be provided with reference to the type of study (e.g. observational or intervention trial), study period, inclusion/exclusion criteria and outcomes. Additional tables will be provided listing specific characteristics of each study (e.g. sample size, age, gender). Additional tables will summarise the results obtained by the quality tools.

Analysis of subgroups or subsets

None planned.

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Anticipated or actual start date
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Conflicts of interest
CH is a member of the scientific advisory board of the 4sigma GmbH. HH is a member of the scientific advisory board of NovoNordisk, Boehringer Ingelheim and Orexigene. TD, JG, and LP have no conflicts of interest.

Language
English

Country
Germany

Stage of review
Review_Completed_published

Details of final report/publication(s)
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Subject index terms
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Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

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Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Versions
27 August 2015
23 December 2015
07 November 2016
28 August 2017
02 August 2018

A2 – Informed consent of the cohort study

Else Kröner-Fresenius-Zentrum für Ernährungsmedizin
Klinikum rechts der Isar
Technische Universität München

Direktor: Univ.-Prof. Dr. med. Hans Hauner

Teilnehmerinformation

Genetische Zusatzuntersuchungen im Rahmen der Grundumsatzmessung

Sehr geehrte Teilnehmerin, sehr geehrter Teilnehmer!

Bei Ihnen wird heute eine Bestimmung des Grundumsatzes (Ruheenergieverbrauch) durchgeführt. Mit dieser Untersuchung wird durch Analyse der Atemluft gemessen, wie viel Energie Ihr Körper in Ruhe verbraucht. Bislang wissen wir, dass vor allem die Muskelmasse den Ruheenergieverbrauch bestimmt. Sehr wahrscheinlich spielen auch die Erbanlagen eine wichtige Rolle. Allerdings sind kaum genetische Faktoren bekannt, die etwas über den Grundumsatz aussagen. Wir möchten untersuchen, ob die Erbanlagen tatsächlich den Ruheenergieverbrauch beeinflussen. Wir bitten Sie deshalb, sich im Rahmen dieser Untersuchung zusätzlich ca. 20 ml Blut (=2 Esslöffel) für Forschungszwecke abnehmen zu lassen. Falls eine Blutabnahme nicht möglich ist, kann auch eine Speichelprobe für die genetischen Analysen abgegeben werden. Die Abgabe einer Speichelprobe ist für Sie mit keinerlei Risiken verbunden.
Zudem bitten wir Sie, einen Fragebogen auszufüllen, in welchem z.B. Krankheiten oder Medikamente erfasst werden.
In die Forschungsaktivitäten wird immer mehr auch das Mikrobiom (z.B. Darmbakterien) mit einbezogen. Um den Einfluss des Mikrobioms auf den Grundumsatz zu untersuchen, werden Stuhlproben benötigt. Optional können Sie für die Studie eine frische Stuhlprobe abgeben. Die Abgabe einer Stuhlprobe ist für Sie mit keinerlei Risiken verbunden. Ebenso können Sie optional eine Urinprobe abgeben.

Die von Ihnen zur Verfügung gestellten Proben sollen im Sinne eines breiten Nutzens für die Allgemeinheit für verschiedene medizinische Forschungszwecke verwendet werden können. Allerdings können zum derzeitigen Zeitpunkt noch nicht alle zukünftigen medizinischen Forschungsziele beschrieben werden.

Risiken

Bei der Blutentnahme kann es in seltenen Fällen zu einer Infektion an der Einstichstelle (allerdings ist die Wahrscheinlichkeit aufgrund der Hygienemaßnahmen sehr gering), einer Blutung oder einer Nervenverletzung kommen.

Bei jeder Datenerhebung, -speicherung und -übermittlung bestehen Vertraulichkeitsrisiken. Der Lehrstuhl für Ernährungsmedizin der Technischen Universität (TU) München versichert Ihnen, nach Möglichkeit alles zum Schutz Ihrer Privatsphäre zu tun (siehe „Wie werden Ihre Biomaterialien und Daten geschützt?“).

Else Kröner-Fresenius-Zentrum für Ernährungsmedizin
Klinikum rechts der Isar
Technische Universität München

Direktor: Univ.-Prof. Dr. med. Hans Hauner

Nutzen

Persönlich können Sie für Ihre Gesundheit keinen unmittelbaren Vorteil oder Nutzen aus der Spende Ihrer Proben und Daten erwarten. Die Ergebnisse sind ausschließlich zu Forschungszwecken bestimmt.

Eine Rückmeldung von Ergebnissen aus der Untersuchung der Biomaterialien ist nicht vorgesehen.

Datenschutz

Ihre schriftliche Einwilligung ist Voraussetzung für die Gewinnung und Nutzung Ihrer Blutprobe/Speichelprobe samt den zugehörigen personenbezogenen Daten zu Forschungszwecken. Ihre Einwilligung ist freiwillig und kann jederzeit widerrufen werden (siehe auch Punkt „Widerrufs- und Informationsrecht").

Ihre Biomaterialien und Daten werden am Lehrstuhl für Ernährungsmedizin der TU München unter standardisierten Qualitäts- und Sicherheitsbedingungen unbefristet aufbewahrt und auf Antrag für Forschungszwecke herausgegeben.

Alle unmittelbar Ihre Person identifizierenden Daten (Name, Geburtsdatum, Anschrift etc.) werden durch einen Code ersetzt (pseudonymisiert, verschlüsselt). Erst in dieser Form erhält die am Lehrstuhl für Ernährungsmedizin vorhandene Biobank die Verfügungsmacht über Ihre Biomaterialien und Daten. Danach wird der Datensatz nochmals neu kodiert und gespeichert. Bei einer derartigen doppelten Kodierung sind Rückschlüsse auf Ihre Person allein auf Grund der Bezeichnung von Biomaterialien/Daten ausgeschlossen.

Voraussetzung für die Verwendung der verschlüsselten Biomaterialien und Daten für medizinische Forschungsprojekte ist, dass das Forschungsvorhaben durch eine Ethikkommission zustimmend bewertet wurde.

Eine Entschlüsselung, d.h. eine Zuordnung der Biomaterialien / Daten zu Ihrer Person (Name, Geburtsdatum, Anschrift etc.), darf nur aus zwingenden wissenschaftlichen Gründen, oder aufgrund Ihres Verlangens erfolgen. Alle Entschlüsselungsvorgänge werden dokumentiert.

Wer hat Zugang zu Ihren Biomaterialien und Daten?

Die verschlüsselten Biomaterialien und Daten können auf Antrag an Dritte für medizinische Forschungsprojekte weitergegeben werden.

Biomaterialien und Daten, die an Dritte weitergegeben wurden, dürfen nur für den beantragten Forschungszweck verwendet und nicht nochmals weitergegeben werden. Nicht verbrauchtes Material wird an die Biobank zurückgegeben oder vernichtet.

Biomaterial und unmittelbar identifizierende Daten (Name, Geburtsdatum, Anschrift etc.) sowie medizinische Daten (z. B. Diagnose, Symptome, Laborwerte etc.) werden an jeweils unterschiedlichen Stellen gelagert und gespeichert. Die Verantwortung für die Einhaltung der Schutzmaßnahmen liegt beim Lehrstuhl für Ernährungsmedizin der TU München. Dort wird sichergestellt, dass kein unbefugter Dritter Zugang zu den Biomaterialien/Daten hat.

Wissenschaftliche Veröffentlichungen von Ergebnissen erfolgen in einer Form, die keine Rückschlüsse auf Ihre Person zulässt.

Else Kröner-Fresenius-Zentrum für Ernährungsmedizin
Klinikum rechts der Isar
Technische Universität München

Direktor: Univ.-Prof. Dr. med. Hans Hauner

Für die Überlassung Ihrer Biomaterialien / Daten erhalten Sie kein Entgelt. Sollte aus der Forschung ein kommerzieller Nutzen erzielt werden, werden Sie daran nicht beteiligt.

Mit der Überlassung der Biomaterialien an den Lehrstuhl für Ernährungsmedizin der TU München werden diese Eigentum dieser Einrichtung. Ferner ermächtigen Sie den Lehrstuhl für Ernährungsmedizin der TU München, Ihre Daten zu nutzen.

Ihre Biomaterialien und Daten werden nicht an Dritte verkauft; für die Nutzung der Biobank kann jedoch eine angemessene Aufwandsentschädigung erhoben werden.

Erfolgt eine erneute Kontaktaufnahme mit Ihnen?

Zur Erhebung von Daten zum weiteren Verlauf Ihrer Genesung bzw. Erkrankung kann es notwendig werden, dass der Lehrstuhl für Ernährungsmedizin der TU München zu einem späteren Zeitpunkt erneut Kontakt mit Ihnen aufnimmt, um ergänzende Informationen und/oder Biomaterialien von Ihnen zu erbitten. Zudem kann die erneute Kontaktaufnahme genutzt werden, um z. B. Ihre Einwilligung zum Abgleich mit anderen Datenbanken einzuholen oder um Ihnen eine Rückmeldung über bestimmte Forschungsergebnisse zu geben. Falls Sie eine erneute Kontaktaufnahme nicht wünschen, streichen Sie bitte den entsprechenden Passus in der Einwilligungserklärung.

Welche Widerrufs- und Informationsrechte haben Sie?

Sie können Ihre Einwilligung zur Verwendung Ihrer Biomaterialien und Daten jederzeit ohne Angabe von Gründen und ohne nachteilige Folgen für Sie widerrufen. Im Falle eines Widerrufs wird die verschlüsselte Verknüpfung der Biomaterialien und Daten mit Ihren unmittelbar identifizierenden Daten (Name, Geburtsdatum, Anschrift etc.) gelöscht. Ihre Daten und Biomaterialien stehen dann auch für zukünftige Projekte nur noch anonymisiert zur Verfügung. Darüber hinaus haben Sie das Recht, die Löschung Ihrer Daten und die Vernichtung Ihrer Biomaterialien zu verlangen. Sobald der Bezug der Daten und Biomaterialien zu Ihrer Person gelöscht wurde, ist dies jedoch nicht mehr möglich. Zudem können Daten aus bereits durchgeführten Analysen nicht mehr entfernt werden.

Wenden Sie sich für einen Widerruf bitte an: Lehrstuhl für Ernährungsmedizin der TU München, Klinikum rechts der Isar, Georg-Brauchle-Ring 62, 80992 München, Tel.: 089-289-24021 oder EKFZ@mri.tum.de

Else Kröner-Fresenius-Zentrum für Ernährungsmedizin
Klinikum rechts der Isar
Technische Universität München

Direktor: Univ.-Prof. Dr. med. Hans Hauner

Einwilligungserklärung

Genetische Zusatzuntersuchungen im Rahmen der Grundumsatzmessung

Teilnehmer: _____

(Name, Vorname)

Adresse _____

Geb.-Datum: _____

Ich bin damit einverstanden, dass meine Blutprobe/Speichelprobe und Daten, wie in der Teilnehmerinformation beschrieben, an den Lehrstuhl für Ernährungsmedizin der Technischen Universität (TU) München gegeben und unbefristet für medizinische Forschungszwecke verwendet werden.

Durch meine Unterschrift bestätige ich, dass ich den Inhalt der Informationsschrift gelesen und verstanden habe. Ich hatte die Gelegenheit, Fragen zu stellen. Meine Fragen wurden mir zufriedenstellend beantwortet.

Ich weiß, dass meine Teilnahme freiwillig ist und ich meine Einwilligung jederzeit ohne Angabe von Gründen widerrufen kann, ohne dass mir daraus irgendwelche Nachteile entstehen.

Ich bin damit einverstanden, dass ich evtl. zu einem späteren Zeitpunkt erneut kontaktiert werde (ggf. streichen).

Datenschutzerklärung:

Ich erkläre mich damit einverstanden, dass der Lehrstuhl für Ernährungsmedizin der TU München Biomaterialien von mir unbefristet lagert und pseudonymisiert (verschlüsselt) für medizinische Forschungsvorhaben nutzt. Ferner stimme ich zu, dass personenbezogene Daten, insbesondere Angaben über meine Gesundheit, über mich erhoben oder aus meinen Krankenunterlagen entnommen und beim Lehrstuhl für Ernährungsmedizin der TU München aufgezeichnet und pseudonymisiert (verschlüsselt) für medizinische Forschungsvorhaben genutzt werden. Die Biomaterialien und Daten dürfen für medizinische Forschungsvorhaben unbefristet verwendet werden und pseudonymisiert (verschlüsselt) an Universitäten, Forschungsinstitute und forschende Unternehmen, ggf. auch ins Ausland, weitergegeben werden.

Ich bin darüber aufgeklärt worden, dass ich jederzeit die Teilnahme ohne Begründung beenden kann. Beim Widerruf meiner Einwilligung gegenüber dem Lehrstuhl für Ernährungsmedizin der TU München habe ich das Recht, die Löschung der Verknüpfung zu den mich unmittelbar identifizierenden Daten (Name, Geburtsdatum, Anschrift etc.) bzw. falls möglich auch die Löschung/Sperrung aller meiner bis dahin gespeicherten personenbezogenen Daten bzw. die Vernichtung der Biomaterialien für die Zukunft zu verlangen.

Else Kröner-Fresenius-Zentrum für Ernährungsmedizin
Klinikum rechts der Isar
Technische Universität München
Direktor: Univ.-Prof. Dr. med. Hans Hauner

Der Lehrstuhl für Ernährungsmedizin der TU München versichert mir, meine Daten entsprechend den datenschutzrechtlichen Bestimmungen vertraulich zu behandeln.

Eine Kopie der Teilnehmerinformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt am Lehrstuhl für Ernährungsmedizin der TU München.

_____

Name des Teilnehmers in Druckbuchstaben

_____ _____

Ort, Datum (vom Teilnehmer einzutragen) Unterschrift Teilnehmer

Ich habe das Aufklärungsgespräch geführt und die Einwilligung des Teilnehmers eingeholt.

_____

Name des Arztes in Druckbuchstaben

_____

Ort, Datum Unterschrift des Arztes

A3 – Documents for MRI examinations

Klinikum rechts der Isar

Technische Universität München

Klinik für Ernährungsmedizin, Klinikum rechts der Isar,
Technische Universität München, Georg-Brauchle-Ring 60/62,
80992 München

Institut für Ernährungsmedizin
Klinikum rechts der Isar
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Dr. Christina Holzapfel
Tel.: +49 (0) 89 289 249 23
Fax: +49 (0) 89 289 249 22
E-Mail: christina.holzapfel@tum.de

Einladung zur Studienteilnahme

Sehr geehrte Studienteilnehmerin! Sehr geehrter Studienteilnehmer!

Herzlichen Dank für Ihre Teilnahme an unserer Studie „Genetische Zusatzuntersuchungen im Rahmen der Grundumsatzmessung“ (Institut für Ernährungsmedizin am Georg-Brauchle-Ring in München).

Hiermit möchten wir Sie auf eine Studie unserer Kolleginnen und Kollegen der Radiologie am Klinikum rechts der Isar der Technischen Universität München aufmerksam machen.

Sie sind eingeladen, auf Basis der Ergebnisse Ihrer Grundumsatzmessung das Vorliegen von stoffwechselaktivem, sogenanntem braunem Fettgewebe bei Ihnen untersuchen zu lassen. Hierzu werden zwei kurze Bildgebungen durchgeführt, die im beiliegenden Infoblatt näher beschrieben sind. Die Untersuchung findet in der Ismaninger Straße in München statt.

Es wäre für weiterführende wissenschaftliche Fragestellungen von großem Nutzen, wenn Sie auch an dieser Untersuchung teilnehmen.

Bei Interesse und bei Fragen wenden Sie sich für weitere Informationen und Terminvereinbarungen bitte direkt an unsere Kollegin in der Radiologie, Frau Dr. Daniela Franz: daniela.franz@tum.de.

Im Falle einer Teilnahme an der Studie teilen Sie Frau Dr. Daniela Franz bitte unbedingt Ihre nachfolgende Studien-ID aus der Grundumsatzstudie mit:

_____

Vielen Dank für Ihr Interesse.

Mit freundlichen Grüßen

Finale Version A, 11. September 2015

Univ.-Prof. Dr. med. Hans Hauner

Klinikum rechts der Isar

Technische Universität München

Klinikum rechts der Isar · Institut für Radiologie · 81664 München

Klinikum rechts der Isar
Anstalt des öffentlichen Rechts

Institut für diagnostische und interventionelle Radiologie

Univ-Prof. Dr. E. J. Rummeny

Ismaninger Straße 22
81675 München
E-Mail: sekretar@roe.med.tum.de
Tel: 089 4140-2621
Fax: 089 4140-4834
www.roe.med.tum.de

Patienteninformation zur wissenschaftlichen Studie:
„Detektion und Charakterisierung von braunem und beigem Fett im Menschen mittels MRT im Hinblick auf Korrelationen mit klinischen Parametern“

Sehr geehrte Studienteilnehmerin, sehr geehrter Studienteilnehmer,

Hiermit möchten wir Sie einladen, an einer wissenschaftlichen Studie der Radiologie am Klinikum rechts der Isar der Technischen Universität München teilzunehmen, die auf der Studie „Genetische Zusatzuntersuchungen im Rahmen der Grundumsatzmessung“ aufbaut, an der Sie am Institut für Ernährungsmedizin am Georg-Brauchle-Ring in München teilgenommen haben.

Hierbei soll auf Basis der Ergebnisse Ihrer Grundumsatzmessung das Vorliegen von stoffwechselaktivem, sogenanntem braunem Fettgewebe bei Ihnen mittels Bildgebung untersucht werden.

Daher möchten wir Sie einladen, an unserem Institut am Klinikum rechts der Isar eine Magnetresonanztomographie (MRT) durchführen zu lassen. Unser Ziel ist es, neue Bildgebungsmethoden auf Ihre Genauigkeit in der Detektion von braunem Fett zu überprüfen und mit den erhobenen Daten aus der Grundumsatzstudie zu korrelieren. Eine Untersuchung wird jeweils ca. 20 Minuten Ihrer Zeit in Anspruch nehmen, insgesamt sollten Sie, da zunächst ein kurzes Aufklärungsgespräch und ein Raumwechsel erforderlich sind, ca. 1h Zeit einplanen.
Wir bieten Ihnen an, an einer klinischen Studie teilzunehmen, die die Wertigkeit der MRT zur Detektion und Charakterisierung von braunem Fett evaluieren soll.

Wie wird die MRT durchgeführt?
Die MRT ist ein bildgebendes Verfahren, mit der das Vorhandensein von braunem Fettgewebe untersucht werden kann. In beiden Verfahren werden keine Röntgenstrahlen eingesetzt. Ein separater Informations- und Aufklärungsbogen über die MRT-Untersuchung liegt dieser Probandeninformation bei. Diesen Informations- und Aufklärungsbogen wird ein Arzt mit Ihnen durchsprechen.
Bei der MRT (Kernspintomographie) werden mit Hilfe eines Magnetfeldes Radiowellen erzeugt, auf bestimmte Körperbereiche geschickt und die entstehenden Echosignale gemessen.

Mögliche Nachteile der geplanten Untersuchung, Gegenanzeigen:
Nach dem heutigen Stand der medizinischen Kenntnisse sind uns keine Nachteile der geplanten Untersuchung bekannt. Als Gegenanzeigen für eine MRT gelten neben starker Platzangst (Klaustrophobie) metallische Implantate oder Metallsplitter im Körper, hierbei insbesondere Herzschrittmacher, künstliche Herzklappen, Aneurysma-Clips im Gehirn, Cochleaimplantate sowie Paukenröhrchen im Ohr. Kein Problem stellen in der Regel nichtmagnetische Gelenkprothesen sowie Schrauben, Drähte und Platten nach Knochenbrüchen dar.

In dieser Studie werden keine risikobehafteten Untersuchungen durchgeführt, es handelt sich um eine wissenschaftliche Studie zu Forschungszwecken. Es kann

Klinikum rechts der Isar Technische Universität München

jedoch sein, dass im Rahmen dieser Untersuchung Auffälligkeiten bzw. Zufallsbefunde erhoben werden, die weitere diagnostische Untersuchungen und / oder eine Behandlung notwendig machen. Die Entdeckung von solchen Befunden kann ggf. die Therapie dieser Veränderungen in einem frühen Stadium ermöglichen. Die Entdeckung eines solchen Befundes kann aber auch psychisch belastend sein, insbesondere wenn es keine oder nur risikoreiche Behandlungsmöglichkeiten gibt. Bitte setzen Sie sich im Vorfeld der Studie mit dieser Situation auseinander und klären Sie Fragen im Gespräch mit dem Studienleiter. Unsere Vorgehensweise bei Zufallsbefunden orientiert sich an Richtlinien, die von der Ethikkommission des Klinikums rechts der Isar veröffentlicht wurden. Die Richtlinien sehen vor, dass Sie mit der Teilnahme an dieser Studie zustimmen, dass Ihnen diese Zufallsbefunde in jedem Fall mitgeteilt werden und zu diesem Zweck die Pseudonymisierung aufgehoben wird (Wiederherstellung des Personenbezugs). Ein individueller Verzicht auf solch eine Befundmitteilung ist nicht möglich. Die Entdeckung eines Zufallsbefundes kann eine weitere Diagnostik möglich machen. Daher ist die Studienteilnahme an die Voraussetzung gebunden, dass bei Ihnen ein ausreichender Krankenversicherungsschutz besteht. Zudem ist die Einwilligung zur Weitergabe der erhobenen Daten an weiterbehandelnde ärztliche Kollegen Im Falle eines relevanten Zufallsbefundes Voraussetzung.
Bitte beachten Sie auch versicherungsrechtliche Konsequenzen aus Zufallsbefunden, insbesondere gegebenenfalls die Mitteilungspflicht gegenüber privaten Krankenversicherungen oder Lebensversicherungen.

Mögliche Vorteile der geplanten Untersuchungen:
Die MRT kann im Vergleich zu den verfügbaren Bildgebungsmethoden (Sonographie, CT) eine genauere Diagnostik von braunem Fettgewebe ermöglichen und das Verfahren kommt ohne Verwendung von Röntgenstrahlung und intravenös applizierten Substanzen aus.

Datenverwendung:
Ihre Daten und Bilder werden anschließend elektronisch gespeichert und zum Zwecke der wissenschaftlichen Auswertung verarbeitet. In pseudonymisierter Form werden diese auch unseren Kooperationspartnern übermittelt. Dabei werden die Bestimmungen des Datenschutzgesetztes beachtet.

Die Probandendaten sowie die akquirierten MRT-Bilder werden wissenschaftlich ausgewertet. Die daraus resultierenden Ergebnisse werden auf Fachkongressen vorgestellt und in Fachjournalen publiziert. Die Veröffentlichung der Daten geschieht dabei völlig anonymisiert.

Die Teilnahme an dieser Studie beruht auf freiwilliger Basis. Es erfolgt keine finanzielle Aufwandsentschädigung für die Teilnahme an dieser Studie. Im Falle einer Teilnahme an dieser Studie können Sie Ihre Zustimmung ohne Angabe von Gründen jederzeit widerrufen. Falls Sie sich dafür entscheiden, die Studie abzubrechen, entstehen Ihnen daraus keine Nachteile.

Bei Rückfragen können Sie sich jederzeit wenden an:
Dr. med. Daniela Franz
Institut für Diagnostische und Interventionelle Radiologie
Klinikum rechts der Isar, Technische Universität München
Ismaninger Str. 22, 81675 München

Klinikum rechts der Isar

Technische Universität München

Klinikum rechts der Isar · Institut für Radiologie · 81664 München

Einverständniserklärung zur Teilnahme an der wissenschaftlichen Studie

„Detektion und Charakterisierung von braunem und beigem Fett im Menschen mittels MRT im Hinblick auf Korrelationen mit klinischen Parametern“

Name: _____

Geburtsdatum: _____

Ich, _____, bestätige mit meiner Unterschrift, dass ich über die oben genannte wissenschaftliche Studie von Ärztin / Arzt _____ vollständig und umfassend informiert wurde und erkläre mein Einverständnis, an dieser Studie teilzunehmen. In die für diese Studie vorgesehene MRT-Untersuchung habe ich schriftlich auf dem entsprechenden Informations- und Aufklärungsbogen eingewilligt.
Inhalte, Ziele und Risiken der Studie sowie persönlicher Zeitaufwand, der aus der Studienteilnahme resultiert, habe ich vollständig verstanden und meine sämtlichen Fragen diesbezüglich wurden von der oben genannten Ärztin / dem oben genannten Arzt ausreichend beantwortet.
Mir ist bekannt, dass meine Teilnahme an dieser Studie auf vollkommen freiwilliger Basis beruht und keine finanzielle Aufwandsentschädigung für die Studienteilnahme erfolgt.
Mir ist ebenso bekannt, dass ich meine erteilte Einverständniserklärung jederzeit und ohne Angaben von Gründen widerrufen werden kann und mir durch einen solchen Widerruf keinerlei Nachteile entstehen.
Eine Probandeninformation bezüglich der oben genannten Studie wurde mir in schriftlicher Form zusätzlich zum persönlichen Aufklärungsgespräch ausgehändigt.

Ich stimme zu, dass sämtliche Untersuchungsergebnisse pseudonymisiert erfasst, verarbeitet und gespeichert werden und die Studienergebnisse auf Fachkongressen vorgestellt und in Fachjournalen anonym publiziert werden dürfen.

Mit meiner Unterschrift bestätige ich mein Einverständnis zur Teilnahme an der oben genannten Studie.

.....
Datum, Unterschrift des Probanden

.....
Datum, Unterschrift der aufklärenden Ärztin / des aufklärenden Arztes

A4 – Prospero registration of the review on associations between SNPs and EE

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

The association between single nucleotide polymorphisms (SNPs) and energy expenditure (EE) in humans: a systematic review of observational studies

Theresa Drabsch, Christina Holzapfel, Hans Hauner

Citation

Theresa Drabsch, Christina Holzapfel, Hans Hauner. The association between single nucleotide polymorphisms (SNPs) and energy expenditure (EE) in humans: a systematic review of observational studies. PROSPERO 2018 CRD42018099482 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018099482

Review question

To investigate the associations between single nucleotide polymorphisms (SNPs) and energy expenditure (EE).

Searches

The electronic databases PubMed, Embase, Web of Science and The Cochrane Library will be systematically searched for associations between SNPs and EE.

The following search terms will be used:
"resting energy expenditure" OR "resting metabolic rate" OR "basal metabolic rate" OR "resting energy requirement" OR "energy expenditure" OR "REE" OR "RMR" OR "BMR" OR "RER" AND "genetic" OR "genetic variant" OR "gene variant" OR "polymorphism" OR "SNP" OR "single nucleotide polymorphism" OR "gene locus" OR "genotype" OR "gene" OR "genome-wide" OR "genomewide" OR "risk allele" OR "FTO" OR "fat mass and obesity associated"
Depending on the database being searched, plural forms of the search terms as well as quotation marks will be used. Furthermore, terms will also be searched using the "all field" option and abbreviations of the search items will also be searched as text words, again, depending on the database being used at the time.

The search will be restricted to articles in the English language, and limited to human studies. Publications in press will also be included.
Studies will be excluded if there is no use of indirect calorimetry (the gold standard for the measurement of EE).
A manual search of the reference lists of all eligible articles will also be carried out to identify further material for inclusion, and the literature search will be re-run for additional studies published between the first search date and the date of the final analysis to ensure completeness.

Types of study to be included

Observational studies.

Condition or domain being studied

SNPs and their association with EE.

Participants/population

Humans.
Studies on persons with specific conditions (e.g. severe diseases, pregnant or breastfeeding women, patients after bariatric surgery, mobility impaired participants, transplant patients) will be excluded.

Intervention(s), exposure(s)

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

The number of the risk alleles of any SNP and EE, as measured by indirect calorimetry.

Comparator(s)/control

Risk and non-risk allele carriers of any SNP will be compared.

Context

Indirect calorimetry is the gold standard for the measurement of resting energy expenditure (REE). REE is determined by different parameters, and the main source of variability of REE is the fat-free mass including the organ and muscle mass. Fat-free mass, fat mass, gender and physical activity explain 80 to 90% of the variation, the rest being attributable to genetic factors, which have not yet been fully explained (Ravussin and Bogardus 1989; Goran et al. 2000). Some studies have identified an association between the fat mass and obesity associated (FTO) gene and REE, but the results were inconsistent (Speakman 2015).
The present systematic review will therefore extend the current knowledge in this area by providing an overview of studies that have investigated associations between SNPs and EE, measured by indirect calorimetry.

Primary outcome(s)

The association between SNPs and EE, measured by indirect calorimetry.

Secondary outcome(s)

None.

Data extraction (selection and coding)

Two independent reviewers will screen the titles, abstracts, and full texts of publications according to the eligibility criteria. Any discrepancies will be discussed with a third reviewer. Studies clearly not meeting the inclusion criteria will be excluded, and the reasons for the exclusions will be documented separately.

Data from the selected articles will then be extracted from the studies selected for inclusion independently by two reviewers to ensure compliance. The literature will be organised using EndNote, and a standardised pilot-tested Excel spreadsheet will be used for the extraction of the following information:
1) Study characteristics: citation (author, year), method of EE measurement, genotype information (gene locus, SNP), statistical analyses;
2) Population characteristics: study population (e.g. inclusion/exclusion criteria), sample size, nationality of participants, age, gender;
3) Outcome of the studies (effect size);
4) Main results and limitations of the study;
Authors will be contacted via email to request missing information, if necessary.

Risk of bias (quality) assessment

The recommendations of the Cochrane Handbook and PRISMA guidelines will be followed. The quality assessment will be performed by two independent reviewers, and any discrepancies between the reviewers will be discussed and resolved by consultation with a third reviewer.

Strategy for data synthesis

A narrative synthesis will be provided for the findings from the included studies. The review should give a wide overview of the impact of any association between SNPs and EE, and detailed tables displaying the information from the eligible studies (e.g. study characteristics, outcome) will be presented.
If applicable, a qualitative and/or quantitative synthesis of study-level statistics will also be assessed.

Analysis of subgroups or subsets

This is a qualitative synthesis, and it is not possible to specify subgroups in advance. Nevertheless, a sensitivity analysis will be carried out if applicable.

Contact details for further information

Theresa Drabsch
theresa.drabsch@tum.de

Organisational affiliation of the review

Institute for Nutritional Medicine, University Hospital Klinikum rechts der Isar, Technical University of Munich

http://www.kem.wzw.tum.de

Review team members and their organisational affiliations

Ms Theresa Drabsch. Institute for Nutritional Medicine, University Hospital Klinikum rechts der Isar, Technical University of Munich
Dr Christina Holzapfel. Institute for Nutritional Medicine, University Hospital Klinikum rects der Isar, Technical University of Munich
Professor Hans Hauner. Institute for Nutritional Medicine, University Hospital Klinikum rechts der Isar, Technical University of Munich

Anticipated or actual start date

05 June 2018

Anticipated completion date

05 June 2019

Funding sources/sponsors

This review is funded by the German Federal Ministry of Education and Research (BMBF), grant number ("Förderkennzeichen"): 01EA1709

Conflicts of interest

Language

English

Country

Germany

Stage of review

Review_Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Basal Metabolism; Calorimetry, Indirect; Energy Metabolism; Genetic Association Studies; Genetic Markers; Humans; Polymorphism, Single Nucleotide

Date of registration in PROSPERO

03 July 2018

Date of publication of this version

03 July 2018

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions

03 July 2018

A5 – Approval for a publication-based dissertation

Einverständniserklärung zur publikationsbasierten Promotion[1]

Anlage 6 (für § 6 Abs. 2)

Hiermit erkläre ich mein Einverständnis, dass die Dissertation von

Frau/Herrn Theresa Drabsch

als publikationsbasierte Dissertation eingereicht wird. Sie erfüllt die nachfolgenden Kriterien:

1. Einleitungs- und Methodenteil (20 Seiten). Ein themenübergreifender Diskussionsteil mit Reflexion zur bestehenden Literatur.
2. Kumulative Einbindung von mindestens zwei akzeptierten Erstautorenveröffentlichungen (full paper in einem englischsprachigen, international verbreiteten Publikationsorgan, peer reviewed)
3. Die eingebundenen Veröffentlichungen müssen federführend vom Doktoranden abgefasst sein.
4. Eingebunden muss sein: je eine einseitige Zusammenfassung der jeweiligen Veröffentlichungen unter Hervorhebung der individuellen Leistungsbeiträge des Kandidaten.
5. Einbindung von ausgewählten Originalveröffentlichungen nur mit einem separaten schriftlichen „Erlaubnisschreiben des jeweiligen Verlags". Alle anderen Originalveröffentlichungen werden unter Nennung der bibliografischen Angaben aufgelistet. In den Exemplaren für die Mitglieder der Prüfungskommission sind alle Originalveröffentlichungen separat dazu abzugeben.

10.1.19
Datum

Unterschrift betreuender Prof.

[1] Zur Vorlage bei der Einreichung der Dissertation.

Acknowledgment

With many thanks to Univ.-Prof. Dr. med. Hans Hauner, head of the Institute, the present research work and finally the Ph.D. thesis have been completed at the Institute for Nutritional Medicine, Technical University of Munich. I am very grateful for the possibility to realize the work and his faith in me.

Further thanks goes to Prof. Dr. med. Andrea Bässler, head of cardiology / lipid outpatient clinic at the university hospital Regensburg, Klinik und Poliklinik für Innere Medizin II, for the acceptation of the task as a second examiner as well as Prof. Dr. Martin Klingenspor, chair of Molecular Nutritional Medicine for the responsibility as chairman.

Special thanks go to Christina Holzapfel, PhD, for all the excellent advice, the supervision of my work with a lot of engagement, for her inexhaustible support, the long meetings and discussions and for proofreading the thesis.

Moreover, I thank my cooperation partners at the University Hospital Klinikum rechts der Isar, Technical University of Munich, the chair of radiology (Dr. Dimitrios Karampinos, head of the institute) for providing data and supporting my work with comments and discussions.

Cordial thanks to Lynne Stecher, PhD, for her intensive support concerning the statistical part.

To all not namely mentioned colleagues, many thanks for your support in every matter, the excellent teamwork and all the helpful comments and discussions, and at least the help when the coffee has gone out.

Thanks to all my friends for the positive motivation, and the support during the time of the thesis. You inspired me to think outside the box and to find the optimum solution for my work and that I am able to master all challenges.

Last but not least, I am very grateful to my whole family, especially to Ferdinand who supported me in every way, thank you for the encouragement, the unconditional support and for your lovely tolerance throughout the whole time.

List of publications and congress contributions

Publications

Drabsch T, Gatzemeier J, Pfadenhauer L, Hauner H, Holzapfel C. Associations between single nucleotide polymorphisms and total energy, carbohydrate and fat intakes: a systematic review. *Advances in Nutrition 2018; 9:425–453*

Drabsch T*, Holzapfel C*, Stecher L, Petzold J, Skurk T, Hauner H. Associations between C-reactive protein, insulin sensitivity and resting metabolic rate in adults: a mediator analysis. *Frontiers in Endocrinology* 2018; 9:556 [*both authors contributed equally to the manuscript]

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Franz D, Weidlich D, Freitag F, Holzapfel C, **Drabsch T**, Baum T, Eggers H, Witte A, Rummeny EJ, Hauner H, Karampinos DC. Association of proton density fat fraction in adipose tissue with imaging-based and anthropometric obesity markers in adults. *International Journal of Obesity (Lond)* 2017; 42(2):175-182

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