From
the Institute of Epidemiology I, Helmholtz Zentrum München -
German Research Center for Environmental Health (GmbH)
Director: Dr. Joachim Heinrich
Former Director: Prof. Dr. Dr. H.-Erich Wichmann
in cooperation with
the Institute of Medical Information Processing, Biometry and Epidemiology,
Ludwig-Maximilians-Universität München
Director: Prof. Dr. Ulrich Mansmann
Chair of Epidemiology: Prof. Dr. Dr. H.-Erich Wichmann (emeritus)

Body Composition and Metabolism associated with Genetic Factors, Nutrition, and Metabolomics Data in Adults

Thesis
Submitted for a Doctoral Degree in Natural Science at the Faculty of Medicine,
Ludwig-Maximilians-Universität München

by
Carolin Jourdan
from
Schwetzingen

2012

Printed with approval of the Faculty of Medicine
of the Ludwig-Maximilians-Universität München

Supervisor/Examiner	Prof. Dr. Dr. H.-Erich Wichmann
Co-Examiner:	Prof. Dr. Ralf Zimmer
Co-Supervisor:	PD Dr. Jakob Linseisen
Dean:	Prof. Dr. med. Dr. h.c. Maximilian Reiser, FACR, FRCR
Date of oral examination:	08.01.2014

To my family.

This thesis contains results presented in the following publications:

C. Jourdan, S. Kloiber, A. Nieters, H. Seiler, H. Himmerich, M. A. Kohli, S. Lucae, G. Wolfram, C. Gieger, H. E. Wichmann, J. Linseisen (2011). Gene-PUFA interactions and obesity risk. *Br J Nutr*, 106(8): 1263-72.
Permission for reuse of this article in this thesis was granted by Cambridge University Press, copyright (2011).

C. Jourdan, A. K. Petersen, C. Gieger, A. Döring, T. Illig, R. Wang-Sattler, C. Meisinger, A. Peters, J. Adamski, C. Prehn, K. Suhre, E. Altmaier, G. Kastenmüller, W. Romisch-Margl, F. J. Theis, J. Krumsiek, H. E. Wichmann, J. Linseisen (2012). Body fat free mass is associated with the serum metabolite profile in a population-based study. *PLoS One*, 7(6): e40009.

C. Jourdan, J. Linseisen, C. Meisinger, A. K. Petersen, C. Gieger, R. Rawal, T. Illig, M. Heier, A. Peters, H. Wallaschofski, M. Nauck, G. Kastenmüller, K. Suhre, C. Prehn, J. Adamski, W. Koenig, M. Roden, H. E. Wichmann, H. Völzke (2014). Associations between thyroid hormones and serum metabolite profiles in an euthyroid population. *Metabolomics*, 10: 152-164.
Permission for reuse of this article in this thesis was kindly granted by Springer Science and Business Media, copyright (2014).

Contents

List of Figures

List of Tables

List of Abbreviations

AA	arachidonic acid
ACE	angiotensin-converting-enzyme
ADIPOQ	adiponectin
alkyl-DHAP	alkyl-dihydroxyacetonephosphate
BCAA	branched-chain amino acid
BIA	bioelectrical impedance analysis
BFMI	body fat mass index
BMI	body mass index
BSV II	second Bavarian food consumption survey
CHR	chromosome
CI	confidence interval
C:D	carbon number and position of double bounds
DHA	docosahexaenoic acid
DIO2	type 2 deiodinases
ELOVL	elongation of very long chain fatty acids protein
EC	extracellular
EPA	eicosapentaenoic acid
EPA&DHA	sum of EPA and DHA
ESI	electrospray ionisation
FADS	fatty acid desaturase
FAME	fatty acid methyl ester
FFMI	fat free mass index
FT3	free triiodothyronine
FT4	free thyroxine
GC	gas chromatography
GGM	Gaussian graphical model
GWAS	genome-wide association study

IL	interleukin
KORA	cooperative health research in the region of Augsburg
KORA F4	follow-up of KORA S4
KORA S4	survey 4 of KORA
LA	linoleic acid
LC	liquid chromatography
LD	linkage disequilibrium
LEP	leptin
LEPR	leptin receptor
MAF	minor allele frequency
MC4R	melanocortin 4 receptor
MET	metabolic equivalent
MET x h	energy expenditure
MS	mass spectrometry
MS/MS	tandem mass spectrometry
NPY	neuropeptide Y
NPY1R	NPY receptor type 1
NPY5R	NPY receptor type 5
OR	odds ratio
$\mathbf{P}_{int}$	p-value of the likelihood ratio test comparing models with and without an interaction term in the BVS II study
PC	phosphatidylcholine
PGE_2	prostaglandin E2
POMC	proopiomelanocortin
PPARγ	peroxisome proliferator-activated receptor gamma
PPARγC1A	PPARγ coactivator 1-alpha
PPY	pancreatic polypeptide
PYY	peptide YY
PUFA	polyunsaturated fatty acid
RETN	resistin
REE	resting energy expenditure
SCD	stearoyl-CoA desaturase-1
SD	standard deviation
SM	sphingomyelin

SM (OH)	hydroxysphingomyelin
SNP	single nucleotide polymorphism
TNF-α	tumour necrosis factor-alpha
TNFRSF	TNF receptor superfamily
TRH	thyrotropin-releasing hormone
TR	thyroid hormone receptor
TSH	thyroid-stimulating hormone; thyrotropin
T3	triiodothyronine
T4	thyroxine

Summary

The human health status is co-determined by the interplay of body composition, metabolism, and energy balance. In turn, these factors are influenced by genetic predispositions, a multitude of environmental factors such as nutritional habits or physical activity, and interactive effects between these parameters. Malnutrition and obesity reflect extreme phenotypes of body composition, and lead to disturbances in metabolism. Especially obesity as a prominent health problem in industrialised countries is linked to an increased risk of morbidity and mortality. Important regulators of energy balance and metabolism are thyroid hormones and disturbances of their homoeostasis are associated with serious health problems.

Metabolomics is an evolving field which has the ability to represent a snapshot of the current metabolic state. Disturbances of pathways can be captured and the utilisation of closely connected metabolites ratios provides proxies for enzymatic reactions. In this doctoral thesis, three projects are presented exploring the interplay of body composition, metabolism, and energy homeostasis by focusing on gene–nutrition interactions and their effect on obesity risk, the relationship between fat free mass and the serum metabolite profile of adults, and the influence of thyroid hormones on the metabolism in euthyroid adult participants.

The first project aims at improving the understanding of inter-individual variance and susceptibility towards obesity. Common obesity is the result of a genetic predisposition in combination with nowadays modern environment which encourages a sedentary lifestyle and often leads to an imbalance in energy intake and expenditure, subsequently followed by weight gain. To this end, adjusted logistic regression models are used to analyse the interaction effects between single nucleotide polymorphisms (SNPs) of different candidate genes for obesity and polyunsaturated fatty acids (PUFAs) analysed in erythrocyte membranes, which are valid biomarkers for PUFA intake, on the obesity risk in adults participating in a cross-sectional population-based study. Several significant SNP–PUFA interactions are identified, indicating regulatory effects of PUFAs by gene variants of interleukin (*IL*)-*2*, *IL-6*, *IL-18*,

tumour necrosis factor receptor superfamily (*TNFRSF*) member 1B and 21, leptin receptor (*LEPR*), and adiponectin (*ADIPOQ*). Due to the limited statistical power of this study, these results have to be reproduced in a sufficiently sized prospective study. If replicated, our results would indicate a beneficial effect of high PUFA supply for a substantial proportion of the population with respect to obesity risk.

Aspiration of the second project is to provide a comprehensive picture of fat free mass induced effects on the metabolite profile in blood samples of adults. Further, it is hypothesised that a sedentary lifestyle leads to derangements in skeletal muscle metabolism, e.g., favouring the development of obesity. Thus, the associations between the fat free mass index (FFMI) and up to 190 serum metabolite concentrations - with a focus on amino acids, acylcarnitines, phosphatidylcholines (PCs), and sphingomyelins - and all intra-class metabolite ratios are investigated by means of adjusted linear regression models in cross-sectional analyses of a cohort study. These analyses reveal 339 significant associations between FFMI and various metabolites and metabolite ratios. Among the most prominent associations with higher FFMI are increasing concentrations of the branched-chain amino acids (BCAAs), ratios of BCAAs to glucogenic amino acids, and carnitine concentrations. These findings are in agreement with the expected metabolic situation in fasted participants. Most of these results are replicated in the follow-up survey of the analysed baseline study. In order to draw a comprehensive picture of the FFMI effects, Gaussian graphical models (GGMs) are computed. These models have previously been shown to reveal the true relationships among metabolites. Further, genetic aspects are investigated. To this end, the relationships between SNPs described to be associated with anthropometric characteristics and the metabolite variables are analysed; however, no significant association is revealed. Sensitivity and stratified analyses are carefully performed. Most interestingly, almost all associations which are found for the entire sample are largely missing in the obese subgroup supporting our hypothesis that the accumulation of body fat tissue may be accompanied by a derangement in skeletal muscle metabolism.

The aim of the third project is to identify thyroid hormone related changes on metabolism of fasting euthyroid participants in a cross-sectional analysis of a cohort study. To this end, the associations between free tyroxine (FT4), thyrotropin (TSH), and 151 metabolites as well as their pairwise intra-class metabolite ratios are analysed in adjusted linear regression models. Increased serum FT4 levels are associated with an overall enhanced transport to the mitochondria and β-oxidation of fatty acids which is reflected by significantly increased serum acylcarnitine concentrations and decreased PC concentrations. Further, these findings

are largely stable as they could be reproduced in different subsets of the population, including obese versus non-obese participants. No significant associations are found between the metabolite variables and the TSH concentrations.

In summary, this doctoral thesis provides indication of a beneficial effect of high PUFA supply for specific genotype carriers with respect to obesity risk. An extensive image of FFMI effects in a data-driven metabolic network is revealed and high body fat accumulation is linked to a derangement in skeletal muscle metabolism. Further, this thesis broadens our knowledge of FT4 triggered pathways in euthyroid participants. Thus, this thesis contributes deeper insight into the interplay of body composition, metabolism, and energy balance.

Zusammenfassung

Der Gesundheitszustand des Menschen wird neben anderen Faktoren durch das Zusammenspiel von Körperzusammensetzung, Stoffwechsel und Energiehaushalt bestimmt. Diese Faktoren werden wiederum durch genetische Prädispositionen, eine Vielzahl von Umweltfaktoren, wie beispielsweise Ernährungsgewohnheiten oder körperliche Aktivität, sowie durch Interaktionseffekte dieser Parameter beeinflusst. Unterernährung und Adipositas reflektieren extreme Phänotypen der Körperzusammensetzung und führen zu Störungen im Stoffwechsel. Insbesondere Adipositas, ein prominentes Gesundheitsproblem in den industrialisierten Ländern, erhöht das Morbiditäts- und Mortalitätsrisiko. Der Energiehaushalt und der Stoffwechsel unterliegen einem starken Einfluss der Schilddrüsenhormone. Störungen ihrer Homöostase sind mit schweren gesundheitlichen Problemen verbunden.

Die Metabolomforschung (englisch "metabolomics") ist ein sich entwickelndes Forschungsgebiet, welches es an Hand der gemessenen Metaboliten ermöglicht, eine Momentaufnahme der aktuellen Stoffwechsellage abzuzeichnen. Darüber hinaus bietet die Untersuchung der Metaboliten die Möglichkeit, Störungen in Stoffwechselwegen zu erfassen und durch die Verwendung von Metaboliten-Quotienten enzymatische Reaktionen zu identifizieren. In dieser Dissertation werden drei Projekte vorgestellt, welche das Zusammenspiel von Körperzusammensetzung, Stoffwechsel und Energiehaushalt erforschen. Die Schwerpunkte liegen dabei auf Gen–Ernährungs–Interaktionen und ihre Auswirkungen auf das Adipositasrisiko, auf der Beziehung zwischen der fettfreien Masse und den Serum–Metaboliten–Profilen Erwachsener, sowie auf dem Einfluss der Schilddrüsenhormone auf den Stoffwechsel; letzterer widergespiegelt in den Serum–Metaboliten–Profilen euthyroider erwachsener Studienteilnehmer.

Das erste Projekt zielt darauf ab, das Verständnis der inter-individuellen Variabilität und Empfänglichkeit gegenüber Adipositas zu verbessern. Adipositas ist das Ergebnis einer genetischen Prädisposition in Kombination mit dem heutigen modernen Lebensumfeld. Dieses ist oft geprägt von einer sitzenden Lebensweise und führt dadurch zu einem Ungleichgewicht in Energieaufnahme und -verbrauch, welches letztendlich mit einer Gewichtszunahme

verbunden ist. Bezüglich des Adipositasrisikos bei Erwachsenen werden die Wechselwirkungen zwischen Einzelnukleotid-Polymorphismen (SNPs) unterschiedlicher Adipositas-Kandidatengene und der Erythrozytenmembranzusammensetzung mehrfach ungesättigter Fettsäuren (PUFAs), welche valide Biomarker für die PUFA–Zufuhr darstellen, mit Hilfe von adjustierten logistischen Regressionsmodellen in einer populationsbasierten Querschnittsstudie untersucht. Mehrere signifikante SNP-PUFA-Interaktionen werden gefunden, die auf einen regulatorischen Effekt der PUFA auf Genvarianten von Interleukin (*IL*)*-2*, *IL-6*, *IL-18*, Tumornekrosefaktor-Rezeptor-Superfamilie (*TNFRSF*) Element 1B und 21, Leptin–Rezeptor (*LEPR*) und Adiponektin (*ADIPOQ*) hinweisen. Aufgrund der begrenzten statistischen Teststärke dieser Studie sollten diese Ergebnisse in einer ausreichend großen prospektiven Studie repliziert werden. Bei Bestätigung der hier dargestellten Ergebnisse, würden diese eine positive Wirkung einer hohen PUFA-Versorgung für einen erheblichen Anteil der Bevölkerung im Hinblick auf das Adipositasrisiko anzeigen.

Im zweiten Projekt soll ein umfassendes Bild der durch die fettfreie Masse (als Proxy für die Muskelmasse) induzierten Effekte auf das Stoffwechselprofil in Blutproben von Erwachsenen ermittelt werden. Ebenso soll die Hypothese geklärt werden, ob eine sitzende Lebensweise zu Störungen des Skelettmuskulatur–Stoffwechsels führen kann, welche z.B. die Entwicklung von Adipositas begünstigen könnten. Dazu werden die Assoziationen zwischen dem fettfreien Masse Index (FFMI) und bis zu 190 Serummetaboliten (unter anderem Aminosäuren, Acylcarnitine, Phosphatidylcholine (PCs) und Sphingomyeline) sowie der paarweisen Metaboliten-Quotienten innerhalb der einzelnen Klassen mit Hilfe von adjustierten linearen Modellen in unabhängigen Querschnittsauswertungen einer Kohortenstudie untersucht. Es werden 339 signifikante Assoziationen zwischen FFMI und den verschiedenen Metaboliten und Metaboliten-Quotienten gefunden. Zu den prominentesten Assoziationen mit höherem FFMI gehören steigende Konzentrationen der verzweigtkettigen Aminosäuren (BCAA), Assoziationen mit Quotienten von BCAAs zu glukogenen Aminosäuren und mit verschiedenen Carnitin-Konzentrationen. Diese Ergebnisse stimmen mit den Erwartungen bezüglich des Stoffwechsels nüchterner Personen überein. Die meisten dieser Ergebnisse werden auch im Follow-Up der analysierten Studie repliziert. Um ein umfassendes Bild der FFMI-Effekte aufzuzeigen, werden Gauß'sche graphische Modelle (GGMs) gerechnet. Vor kurzem wurde gezeigt, dass diese Modelle die wahren Beziehungen zwischen einzelnen Metaboliten offenlegen können. In diesem Projekt werden ebenfalls genetische Aspekte berücksichtigt. Dazu werden die Assoziationen zwischen SNPs, für die ein Zusammenhang mit anthropometrischen Merkmalen beschrieben wurde, und den Metabolitenvariablen un-

tersucht. Jedoch werden keine signifikanten Assoziationen gefunden. Sensitivitätsanalysen und stratifizierte Analysen werden sorgfältig realisiert. Interessanterweise fehlen fast alle Assoziationen, die für die gesamte Population vorhanden sind, in der adipösen Untergruppe. Dieses Ergebnis unterstützt unsere Hypothese, dass eine Akkumulation von Fettgewebe möglicherweise mit einer Störung im Skelettmuskulatur–Stoffwechsel einhergeht.
Die Zielsetzung des dritten Projektes ist es, die Auswirkungen der Schilddrüsenhormone auf den Stoffwechsel bei nüchternen euthyroiden Teilnehmern einer Kohortenstudie in einer unabhängigen Querschnittsauswertung zu analysieren. Zu diesem Zweck werden die Assoziationen zwischen freiem Tyroxin (FT4), Thyreotropin (TSH), und 151 Metaboliten sowie der paarweisen Metaboliten-Quotienten innerhalb der einzelnen Klassen mittels adjustierter linearer Modelle untersucht. Eine erhöhte Serumkonzentration des FT4 ist mit einem insgesamt verbesserten Transport in die Mitochondrien und einer gesteigerten β-Oxidation der Fettsäuren verbunden, welche durch signifikant erhöhte Serum–Konzentrationen von Acylcarnitinen und verringerte Konzentrationen von PCs angezeigt wird. Diese Ergebnisse sind weitgehend stabil, da sie in verschiedenen Subgruppen, unter anderem in adipösen versus nicht-adipösen Studienteinehmern, reproduziert werden können. Zwischen den TSH–Konzentrationen und den Serum–Metaboliten-Profilen sind keine signifikanten Beziehungen gefunden worden.
Zusammenfassend liefert diese Dissertation Hinweise auf einen positiven Effekt einer erhöhten PUFA–Versorgung für spezifische Genotyp–Träger mit Bezug auf das Adipositasrisiko. Sie zeigt ein umfangreiches Bild der FFMI–Effekte auf den Stoffwechsel in einem datengesteuerten Netzwerk auf und gibt Hinweise darauf, dass eine hohe Körperfettakkumulation mit einer Störung des Skelettmuskulatur-Stoffwechsels verbunden ist. Darüber hinaus wird unser Wissen über FT4–gesteuerte Stoffwechselwege in euthyroiden Personen erweitert. Somit gewährt diese Arbeit einen tieferen Einblick in das Zusammenspiel von Körperzusammensetzung, Stoffwechsel und Energiehaushalt.

1 Introduction

Among the multitude of factors which influence the human health status are body composition, metabolism, and energy homeostasis. These factors do not only co-determine our health status, they are also dependent on one another, and are themselves influenced by many environmental and genetic parameters. This doctoral thesis aims at contributing new aspects to this broad research area. Gene–Nutrition interactions and their effects on obesity risk are explored. The relationship between the fat free mass and adult serum metabolite profiles is investigated, and the influence of thyroid hormones on the metabolic makeup of euthyroid participants is analysed.

For our research important topics such as body composition (1.1), blood metabolites (1.2), and thyroid hormones (1.3) are introduced in this chapter. The three studies in which we explored our research questions and the utilised analyses methods are described in chapter 2. The results are given in chapter 3 and are followed by a comprehensive discussion. The last chapter of this doctoral thesis provides future prospects in this scientific field.

1.1 Body Composition

The characterisation and classification of the human body in the context of health and disease have been discussed ever since. There is hardly any epidemiological setting in which anthropometric aspects of the human body or its composition are not involved, either as adjustment parameters or as primary point of interest. The composition of the human body can be measured at the atomic (oxygen, carbon, hydrogen, nitrogen, calcium, and phosphorus), molecular (water, lipid, protein, mineral, and glycogen), cellular (extracellular (EC) fluid, EC solids, and cell mass), tissue (skeletal muscle, adipose tissue, bone, and blood), or at the whole body level (Wang et al., 1992) and over the past decades numerous techniques have therefore evolved (Duren et al., 2008). The major components of the different body composition level models are illustrated in Figure 1.1.

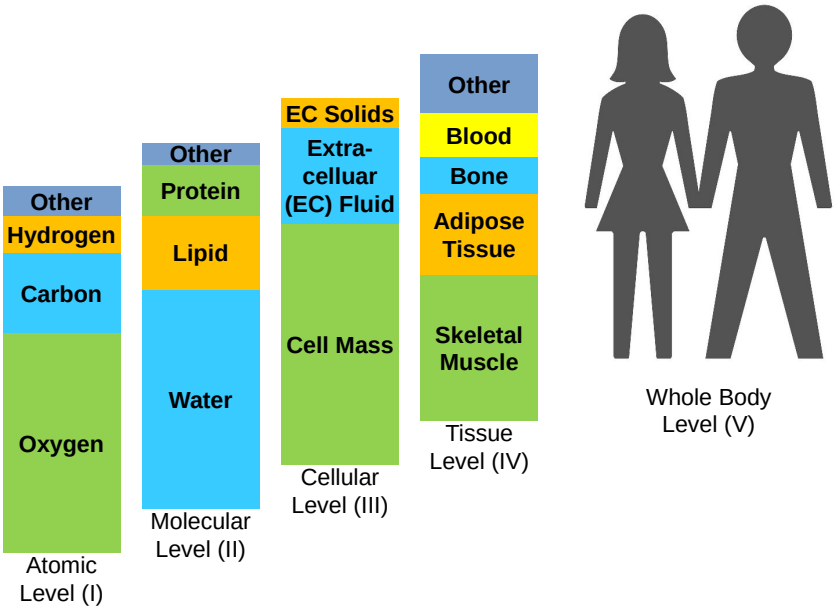

Figure 1.1: Body composition at different levels. *Adapted by permission from the American Society of Nutrition: Wang et al., copyright (1992).*

Neutron activation, isotope dilution or total body counting are methods which assess the body composition at the atomic, molecular or cellular level and have been described in more detail by Beechy et al. (2012) and Duren et al. (2008). In this thesis we concentrate on the body composition measured at the tissue level and the derived two compartment (body fat mass and fat free mass) model of it. There are direct and indirect methods to assess a person's body composition at the tissue level. Direct methods such as computed tomography, magnetic resonance imaging, dual-energy X-ray absorptiometry, or densitometry measure the amount and distribution of at least one tissue or the body's density. Indirect methods include bioelectrical impedance analysis (BIA) and anthropometric measurements.

Anthropometry is the most basic instrument to assess a person's body composition. It is a universally applicable, non-invasive, and inexpensive method to describe body mass, size, shape, and level of fatness (World Health Organization, 1995; Duren et al., 2008). Measurements include amongst others weight, height, as well as circumferences of waist and hip (Beechy et al., 2012). The most prominent anthropometric index, the body mass index (BMI), was introduced in the late 1980s as a measurement of malnutrition and obesity (Keys et al., 1972; James et al., 1988). The BMI is defined as the ratio of body

Table 1.1: The World Health Organisation's classification of underweight, overweight and obesity of adults according to BMI. *Adapted from the World Health Organization by permission from the World Health Organization, copyright (2000).*

Classification	BMI (kg/m^2)	Risk of Comorbidities
underweight	< 18.5	low (but risk of other clinical
severe thinness	< 16.0	problems increases)
moderate thinness	16.0 to < 17.0	
mild thinness	17.0 to < 18.5	
normal range	18.5 to < 25.0	average
overweight	25.0 to < 30.0	increased
obese	≥ 30.0	
obese class I	30.0 to < 35.0	moderate
obese class II	35.0 to < 40.0	severe
obese class III	≥ 40	very severe

weight to squared body height (kg/m^2). The World Health Organization (2000) divides the BMI in four categories (underweight, normal range, overweight, and obese) with three subcategories to classify each, the severity of underweight and obesity (Table 1.1).

The BMI is often regarded and used as a surrogate measurement of a person's body composition as it is presumed to represent the degree of fatness (Duren et al., 2008). For adults, the correlation between excessive accumulation of body fat mass and a BMI in the obesity range is quite modest. However, this relationship is influenced by a person's physical activity level, age, and race (Dulloo et al., 2010). For example athletes, in particular bodybuilder, have a very low percentage of body fat, but a great amount of muscle mass and according to their BMI, they would be classified as obese. Although, the BMI is seen as a reasonable good predictor of disease risk and early mortality (World Health Organization, 2000), BMI and weight taken on their own are not sufficient to characterise underlying changes in body composition during ageing or illness (Kyle et al., 2003b). The main drawback of the BMI, however, is that the actual body composition, e.g., the distribution of body fat mass and fat free mass, is not considered (Schutz et al., 2002). Nevertheless, the accessibility to extensive national reference data in adult populations, and the established relationships between BMI and degree of fatness, mortality and morbidity are considerable advantages of the BMI (World Health Organization, 1995).

In BIA measurements, the human body functions as a conductor to a small alternating electrical current (in general 50 kHz) and its resistance in combination with the phase angle

allows the estimation of total body water. With the assumption of a constant hydration of the fat free mass of 73.2 % (Wang et al., 1992) and the application of established equations, e.g., Kyle's equation (Kyle et al., 2001), body composition can be estimated in two compartments: the fat free mass and the body fat mass. Because of its feasibility, minimal cost, portability, and safety, BIA measurements are quite attractive for large-scale studies (Lee & Gallagher, 2008). However, adequate equations have to be applied as the accurateness of the calculated values is dependent on the healthy underlying population they are derived from and on the assumptions made regarding the biological interrelationship among the body compartments and their distribution (Duren et al., 2008). These equations are influenced by age, gender, illness, race, or degree of fatness (Rush et al., 2006) and most often they do not apply to or exist for sick or obese people (Beechy et al., 2012).

Research has indicated that body composition is a principal determinant of health (Segal et al., 1987). Therefore, Kyle et al. (2003b) propose that the measurement of fat free mass and body fat mass should be regularly included in health assessments. Depending on the distribution of fat free mass and body fat mass, two individuals with the same weight and height may look completely different. As fat free mass and body fat mass change with weight, height and age it is difficult to classify if a person's fat free mass or body fat mass is in the higher or lower range. Therefore, similar to the BMI, the fat free mass index (FFMI, kg/m^2) and accordingly the body fat mass index (BFMI, kg/m^2) have been established and allow for height- and weight-independent interpretations and comparisons between studies (Kyle et al., 2003b).

In an apparently healthy Caucasian population (n = 5635) aged 18 to 98 years, Schutz et al. (2002) established the FFMI and BFMI for the 25^{th} and 75^{th} percentiles and different BMIs (Table 1.2). Deviations from those values might indicate disease, derangement, or obesity (Kyle et al., 2003b). Four extreme cases are shown in Figure 1.2 (Dulloo et al., 2010): (i) Combination of low FFMI and low BFMI corresponds to chronic energy deficiency – people having a low BMI and are probably suffering from anorexia or protein-energy malnutrition; (ii) Combination of low BFMI and high FFMI corresponds to muscle hypertrophy – people having a high BMI in the obesity range, without actually being overfat, such as bodybuilders; (iii) Combination of low FFMI and high BFMI corresponds to sarcopenic elderly or sarcopenic obesity – people are classified as overfat at different levels of BMI having a substandard amount of muscle mass in relation to their body fat mass; and (iv) Combination of high FFMI and high BFMI corresponds to the sumo wrestler type – people having a BMI in the obese range representative of their excessive body fat and muscle mass. Schutz et al.

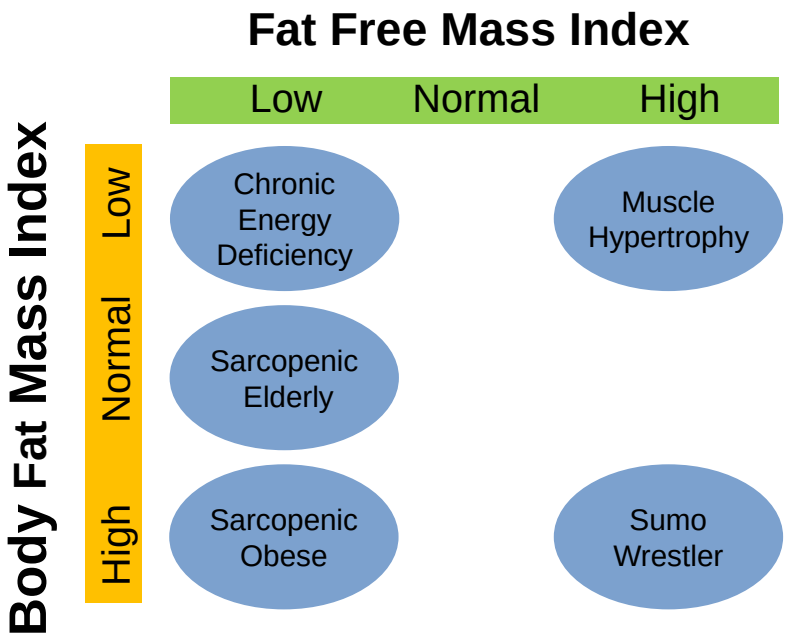

Figure 1.2: Combinations of Fat Free Mass Index (kg/m^2) and Body Fat Mass Index (kg/m^2) indicating various conditions. *Adapted by permission of the Macmillan Publishers Ltd.: Dulloo et al., copyright (2010).*

(2002) proposed that men with a larger BFMI than 8.2 kg/m^2 and women with a larger BFMI than 11.8 kg/m^2 are declared as overfat. In the following the two compartments fat free mass and body fat mass are further discussed.

1.1.1 Fat Free Mass

In the two compartment model, fat free mass equals body weight minus body fat mass. Thus, the fat free mass includes next to the skeletal muscles inter alia organs, blood, and bones (Wang et al., 1992). It is the major contributor to the resting energy expenditure (REE). This, however, is not so much due to the skeletal muscles, which accounts for about 20 to 30 % of REE, but it is the merit of the organs, such as brain, heart, liver, and kidneys (Dulloo et al., 2010). Nevertheless, the largest fraction of the fat free mass is the skeletal muscle (about 50 to 60 % (Dulloo et al., 2010)). It accounts for one-third to one-half of total body protein, depending on gender, age, and health status (Heymsfield et al., 1990). As the skeletal muscle mass itself is difficult to measure in most epidemiological studies, data on fat free mass is often used as a proxy instead.

Table 1.2: Fat Free Mass Index (FFMI) and Body Fat Mass Index (BFMI) for the 25^{th} and 75^{th} percentile and different BMIs. *Adapted by permission from Macmillan Publishers Ltd.: Schutz et al., copyright (2002).*

	Percentiles		BMI (kg/m^2)		
	25%	75%	18.5	20.0	25.0
Men					
FFMI (kg/m^2)	18.2	20.0	16.7	17.5	19.8
BFMI (kg/m^2)	3.5	5.9	1.8	2.5	5.2
Women					
FFMI (kg/m^2)	15.0	16.6	14.6	15.1	16.7
BFMI (kg/m^2)	4.9	7.8	3.9	4.9	8.3

The skeletal muscle mass is a major determinant of overall energy requirement of the body. It is a predictor of basal metabolic rate and especially of energy turn-over during physical activity. In addition, it has recently been identified as an endocrine organ (Pedersen & Febbraio, 2008); producing and releasing peptides and cytokines which exhibit various biological effects on the muscle tissue itself and beyond (Pedersen, 2011). Among the most important effects of muscle mass and activity with respect to chronic diseases are an enhanced fat oxidation, improved insulin sensitivity, and a reduced body fat mass. Further, the effects of the released myokines (peptides and cytokine) during regular exercise seem to be protective against diseases with chronic inflammation (Pedersen, 2009), e.g., by modulating the immune response. However, if these endocrine functions of the skeletal muscles are not stimulated by physical activity, none of these positive effects will occur which might result in malfunctioning of several organs and tissues and the risk of cardiovascular disease, cancer, diabetes, or depression could rise (Pedersen & Febbraio, 2008). Pedersen (2009) summarises those unfavourable health effects under the concept of the "diseasesome of physical inactivity". Further, a loss of fat free mass (sarcopenia) is associated with increased mortality (Allison et al., 1997), especially in the elderly.

1.1.2 Body Fat Mass

Body fat mass is dividable into essential fat mass, the crucial amount of fat which our bodies need to maintain life and reproductive functioning, and storage fat which is accumulated in adipose tissue (Wang et al., 1992). Body fat is of multiple uses, e.g., as energy storage, physical protection for organs, regulation of body temperature, and body fat is involved in

the fabrication of cell membranes. For quite a while, adipose tissue was only seen as the largest, inert energy reservoir in the human body. However, since the late 1980's it has started to be recognised as a highly active endocrine and metabolic organ (Siiteri, 1987; Zhang et al., 1994; Ahima & Flier, 2000; Fruhbeck et al., 2001), producing cytokines and a variety of bioactive peptides, known as adipokines. Further, a large number of receptors are expressed in the adipose tissue enabling it to communicate with organs and the central nervous system, as well as to influence a number of processes such as energy metabolism, neuroendocrine functions, and immune response (Kershaw & Flier, 2004). However, the excessive storage of body fat leads to obesity and high amounts of body fat, especially visceral fat and fat in liver tissue (Pischon et al., 2008), are associated with an increased risk of diseases such as type II diabetes, cardiovascular diseases, several types of cancer, or renal failure (Galic et al., 2010).

Obesity

Obesity, defined as excessive fat accumulation, is in general measured by the BMI, and represents a major health burden. By doubling its worldwide prevalence since 1980 (World Health Organization, 2012), obesity has reached a pandemic state. In May 2012, the World Health Organization reported, that more than one out of ten adults of the world population is obese and that each year more than 2.8 million adults die as a consequence of being obese or overweight (World Health Organization, 2012). Furthermore, obesity and overweight are responsible for about 44 % of diabetes cases, 23 % of heart disease, and 7 to 41 % of certain cancers (World Health Organization, 2012). According to the National Nutrition Survey II (Max Rubner-Institut – Bundesforschungsanstalt für Ernährung und Lebensmittel, 2008), the obesity prevalence in German adults is about 20 % (20.5 % men, 21.2 % women).

Obesity is a multifactorial disorder reflecting complex interactions of genes, environment and lifestyle (Newell et al., 2007). Industrialisation and modernisation encourage a sedentary lifestyle with concomitantly increased energy intake, resulting in an imbalance of energy intake and expenditure (Bell et al., 2005) and consequently in gaining surplus weight. Further, about 40 to 70 % of the variance in the BMI is accounted for by genetic factors as several studies of twins, adoptees and families have shown (Maes et al., 1997; Atwood et al., 2002; Salsberry & Reagan, 2010). Screenings of candidate regions as well as genome-wide scans have helped to identify single nucleotide polymorphisms (SNPs) which increase the risk of becoming overweight or obese (Peeters et al., 2009).

Thus, obesity is the result of an interaction between genetic predisposition and the modern obesogenic environment (Bouchard, 1991). As it is spreading rather rapidly and representing a major health problem, it is important to improve the understanding of inter-individual variance and susceptibility.

1.2 Blood Metabolites

Our blood consists of erythrocytes, leukocytes, and platelets which are suspended in a liquid straw-coloured carrier called plasma which is responsible for 50 to 55 % of our blood volume (Fox, 1999; Psychogios et al., 2011). To separate plasma from the cellular part, whole blood sample are mixed with anticoagulants, centrifuged and then the liquid (plasma) is lifted off the separated cell mass. If no anticoagulants are added and whole blood samples are left to clot before they are centrifuged then the liquid which separates from the cellular component is called serum. Plasma as well as serum includes inter alia proteins, peptides, nutrients, electrolytes, and organic wastes (Psychogios et al., 2011). The main difference between plasma and serum is attributable to the (non-) clotting process. For example, eicosanoid biosynthesis is fully stimulated during the clotting process and thus levels of those serum metabolites are not reflective of the physiological concentration (Fischer, 1986).
Psychogios et al. (2011) described it in a nutshell: *"... blood bathes every tissue and every organ in the body, it essentially serves as a liquid highway for all the molecules that are being secreted, excreted or discarded by different tissues in response to different physiological needs or stresses."* As the functioning of our whole body seems to be reflected in our blood, it is not surprising that its chemical analyses has been focused on for over 70 years (Kekwick, 1939; Grant & Butt, 1970).

1.2.1 Fatty Acid Composition of the Erythrocyte Membranes

The assessment of dietary fat intake is a task which has not been resolved sufficiently for many reasons (Arab & Akbar, 2002). Although our nutrition is in part reflected in our blood constituents, good biomarkers for total fat intake have not yet been found, as our blood is also reflective of the subsequent metabolism of those fatty acids. However, the correlation between dietary intake of polyunsaturated fatty acids (PUFAs) and the PUFA composition of the erythrocyte membranes is quite stable. Thus, the PUFA composition of erythrocyte membranes is accepted as good biomarker of PUFA intake and metabolism.

Type of Fatty Acid	C:D	Common Name	Mean ± SD
Saturated Fatty Acids	16:0	Palmitic Acid	25.17 ± 6.70
	18:0	Stearic Acid	20.27 ± 3.02
Mono-unsaturated Fatty Acids	18:1	Oleic Acid	15.12 ± 2.48
***n-6* Polyunsaturated Fatty Acids**	18:2	Linoleic Acid	11.06 ± 2.25
	18:3	γ-Linolenic Acid	0.04 ± 0.02
	20:3	Dihomo-γ-Linolenic Acid	1.54 ± 0.56
	20:4	Arachidonic Acid	13.98 ± 5.22
	22:4	Adrenic Acid	2.65 ± 1.24
***n-3* Polyunsaturated Fatty Acids**	18:3	α-Linolenic Acid	0.09 ± 0.05
	20:5	Eicosapentaenoic Acid	0.90 ± 0.71
	22:5	Docosapentaenoic Acid	2.21 ± 1.17
	22:6	Docosahexaenoic Acid	4.66 ± 2.51

Figure 1.3: Mean and standard deviation (SD) of major fatty acids (% of total fatty acid methyl ester) measured in the erythrocyte membranes of participants of the BVS II.

In most cases, the fatty acid composition of the erythrocyte membranes is chromatographed as fatty acid methyl esters. Different methods are described in more detail by Arab & Akbar (2002). The fatty acid composition of the erythrocyte membranes of participants of the second Bavarian Food Consumption Study (BVS II) which is part of the first project, was analysed by means of gas chromatography (GC) coupled to a flame ionisation detector. There, analyses were carried out on a polar column which separated the fatty acid methyl esters based on carbon number and position of double bounds (C:D) and quantification was done with the help of a flame ionisation detector (2.1.3).

Figure 1.3 shows the main fatty acids which were assessed in the BVS II. For the present project, linoleic acid (LA, 18:2), arachidonic acid (AA, 20:4) as well as eicosapentaenoic (EPA, 20:5) and docosahexaenoic acid (DHA, 22:6) were chosen. The PUFA composition of the erythrocyte membranes reflects both PUFA intake and subsequent metabolism of the fatty acids over a period of weeks and months (Arab & Akbar, 2002). There is considerable evidence that not all fatty acids are obesogenic (Storlien et al., 2001). Approximately 6.2 to 7.4 % of our average daily energy intake is accounted for by PUFAs (*n-3* PUFA 0.7 to 0.9 %; *n-6* PUFA 5.5 to 6.5 %; (Linseisen et al., 2003)). PUFAs exert

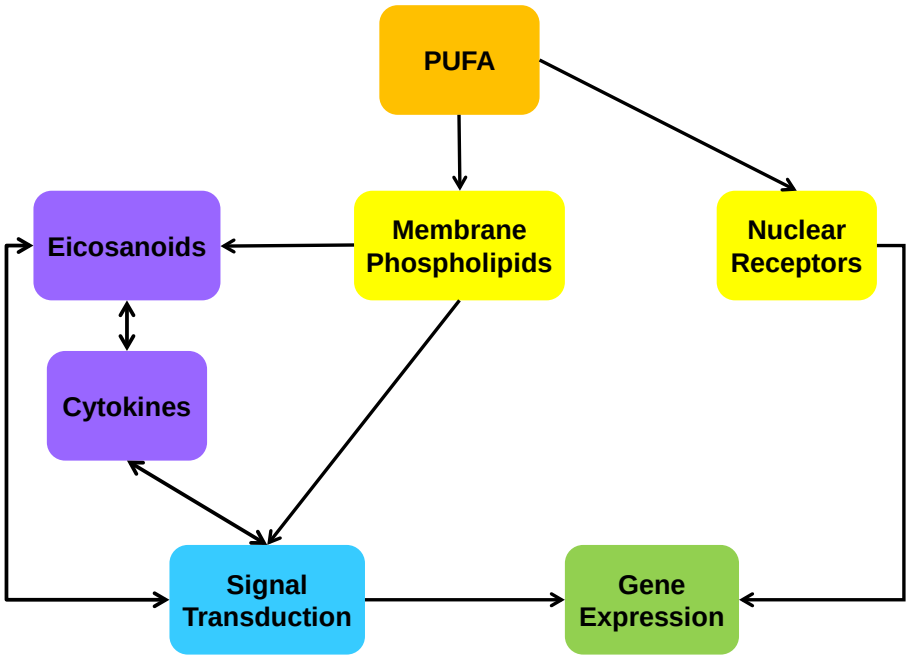

Figure 1.4: How PUFAs exert their influence on gene expression and metabolism. *Adapted by permission from S. Karger AG, Basel: Stulnig, copyright (2003).*

their influence on cardiovascular function, insulin action, plasma lipid levels (Harris et al., 1997), neuronal development and the immune system inter alia through modulation of eicosanoid (prostaglandin and leukotrine) synthesis, activation of orphan nuclear receptor and T-lymphocyte signalling (Harris et al., 1997; Stulnig, 2003). They also regulate the transcription and activation of multiple genes (Jump, 2004; Pegorier et al., 2004; Sampath & Ntambi, 2004). Figure 1.4 shows how PUFAs exert their influence on gene expression and metabolism.

Hence, PUFAs affect several metabolic pathways, and thus may have an impact on the development of a series of diseases, including obesity (Storlien et al., 1998; Sampath & Ntambi, 2004) either directly or through interactive effects with the genetic background. This hypothesis is supported by the results of different experimental studies (Reseland et al., 2001; Iwaki et al., 2003; Verlengia et al., 2003; Merzouk et al., 2008).

1.2.2 Metabolomics

As outlines by Fiehn (2002) *"Metabolites are the end products of cellular regulatory processes, and their levels can be regarded as the ultimate response of biological systems to genetic*

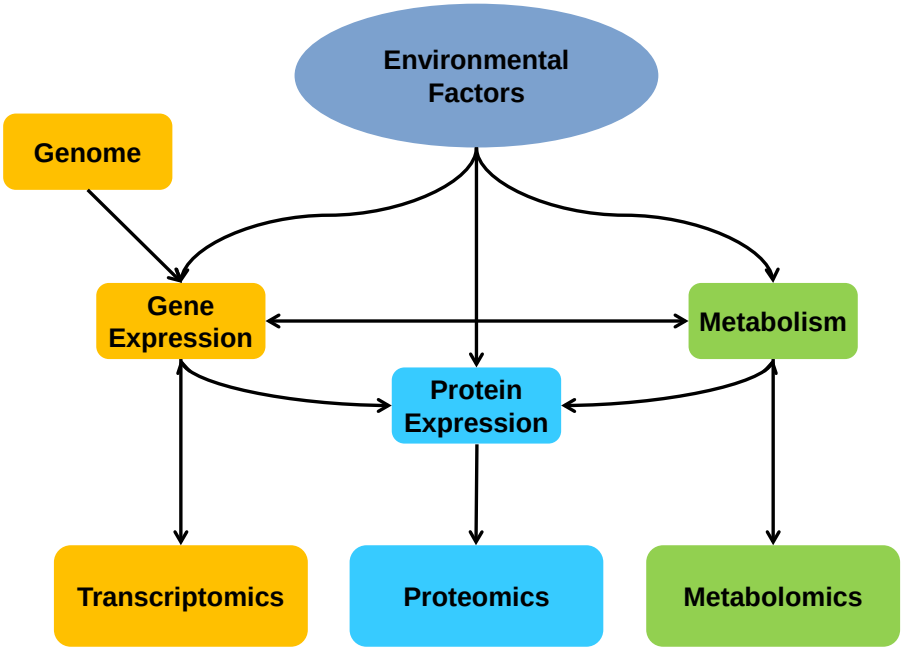

Figure 1.5: Metabolomics among the "omics". *Courtesy: LipoFIT Analytic GmbH.*

or environmental changes". Metabolomics is the corresponding "new" research area which deals with the measurement and quantification of those endogenous organic compounds in body cells or fluids, thereby fitting well in the world of "omics" which includes genomics, transcriptomics and proteomics (Figure 1.5). Though, on the basis of biochemical knowledge the interpretation of metabolomics data is more refined (Krug et al., 2012). There are two different approaches on the quantification of metabolites. The non-targeted approach aims at measuring all metabolites within a biospecimen (most analyses are based on blood or urine). Whereas the concept of targeted metabolomics is the quantification of a defined set of metabolites in a body fluid, representing an image of the current metabolic state of the organism (Altmaier et al., 2009). A series of high-throughput quantification methods has been established inter alia liquid chromatography (LC) or gas chromatography (GC) coupled to mass spectrometry (MS), or nuclear magnetic resonance spectroscopy. For comprehensive comparison of these methods see Psychogios et al. (2011).

So far, with an enormous effort over 4000 serum and plasma metabolites belonging to more than 50 different chemical classes have been identified, validated and characterised in the Serum Metabolome Database (Psychogios et al., 2011). As this number exceeds the scope of most studies, a targeted metabolomics approach was chosen for our studies. It has been

shown previously that this method has the power to identify perturbations of the body's metabolic homeostasis and allows for the identification of and access to biomarkers of metabolic pathways that are impacted for example by diseases (Watson, 2006; Dumas et al., 2007; Altmaier et al., 2008; Assfalg et al., 2008; Vinayavekhin & Saghatelian, 2009; Suhre et al., 2010). The analysis kits utilised in the Cooperative Health Research in the Region of Augsburg (KORA) studies which are part of the second and third project, include amongst others amino acids, acylcarnitines, phosphatidylcholines (PCs), hexose, sphingomyelins, and biogenic amines as analytes (2.2.6).

1.3 Thyroid Hormones

Thyroid hormones such as thyroxine (T4) and triiodothyronine (T3) are major regulators of energy metabolism, especially REE, and are therefore determinants of body weight (Kim, 2008; Reinehr, 2010). The release of T4 and T3 by the thyroid gland is controlled by thyroid stimulating hormone (thyrotropin; TSH) which is synthesised by the anterior pituitary gland in response to TSH-releasing hormone (TRH), which in turn is secreted by the hypothalamus (Figure 1.6). With a 40-fold higher production, T4 is the quantitatively main product of the thyroid gland (Yen, 2001). Nevertheless, T3 is the biologically active hormone and it is produced by local deiodination of T4 in peripheral tissues (Boelaert & Franklyn, 2005; Moreno et al., 2008). Almost all of T3 and T4 in the circulation is bound to proteins, such as T4-binding globulin or albumin (Boelaert & Franklyn, 2005). Only about 0.03 % and 0.3 % of total serum T4 and T3, respectively, are free or unbound (Yen, 2001). However, it is the free thyroid hormones which enter target cells and trigger a biological reaction (Yen, 2001). Free T3 (FT3) and free T4 (FT4) also exert a negative feed-back on the production and release of TSH and TRH (Boelaert & Franklyn, 2005; Williams & Bassett, 2011). Thus, TSH and FT4 have a log-linear relationship in which small changes in FT4 concentration lead to great differences in TSH concentration (Panicker et al., 2010). For the synthesis of thyroid hormones, micronutrients such as selenium or iodine are crucial (Brix et al., 2011).

Thyroid hormones are responsible for the proper function of nearly all organ systems (Brix et al., 2011). They do not only modulate the metabolism of carbohydrates and lipids, influence protein synthesis, affect the cellular reaction to catecholamines in almost every tissue, they are also unique in their ability to influence all over energy expenditure, in particular the basal metabolic rate, e.g., via the regulation of thermogenesis (Kim, 2008;

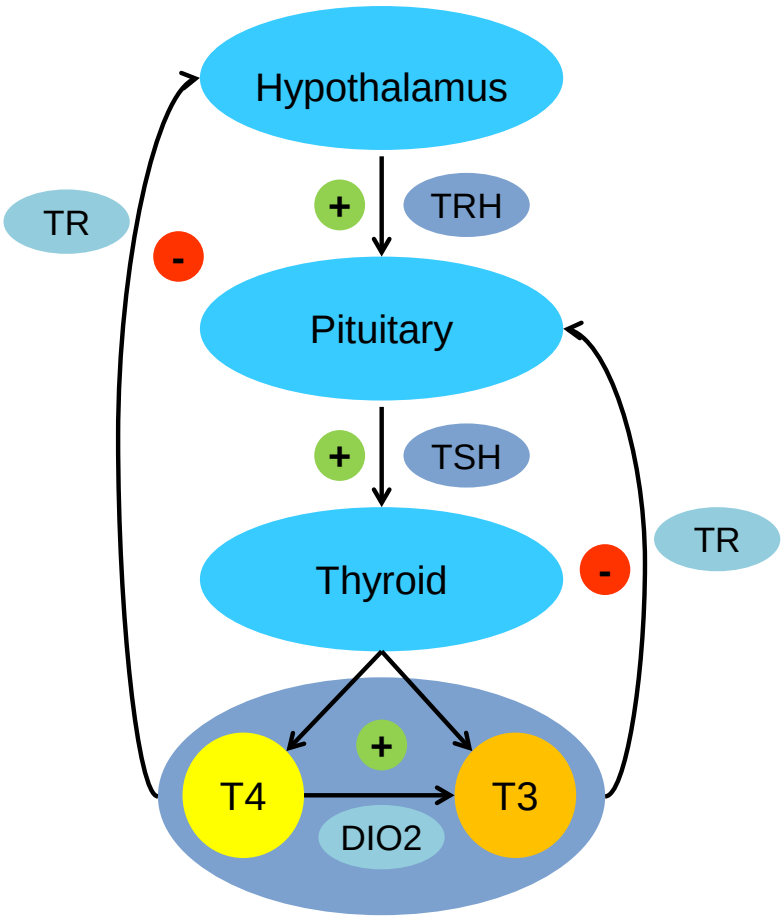

Figure 1.6: Hypothalamic-Pituitary-Thyroid Axis. *Adapted from Williams & Bassett; ©Society for Endocrinology (2011). Reproduced by permission.*

Moreno et al., 2008; Panicker et al., 2010). Their main target tissues are the central nervous system, cardiovascular system, as well as the skeleton (Brix et al., 2011) and they are essential for the development (Panicker et al., 2010). With the increasing prevalence of obesity, a better understanding of energy homeostasis has reclaimed focus (Obregon, 2008). While it is accepted, that thyroid hormones are major determinants of energy expenditure, the exact mechanisms concerning these effects are still unknown (Kim, 2008; Moreno et al., 2008). The "uncoupling hypothesis", i.e., the transformation of energy into heat (thermogenesis) by uncoupling of the respiratory chain, is probably the oldest hypothesis, and explains thyroid hormone effects by a direct action at the mitochondrial level (Moreno et al., 2008). Since the successful molecular cloning of nuclear thyroid hormone receptors (TR) (Wagner et al., 1995; Ribeiro et al., 1998), understanding of how thyroid hormone

exert their effects has further increased (Yen, 2001; Flamant et al., 2007). Most of the physiological effects of thyroid hormones are exerted through thyroid hormone receptor complexes and the response elements of regulatory regions of target genes (Brix et al., 2011; Biondi, 2012a). For example, in a recent microarray study on the transcriptome of the vastus lateralis, a daily doses of 75 µg T4 was administered to healthy male volunteers (Clement et al., 2002). As a result, 8 genes involved in the metabolism of glucose and lipids and 22 genes related to the energy metabolism within the mitochondrion were up-regulated. Important regulatory elements in these pathways are the different types of deiodinases which are responsible for the availability of thyroid hormones in tissue (Tarim, 2011). For example, the type two deiodinases (DIO2) increases local, intercellular T3 production from T4 (Kim, 2008). Nevertheless, not all thyroid hormone effects are attributable to nuclear mediated pathways (Moreno et al., 2008) and an increasing number of non-genetic effects such as the transportation of ions, such as calcium, sodium, and potassium, or glucose and amino acids across plasma membranes have been described recently (Biondi et al., 2002; Fazio et al., 2004).The complexity of understanding thyroid hormone actions even increases if the biological effects shown for metabolites derived from T4 and T3 are considered as well (Moreno et al., 2008; Cheng et al., 2010; Williams & Bassett, 2011). However, the proper supply of thyroid hormones is crucial in all phases of life (Brix et al., 2011).

Perturbations of thyroid hormone release and functioning belong to the most common endocrine disorders and are connected to major health problems during development, in disease or while ageing (Brix et al., 2011). The absence of thyroid hormones in the brain can lead to impaired cognitive functioning (Bauer et al., 2008), the absence or abundance of thyroid hormones in the central nervous system can result in agitation or mismanagement of body temperature, and further an increased risk for cardiovascular morbidity and mortality has been linked to an imbalance in thyroid hormones as well (Brix et al., 2011). This imbalance leads to thyroid diseases such as hyperthyroidism, the excess of T3 and T4 hormones or hypothyroidism characterised by a deficit of T3 and T4 in the body. About 10 % of the population are affected by thyroid diseases (Panicker et al., 2010) and they are more common in women than men. The pre-stages to hyper- and hypothyroidism are called subclinical hyper- and hypothyroidism. There, FT3 and FT4 levels are in the reference ranges, but the TSH concentrations are not (Boelaert & Franklyn, 2005). As a result of the tremendous consequences of untreated thyroid dysfunction on the cardiovascular functioning, much attention has been focused on possible links between subclinical thyroid diseases and the cardiovascular system (Boelaert & Franklyn, 2005; Biondi, 2012b). With

respect to body weight, hyperthyroidism results in weight loss despite increased appetite due to the increased metabolic rate, whereas hypothyroidism is accompanied by a moderate weight gain and a decrease in thermogenesis and metabolic rate (Reinehr, 2010). An imbalance in thyroid hormones might also be associated with conditions, such as obesity or low lean body mass. Weight status is the result of energy intake and energy consumption, whereas the latter is distributable into REE and physical activity (Reinehr, 2010). T3 and T4 are modulators of many pathways involved in REE and therefore it is not surprising that an imbalance in thyroid hormones is associated with a change in weight. However, in most cases obese subjects have a normal functioning thyroid with comparable T4 and FT4 levels to non-obese subjects.

1.4 Aim of this Thesis

The main objective of this doctoral thesis was to contribute to the ongoing exploration of genetic and environmental factors which influence the interplay between body composition, metabolism, as well as energy homeostasis which co-determine our health status. Thus, we explored the following topics in three different projects:

(i) Gene–PUFA interactions that are associated with obesity risk in adults

(ii) Serum metabolite profiles related to body fat free mass

(iii) Effects of thyroid hormones on the serum metabolite profile in euthyroid adults

In the first project, gene–environment interactions were analysed with respect to obesity risk in adults. Obesity with a national prevalence of about 20 % has become a worldwide major public health burden reaching a pandemic state (Max Rubner-Institut – Bundesforschungsanstalt für Ernährung und Lebensmittel, 2008; World Health Organization, 2012). Obesity is considered co-responsible for conditions such as diabetes, certain types of cancers, or heart diseases and is particular cost-intensive for the health care systems (World Health Organization, 2012). Thus, expanding our knowledge about the individual susceptibility towards common obesity is of great urgency. The western lifestyle is associated with a decrease in physical activity and easy access to high calorie dense food (Bell et al., 2005). This leads consequently to an imbalance in energy intake and expenditure and therefore subsequent weight gain. Also, genome-wide scans of candidate genes have helped to identify gene regions which increase the risk of becoming obese (Peeters et al.,

2009). We hypothesised that common obesity is the result of a genetic predisposition in combination with environmental factors. In this project we chose the PUFA composition of the erythrocyte membranes which reflects PUFA intake as well as its metabolism as the environmental component to be investigated. PUFAs are known to influence a variety of body functions, such as the cardiovascular system, insulin action, the immune system, or the activation and transcription of genes (Harris et al., 1997; Stulnig, 2003; Jump, 2004; Pegorier et al., 2004; Sampath & Ntambi, 2004) and thus may influence the development of obesity (Storlien et al., 1998). For this project, we carefully selected 21 genes including cytokines, neurotransmitters, transcription factors and adipokines out of an existing genetic dataset, for which a potential influence of PUFAs has been reported and calculated the interaction effects with different PUFA concentrations of the erythrocyte membranes on the obesity risk in adults by means of adjusted logistic regression models.

The second project incorporated metabolomics as well as genetics. The aim was to identify fat free mass – a proxy for muscle mass – related characteristics of human metabolism and to confirm the findings in a follow-up study. Lewis et al. (2010) investigated the metabolic signature of physical activity on human plasma metabolites and demonstrated increased lipolysis during and after exercise in participants with higher endurance as compared to less fit participants. Hence, we hypothesised that a sedentary lifestyle leads to derangements in skeletal muscle metabolism favouring the development of obesity and metabolic disease which is supposedly reflected in the metabolic makeup. The associations between the FFMI and up to 190 serum metabolites and pairwise intra-class metabolite ratios were analysed in adjusted linear regression models, Gaussian graphical models (GGMs) were established to map the true relationship among pairs of metabolites, and also genetic aspects were investigated in this project. The associations between SNPs which were described to be associated with anthropometric measurements in genome-wide association studies (GWAS) and the different metabolite variables were investigated.

Thyroid hormones are involved in the proper function of most organ systems, they are major modulators of carbohydrate, lipid, and protein metabolism, and they are highly engaged in the regulation of energy expenditure (Kim, 2008; Moreno et al., 2008; Panicker et al., 2010). Affecting metabolism and energy balance and thereby body composition thyroid hormones influence three key factors determining our health status. Although, FT4, FT3, and TSH are thought to have a strong heritable component, GWAS concerning FT4 or FT3 have been few and not very fruitful (Panicker et al., 2010). Thus, for the third project we focused on metabolomics aiming at the identification of pathways which are affected by thyroid

hormones in euthyroid participants. To this end, the relationship between FT4 as well as TSH and up to 151 serum metabolite concentrations as well as intra-class metabolite ratios in thyroid-healthy participants were investigated by means of adjusted linear regression models.

2 Materials and Methods

2.1 Second Bavarian Food Consumption Survey

2.1.1 Study Design and Population

The BVS II is a cross-sectional study, representative of the Bavarian population and designed to investigate dietary and lifestyle habits. German-speaking subjects (n = 1050) aged 13 to 80 years were recruited between September 2002 and June 2003 following a three-step random route sampling procedure. A total of 42 communities served as sampling points and were stratified by county and community characteristics. With a given start address, a random walk (every third household) was conducted and one random household member who met the inclusion criteria was selected. Information on the subjects' characteristics, lifestyle as well as health and socioeconomic status were collected during a personal computer-assisted face-to-face interview at baseline. The participation rate was 71 %. A non-responder analysis was performed. On average, non-responders had – among other characteristics – a higher BMI than the study participants. Within the following two weeks, data of the subjects' dietary intake and physical activity were assessed by three 24 hours dietary recalls (two weekdays and one weekend day), which were conducted via telephone and by trained interviewers. For the 24 hours dietary recalls, the software EPIC-Soft (International Agency for Research on Cancer, Lyon, France) was used (Voss et al., 1998; Slimani et al., 1999, 2000). The participants had to recall their dietary intake as well as their physical activity of the previous day. All adult subjects ($\geq$ 18 years) who completed at least one 24 hours recall (n = 879) were invited to their nearest public health office for blood sampling and standardised anthropometric measurements within 6 weeks after recruitment. Of these subjects, 65 % (n = 568) accepted this invitation and represented the subgroup on which this evaluation is based on.

Ethics Statement

The BVS II study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Bavarian Medical Association. Written informed consent was obtained from all study participants.

2.1.2 Anthropometric, Dietary and Physical Activity Assessment

Height was measured to the nearest 0.5 cm and weight to the closest 0.5 kg. BMI was calculated as weight/height^2 (kg/m^2). Participants were classified according to the definition of the World Health Organization (2000) as obese (BMI $\geq$ 30 kg/m^2) and non-obese (BMI $<$ 30 kg/m^2). Hip size was determined as the widest circumference measured over the buttocks and waist measurements were taken midway between the iliac crest and the margin of the lower rip. The German food composition table (Bundeslebensmittelschlüssel, version II.3; BgVV, Berlin, Germany) was used to calculate nutrient intake. Data were weighted correspondingly to weekday or weekend day in order to calculate a mean daily intake per participant. In the telephone interviews, participants were asked to recall their physical activity of the last 24 hours. Standardised questions on type and duration of the physical activity in the categories of sports, occupation and other strenuous activities during leisure time as well as non-occupational television/personal computer use and duration of sleeping were part of the computer-based interview. Metabolic equivalents (MET) were matched to each activity and the energy expenditure (MET $\times$ h) of every individual was estimated (Schaller et al., 2005).

2.1.3 Blood Analyses

Blood Sampling

Venous blood was drawn, chilled at 4 °C and further processed within 3 hours. Plasma and buffy coat were separated from erythrocytes by centrifugation (2,000 *g* for 15 minutes) before being divided into aliquots and stored at -80 °C for further analyses.

Fatty Acid Composition of Erythrocyte Membranes

Membrane fatty acid analysis was conducted using an aliquot of 0.5 ml erythrocyte suspension. After cell lyses through addition of aqua destillata, the erythrocyte membranes

were isolated via centrifugation (20,000 *g* for 20 minutes at 4 °C) and the pellet was resuspended with Tris-buffer (11 mM-Tris, 1 mMNa-EDTA, pH 7.4); the washing procedure was repeated twice before adding 800 ml aqua destillata (Golik et al., 1996). Fatty acid extraction was performed using a mixture of chloroform and methanol (2:1, v/v) according to a modification of the method described by Folch et al. (1957). The lipids were extracted twice using a chloroform-methanol mixture with the added antioxidant butylated hydroxytoluene (50 mg/l) (Wren & Szczepanowksa, 1964). The combination of these extracts was washed with a $CaCl_2$ solution. The organic phase was collected and evaporated until dry. Resuspension of that extract was done using chloroform, and via transesterification with trimethylsulphonium hydroxide, the fatty acid methyl esters were obtained (Butte, 1983). A 100m CP-Sil-88 capillary column (Varian-Chrompack, Darmstadt, Germany), which was installed in an HP 5890 series II gas chromatograph with a flame-ionisation detector (Hewlett Packard, Munich, Germany), was used to identify and separate the different fatty acid methyl esters. Authentic standards (Sigma-Aldrich, Steinheim, Germany) were applied to assure a correct identification and quantification of the fatty acid methyl ester peaks. As a result, the content of twenty-two types of fatty acids was measured and is expressed as a percentage of the total identified fatty acid methyl esters (Hoff et al., 2005). For each sample, data represent the mean of two injections.

Analysis of Plasma IL-6

Plasma IL-6 was measured by means of a commercial ELISA kit (Biosource, Brussels, Belgium). The intra- and inter-assay coefficients of variance were below 7 and 9 %, respectively.

2.1.4 SNP Selection, Genotyping and Quality Control

The genetic dataset was developed in 2006 and consists of different candidate genes, which were chosen on the basis of an extensive literature research (Figure 2.1). SNPs covering these genes as well as 100 kb of region 5' and 50 kb of region 3' were selected based on hapmap data (www.hapmap.org; phases 1 and 2) with a minimum minor allele frequency (MAF) of 0.05 according to the data of dbSNP Build 125 (a SNP database).
For our analyses, we carefully selected only genes for which an indication of a potential interaction with PUFAs was provided by the literature. These include different cytokines and their receptors (interleukin *(IL)-2*, *IL-6*, *IL-10*, *IL-18*, tumour necrosis factor-α (*TNF-*α), *TNF*

CHR 1	CHR 2	CHR 3	CHR 4	CHR 5	CHR 6	CHR 7	CHR 8	CHR 9	CHR 10
IL-10	*GCG*	***ADIPOQ***	***IL-2***	*CART*	***TNF-α***	***LEP***		*ABCA1*	
TNFRSF1B	***POMC***	*GHRL*	***NPY1R***	*IL-4*	***TNFRSF21***	*INSIG1*			
LEPR	*INSIG2*	*SCAP*	***NPY5R***		*GLP1R*	***IL-6***			
		PPARγ	***PPARγC1A***			***NPY***			
						ABCB1			
CHR 11	***CHR 12***	***CHR 13***	***CHR 14***	***CHR 15***	***CHR 16***	***CHR 17***	***CHR 18***	***CHR 19***	***CHR 20***
IL-18	***TNFRDF1A***				*AGRP*	***PYY***	***MC4R***	***RETN***	*MC3R*
INS	*GNB3*					***PPY***			*GNAS*
	IGF1					*SREBF1*			

Figure 2.1: Genetic datatset of the obesity candidate genes across the chromosomes (CHR) in 2006. For the project selected genes are printed in bold.

receptor superfamily 1A, 1B, and 21 (*TNFRSF1A*, *TNFRSF1B*, and *TNFRSF21*)), neurotransmitters and receptors (neuropeptide Y (*NPY*), *NPY* receptors type 1, and 5 (*NPY1R*, *NPY5R*), melanocortin 4 receptor (*MC4R*), proopiomelanocortin (*POMC*), pancreatic polypeptide (*PPY*), and peptide YY (*PYY*)), transcription factors (peroxisome proliferator-activated receptor gamma (*PPARγ*) and *PPARγ* coactivator 1-alpha (*PPARγC1A*)) and adipokines (leptin (*LEP*), leptin receptor (*LEPR*), adiponectin (*ADIPOQ*), and resistin (*RETN*)). For these genes, the genetic dataset holds a total number of 187 SNPs, consisting of 180 tagging SNPs, eighteen coding SNPs and twelve candidate SNPs previously reported to be associated with obesity. The median number of SNPs per gene locus is 11 with a range of 2 to 16 SNPs. Genotyping was performed by GoldenGate Genotyping Assay (Illumina, Inc., San Diego, CA, USA) according to the standard protocol of the manufacturer. Additional inclusion criteria were a MAF of at least 5 % and genotyping call rate of not less than 95 %, leaving 157 SNPs in the dataset.

2.1.5 Statistical Analyses

The descriptive data are presented as mean and standard deviation for continuous parameters or as percentage and absolute frequency for qualitative variables. Comparisons between the groups of obese and non-obese subjects were made by means of either the Mann–Whitney U test or the Kruskal–Wallis test. Socioeconomic status was categorised based on the values of three characteristics on a point scale including educational level, social position and the households' net income (Winkler & Stolzenberg, 1999). Physical activity data represent the estimated overall energy expenditure (MET $\times$ h) of every individual (Schaller et al., 2005).

Departure from the Hardy–Weinberg equilibrium was tested with an exact test (Wigginton et al., 2005). All selected SNPs were in the Hardy–Weinberg equilibrium except for rs1061624 (*TNFRSF1B*), rs16475 (*NPY*), rs16480 (*NPY* region 5') and rs17366743 (*ADIPOQ*), applying a p-value of 3.09×10^{-4} (corrected for multiple testing) as the significance level. For comparison of the allele frequencies between obese and non-obese subjects, an approximated X^2–test was used. The main effects of SNPs and PUFAs as well as their interaction effects are derived from a logistic regression model assuming additive genetic effects, and are presented as odds ratios (OR) with the corresponding 95 % confidence interval (CI). For the genetic main effect models, SNPs were introduced as discrete parameters with either three categories (homozygous wild type, heterozygous or homozygous mutant type) or two categories (homozygous wild type and one or more mutant allele carriers), depending on the number of subjects in the third category (homozygous mutant type; minimum of ten subjects). As EPA and DHA were highly correlated, their sum (EPA&DHA) was used. The fatty acid variables (presented as percentage of fatty acid methyl esters) were established as continuous parameters. For the interaction models, both SNPs and PUFAs were introduced as continuous parameters. A likelihood ratio test was used to compare the models with and without an interaction term and a p-value of 0.05 was regarded as nominally statistically significant. These p-values are denoted as P_{int}. The interaction models were adjusted for sex, age, physical activity, and socioeconomic status and significant SNP–PUFA interactions were analysed further. The effect of each PUFA with respect to obesity risk was estimated within the gene strata (homozygous wild type and one or more mutant allele carriers) of the SNPs using logistic regression models adjusted for sex, age, physical activity, and socioeconomic status. As the analyses were done within the SNP strata and the number of people carrying two minor alleles was often quite small, two categories were used for sample size reasons. We tried different procedures, inter alia by Bonferroni, Holm, Hochberg, Sidak or Benjamini and Hochberg, to correct our results for multiple testing. However, the application of each procedure reduced the amount of significant results to zero. Therefore, all p-values reported in context with the BVS II project are uncorrected and only nominally significant at $\alpha = 5$ %. The SNPs were tested for pairwise linkage disequilibrium (LD). If SNPs were in high LD ($r \geq 0.7$), one of them was selected as representative for the LD block. We chose rs1800795 to represent the *IL-6* LD block with rs1800797 ($r = 0.935$) and rs2069833 ($r = 0.967$) and *IL-18* SNP rs3882891 to represent rs1946519 ($r = 0.77$).

As five values of plasma IL-6 were declared as outliers (greater than mean plus five times the standard deviation), they were excluded from analyses. While plasma IL-6 levels ranged

between 0.25 and 11.64 pg/ml, the levels of those five outliers were substantially higher (51.5, 61.8, 68.92, 93.62 and 620.6 pg/ml). The reason for those high values could neither be clarified nor was a re-analysis of the samples possible. To account for skewness, the parameter was log-transformed. Plasma IL-6 is presented as geometric mean and 95 % CI.

2.2 KORA S4 and KORA F4 Studies

2.2.1 Design and Study Population

KORA is a research platform performing population-based surveys and subsequent follow-ups in the region of Augsburg in Southern Germany. The KORA S4 survey includes 4261 participants aged 25 to 74 years (response rate 67 %) and was conducted in 1999 to 2001 (Holle et al., 2005). The KORA F4 survey comprises of 3080 participants which participated in the seven-year follow-up examination of the KORA S4 survey in 2006 to 2008. In both studies, baseline information on sociodemographic variables, lifestyle factors, medical history and medication use, amongst others, was gathered in an extensive standardised face-to-face interview. Additionally, all participants underwent standardised examinations such as anthropometric measurements and provieded blood samples.
The analyses in this thesis are based on the metabolically characterised participants of the KORA S4 and KORA F4 studies and different subsamples of those. The metabolomic profiles of 1614 participants in KORA S4 (aged 54 to 75 years at the time of examination) and 3061 participants in KORA F4 (aged 31 to 82 years) were determined. The overlap in participants is 1134.
The BIA measurements of the participants' body composition (fat free mass and body fat mass) were only conducted in KORA S4. As those measurements were also to be used in connection with the analyses of the KORA F4 data, adjustments had to be made. For this purpose the KORA F4 weight-stable dataset was generated. A person was defined as weight-stable if their weight gain or loss did not exceed more than 0.5 % per year since their body weight was measured in KORA S4 (Nimptsch et al., 2010).

Ethics Statement

The KORA S4 and F4 studies were approved by the ethics committee of the Bavarian Medical Association. Written informed consent was obtained from each participant in accordance with institutional requirements and the Declaration of Helsinki Principles.

Samples for the Metabolomics and FFMI Analyses

The associations between serum metabolite concentrations and FFMI were analysed in KORA S4 and the KORA F4 weight-stable datasets. Therefore, participants with a known history of myocardial infarction, stroke, diabetes or cancer were excluded as well as participants taking angiotensin-converting-enzyme (ACE) inhibitors or anti-lipidemic drugs. This resulted in a sample size of n = 965 for KORA S4 and n = 890 for KORA F4 weight-stable subgroup with an overlap of n = 725 participants.

Samples for the Metabolomics and Thyroid Hormones Analyses

For this project only euthyroid participants were included. A person was defined as euthyroid if their FT4 and TSH hormone levels were in the ranges of 9.8 to 18.8 pmol/l and 0.3 to 4.0 mIU/l, according to the assay manuals and Brabant et al. (2006) as well as Surks et al. (2004), respectively, their thyroid peroxidase antibody level did not exceed 200 IU/ml (Knudsen et al., 1999; Demers & Spencer, 2003) and there was no known history of thyroid disease or thyroid medication use in accordance with the anatomical therapeutic chemical code for thyroid therapy (H03). Further, participants also with a known history of myocardial infarction, stroke, diabetes or cancer were excluded as well as subjects taking ACE inhibitors or anti-lipidemic drugs, and women being pregnant at the time of blood collection. For a subanalysis, data on the subjects' body composition was used. The sample sizes were n = 1469 for KORA F4 and of n = 621 for the KORA F4 weight-stable subgroup.

2.2.2 Blood Sampling

In both studies, fasting serum samples for metabolic analysis were collected during study centre visits. For KORA S4, the blood drawing occurred after a period of overnight-fasting (minimum of 8 hours) using S-Monovette® serum tubes (SARSTEDT AG & Co., Nümbrecht, Germany). Tubes were inverted two to three times, spent 5 minutes on the universal shaker (SARSTEDT AG & Co., Nümbrecht, Germany) before being allowed to rest for 40 minutes at 4 °C for total coagulation. Later on, tubes were centrifuged for 15 minutes at 2,660 *g*, serum was separated and filled into synthetic straws (Cryo Bio System, Paris, France) which were stored in liquid nitrogen (-196 °C) until analysis. For KORA F4, the blood drawing occured between 8 and 10 o'clock in the morning in order to control variability by circadian rhythm and after a period of overnight fasting. S-Monovette® serum gel tubes (SARSTEDT AG & Co., Nümbrecht, Germany) were used. After blood

was drawn, tubes were inverted twice and then allowed to rest for 30 minutes at room temperature (18 to 25 °C) to achieve total coagulation. Later, tubes were centrifuged for 10 minutes at 2,660 *g* at 15 °C and afterwards serum was divided into aliquots, chilled for a maximum of 6 hours at 4 °C before being stored at -80 °C until analysis.

2.2.3 Anthropometric, Physical Activity, and BIA Assessment

Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. Waist circumference was measured to the closest 0.1 cm at the smallest position between the lower rip and the upper margin of the iliac crest. Hip size was determined exactly to 0.1 cm as the widest circumference measured between the upper margin of the iliac crest and the crotch. The BMI was calculated as the ratio of weight by squared height (kg/m^2) and obesity was defined as having a BMI $\geq$ 30 kg/m^2 according to the World Health Organization (2000).

In KORA S4 and KORA F4, physical activity was assessed on a four-level grated scale by the amount of regular leisure time exercise per week during summer and winter. Based on those assessments, Meisinger et al. (2007) defined four levels of physical activity: (i) 'No sports activities in leisure time' - almost no sports activity or no activity in summer and in winter; (ii) 'Low level of sports activities in leisure time' - irregular exercise of 1 hour per week at least in summer or winter; (iii) 'Moderate level of sports activity in leisure time' - regular exercise of 1 hour per week at least in summer or winter; (iv) 'High level of sports activities in leisure time' - more than 2 hours per week of regular exercise in summer and winter. Based on this variable, the physical activity variable which was used in the present KORA projects was created representing two levels: 'physically inactive' - category (i) or (ii), and 'physically active' - category (iii) or (iv).

For the assessment of body composition, two BIA measurements of resistance, reactance and the phase angle were taken between the dominant hand wrist and dorsum, and the dominant foot angle and dorsum (placement of the electrodes) by means of a body impedance analyser (BIA 2000-S; Data Input GmbH, Frankfurt, Germany) while participants were spreading their arms and legs and lying in a relaxed and supine position on a nonconductive surface with 50 kHz. Fat free mass, body fat mass, and the appendicular skeletal muscle mass were then calculated by means of Kyle's equations (Kyle et al., 2001, 2003a) on which the following indices are based: FFMI (fat free mass in kg/(height in m)^2), BFMI (body fat mass in kg/(height in m)^2) and the appendicular skeletal muscle mass index (appendicular skeletal muscle mass/(height in m)^2).

2.2.4 Genotyping, Imputation and SNP Selection

In KORA F4, genotyping was done by means of Affymetrix Human SNP Array 6.0. HapMap CEU version 22 was used as population reference and as reference for the imputation of the genotyped SNPs with IMPUTE v0.4.2. The complete procedure has been described in more detail (Illig et al., 2010). For a subanalysis within the metabolomics and FFMI project, 170 SNPs were investigated. The selection of these SNPs is based on an extensive literature research of GWASs with an anthropometric characteristic, such as lean body mass (Liu et al., 2009), waist-to-hip ratio (Heid et al., 2010), or BMI (Thorleifsson et al., 2009; Willer et al., 2009; Speliotes et al., 2010), as outcome. A list of the selected SNPs is found in Supplementary Table B4.

2.2.5 Measurement of Thyroid Hormones

Concentrations of TSH and FT4 were analysed by immunochemiluminescent procedures (Dimension Vista System, Siemens, Germany). The functional sensitivity of the TSH assay was 0.005 mIU/l; the TSH and FT4 working ranges were 0.005 to 100 mIU/l and 1.3 to 103 pmol/l, respectively. The (low or high) inter-assay coefficients of variations were 2.0 or 2.2 % for TSH, and 1.7 or 4.1 % for FT4. All assays were performed according to the manufacturer's recommendations. The thyroid peroxidase antibodies were determined by an enzyme immunoassay (VARELISA, Elias Medizintechnik GmbH, Freiburg, Germany) with a functional sensitivity of 1 IU/ml.

2.2.6 Metabolomics Datasets

Quantification

Metabolic characterisation of the KORA F4 serum samples was done in 2009 in three batches of approximately 1000 samples at three time points with a recalibration of the equipment in between; whereas the complete KORA S4 set was characterised in 2011 in one batch. The targeted metabolomics approaches for KORA F4 and KORA S4 were based on electrospray ionisation (ESI)-(LC-)tandem mass spectrometry (MS/MS) measurements by the Absolute*IDQ*^{TM} p150 kit and p180 kit (BIOCRATES, Life Sciences AG, Innsbruck, Austria), respectively. The assays allow simultaneous quantification of 163 (kit p150; KORA F4) or 186 (kit p180; KORA S4) metabolites out of 10 µl serum in each case. The Absolute*IDQ*^{TM} p150 kit has previously been described in detail (Illig et al., 2010;

Römisch-Margl et al., 2012). The p180 kit is an extension of the p150 kit, using additional LC-MS/MS separation. For both kits, sample handling was performed by a Hamilton Micro Lab Star robot (Hamilton Bonaduz AG, Bonaduz, Switzerland) and a nitrogen evaporator (Porvair, Ultravap). MS analyses were done on a 4000 QTRAP mass spectrometer (AB Sciex) coupled to Promincence HPLC (Shimadzu) apparatus (KORA F4) and an API 4000 LC-MS/MS System (AB Sciex Deutschland GmbH, Darmstadt, Germany) equipped with an Agilent 1200 Series HPLC and a HTC PAL auto sampler (CTC Analytics, Zwingen, Switzerland) (KORA S4) controlled by the software Analyst 1.4 for kit p150 (KORA F4) 1.5.1 for kit p180 (KORA S4). Data evaluation for quantification of metabolite concentrations and quality assessment was performed with the Met*IDQ*^{TM} software package, which is an integral part of the Absolute*IDQ*^{TM} kits. Internal standards serve as reference for the calculation of metabolite concentrations. The methods of the Absolute*IDQ*^{TM} p150 and p180 kits have been proven to be in conformance with the FDA guideline (U. S. Department of Health and Human Services and Food and Drug Administration and Center for Drug Evaluation and Research (CDER) and Center for Veterinary Medicine (CVM), May 2001), which implies proof of reproducibility within an given error range. Measurements were performed as described in the manufacturer manuals. Concentrations are reported in µmol/l.

Metabolite Spectrum

In total, up to 190 different metabolites were quantified. Kit p150 (KORA F4; 163 metabolites) contains 14 amino acids (13 proteinogenic + ornithine), hexose (sum of hexoses - about 90 to 95 % glucose), free carnitine and 40 acylcarnitines (C*x:y*), 15 sphingomyelins (SM*x:y*), 77 phosphatidylcholines (PCs; aa = diacyl, ae = acyl-alkyl) and 15 lyso-phosphatidylcholines (lysoPCs). The lipid side chain composition is abbreviated as C*x:y*, with *x* denoting the number of carbons in the side chain and *y* denoting the number of double-bonds. Kit p180 (KORA S4; 186 metabolites) includes 21 amino acids (19 proteinogenic, citrulline, and ornithine), hexose, free carnitine, 39 acylcarnitines, 15 sphingomyelins, 90 phosphatidylcholines (14 lysoPCs and 76 PCs) as well as 19 biogenic amines. The overlap of both kits is 159 metabolites. Full biochemical names and abbreviations are provided in Supplementary Table B1.

Quality Control

The quality control of the metabolomics dataset of KORA F4 was done in a two-step procedure. First, the quality of all metabolites was assessed using a reference blood which

was measured five times on ten plates. With this data, a coefficient of variation was calculated for every metabolite and plate. All metabolites having a mean coefficient of variation over all ten plates greater than 25 % were removed from the dataset (eleven in total). One further metabolite was excluded as the number of missing values exceeded 5 %. In the second step, the dataset was controlled for outliers. A participant's metabolite concentration was defined as an outlier if the concentration was greater or less than the mean plus or minus five standard deviations of the particular metabolite over the whole population. All participants having more than three independent outlying metabolite concentrations were excluded from the dataset. An outlier was defined as independent if the correlation with all other outliers was less than 70 %. If there were three or less independent outliers, only the data points were removed. All missing values were imputed with the R-package "mice" which uses a linear regression approach. For the quality control of the KORA S4 metabolite dataset, a new coefficient of variation was calculated using the reference blood which was on all KORA S4 plates. The same quality criteria were applied to the KORA S4 sample, resulting in 20 metabolites being excluded from the dataset. This left us with 151 metabolites for the KORA F4 dataset and 166 metabolites for KORA S4, with an overlap of 141 metabolites. As the metabolic profile in KORA F4 samples was assessed in three batches a so called batch variable was included in all analyses of the KORA F4 metabolomics dataset in order to avoid possible effects due to technical issues or different time points of analyses. This step was not necessary for the KORA S4 dataset.

2.2.7 Statistical Analyses of the FFMI Project

The descriptive data is presented as mean and standard deviation for the continuous variables and as absolute quantities and percentages for the qualitative parameters. The KORA S4 and KORA F4 samples were analysed as independent cross-sectional studies. Besides the absolute metabolite concentrations, all pairs of intra-metabolite class ratios (n = 4629 for KORA S4 and n = 4518 for KORA F4) were part of the metabolomics datasets. Associations between metabolite concentrations or metabolite ratios and the FFMI were assessed by means of linear regression models. First, metabolite variables (absolute concentrations and ratios) were standardised with an inverse log-normal transformation to allow for comparison of the estimates derived from the linear regression models. Then, linear regression models were applied with the metabolite parameters as dependent variables and the FFMI as explanatory variable. The models for the KORA S4 metabolomics data were adjusted for age and sex, whereas the models for KORA F4 were adjusted for age,

sex, and batch. To control for multiple testing and with regard to the dependencies among the various metabolites and metabolite ratios, a p-value of 3.12x10^{-4} for KORA S4 and a p-value of 3.5x10^{-4} for KORA F4 were considered to be statistically significant at $\alpha = 5$ %. For an association with a metabolite ratio to be regarded as statistically significant, an additional criterion (the p-gain) had to be fulfilled next to a significant p-value. The p-gain is defined as the fold decrease in the p-value of association for the pair of metabolites compared to the lowest of the two p-values for the single metabolites (Suhre et al., 2010). Thus, an association between a metabolite ratio (M1/M2) and FFMI is considered to be significant, if the p-value of this association is significant and the p-gain exceeds a certain value. To calculate the p-gain we first have to determine the minimum p-value of the associations between metabolite M1 and FFMI as well as metabolite M2 and FFMI. The p-gain is the quotient of this minimum to the p-value of the association between the metabolite ratio and FFMI. This p-gain had to exceed 170 for KORA S4 and 150 for KORA F4 which are approximately the numbers of tested metabolite concentrations in each study. These cut-offs are seen as Bonferroni related corrections in order to identify metabolite concentration pairs for which the strength of association improves considerably by using ratios (Suhre et al., 2010).

Subanalyses

Different subanalyses were performed. First, a different main explanatory variable was used. Instead of FFMI, the appendicular skeletal muscle mass index was included in the linear regression models with the same adjustments. Second, stratified analyses were conducted by age, sex, physical activity, and obesity status as potential confounders or effect modifiers.

Gaussian Graphical Models

In addition to the linear regression analyses, we investigated the relationships between metabolites as well as the propagation of FFMI effects through the metabolic network by means of GGMs. In order to obtain a GGM, the partial correlation coefficients between all pairs of metabolites were calculated (Krumsiek et al., 2011). For KORA S4 each partial correlation coefficient was controlled for age, sex, FFMI, and the other 164 metabolites and tested for significance. Bonferroni correction was applied, maintaining a significance level of $\alpha = 1$ %. In order to focus on particularly strong effects between metabolites a cut-off of r = 0.3 (partial correlation coefficient) was applied to the network. Each node represents a metabolite, whereas edges represent significant partial correlations. Nodes

were coloured according to the β-estimates and the p-values from the linear models (red = positive estimate; blue = negative estimate; white = not significant estimate). The same procedures were applied to the KORA F4 metabolite concentrations including the batch variable as a confounder.

Genetic Analyses

The associations between serum metabolite concentrations or metabolite ratios and SNPs which are found to be associated with anthropometric characteristic were analysed using linear models with the assumption of additive genetic effects. For the metabolite concentrations of the genotyped KORA S4 participants (n = 668), models were adjusted for age and sex. For the analysis with KORA F4 metabolomics dataset (n = 890), adjustments were made for age, sex and batch. A p-value of 4.73x10^{-6} for KORA S4 and 5.3x10^{-6} for KORA F4 was considered as statistically significant at α = 5 %.

2.2.8 Statistical Analyses of the Thyroid Hormones Project

The descriptive data is presented as described in (2.2.7). For the analyses of the metabolomics dataset (absolute metabolite concentrations (n = 151) and intra-metabolite class ratios (n = 2188)) and the thyroid hormone levels (FT4 and TSH) linear regression models were applied. For interpretational reasons, the amount of intra-PC class ratios, as used in (2.2.7), was restricted to the sub-intra-PC class ratios, i.e., no mixed metabolite ratios between the PC aa, PC ae, or lysoPC classes. The metabolite variables formed the dependent parameters and the hormone levels constituted the explanatory variables. Before analyses, the metabolite variables were standardised as well with an inverse log-normal transformation to allow for comparison of the estimates. Models were adjusted for age, sex, BMI, and batch. A p-value of 1.75x10^{-4} was considered to be statistically significant at α = 5 % and additionally the ratios' p-gain had to exceed 2.86x10^{+03}. Since the metabolomics and FFMI project, Petersen et al. (2012) established a formula to calculate p-gain cut-off values which replaces the before used common rule of thumb.

Subanalyses

In a subanalysis, the effect of FFMI on the association between FT4 and the metabolomics data was examined. Therefore, the weight-stable set was used and the applied linear models were adjusted for FFMI instead of BMI. Stratified analyses of the entire sample were also

conducted by sex, obesity status, and physical activity as potential confounder or effect modifiers. The equality of the strata-specific regression coefficients was tested by means of an approximately normally distributed test-statistic as described by Paternoster et al. (1998). Further, the influence of different liver, kidney, and inflammation parameters on the identified associations between the metabolites and FT4 were analysed by including an interaction term between FT4 and those parameters in the described models.

3 Results and Discussions

3.1 Gene–PUFA Interactions and Obesity Risk

3.1.1 Background

Obesity is a multifactorial disease (Newell et al., 2007) and over the past decades it has reached a pandemic state by doubling its worldwide prevalence (World Health Organization, 2012). Common obesity is not solely attributable to a genetic predisposition or to physical inactivity in combination with excessive caloric intake. We hypothesised that common obesity is the result of interacting environmental and genetic factors. In this project, we set out to investigate the interaction effects between SNPs of obesity candidate genes and the PUFA content of erythrocyte membranes, a good biomarker for PUFA intake, with the aim at increasing our understanding of the individual susceptibility towards obesity. So far, only a few studies have investigated SNP–PUFA interactions with respect to obesity risk. We have mainly found human or animal cell studies or dietary intervention studies showing PUFAs to have an increasing or decreasing effect on the expression of different candidate genes for obesity. Reseland et al. (2001), for example, found *n-3* PUFAs to decrease leptin gene expression in a dose and time dependent manner within a human trophoblast cell line. Alnajjar et al. (2006) described the effects of PUFAs on the interleukin production on the basis of a dietary intervention study (Jordan population). A case-control study in the European Prospective Investigation into Cancer and Nutrition by Nieters et al. (2002) has obtained indications for possible interactive effects between dietary intake of PUFAs and polymorphisms of different obesity candidate gene variants.

3.1.2 Results

Table 3.1 summarises the characteristics of the study population. Obese participants had a mean BMI of 34.28 $\pm$ 4.18 kg/m^2 and were on average about 8 years older than non-obese participants (mean BMI of 24.82 $\pm$ 2.99 kg/m^2). The mean hip and waist circumference

Table 3.1: Characteristics (mean, SD, % or *N*) of obese (BMI $\geq$ 30 kg/m^2) and non-obese (BMI $<$ 30 kg/m^2) participants of the analysed sample of the second Bavarian Food Consumption Survey *(Jourdan et al., 2011)*.

		Obese Subjects 20.07%		Non-Obese Subjects 79.93%		
Parameter	Unit	Mean	SD	Mean	SD	P-Value[a]
Age	years	54.86	13.90	46.87	15.17	$<$ 0.001
Weight	kg	94.55	13.52	70.85	11.39	$<$ 0.001
Height	cm	166.07	9.79	168.7	8.36	0.005
Body Mass Index	kg/m^2	34.28	4.18	24.82	2.99	$<$ 0.001
Waist	cm	113.05	9.94	89.81	10.99	$<$ 0.001
Hip	cm	119.74	8.77	104.51	6.18	$<$ 0.001
Waist to Hip Ratio		0.95	0.07	0.86	0.08	$<$ 0.001
Physical Activity	MET*h/d[b]	38.94	8.45	39.43	6.79	0.116
Erythrocyte Membranes						
Linoleic Acid	(% FAME[c])	10.61	2.42	11.17	2.19	0.004
Arachidonic Acid	(% FAME[c])	13.30	5.59	14.16	5.12	0.344
EPA&DHA[d]	(% FAME[c])	5.29	3.43	5.64	2.81	0.230
Dietary Intake						
Energy Intake	kJ/d	7841.53	2727.63	8447.79	2615.88	0.014
Linoleic Acid	% en.	5.39	2.27	5.38	2.18	0.828
Arachidonic Acid	‰ en.	0.89	0.61	0.85	0.66	0.148
EPA&DHA[d]	% en.	0.13	0.22	0.11	0.17	0.242
Plasma Concentration[e]						
Interleukin-6	pg/ml	2.37	2.12-2.65	1.38	1.30-1.48	$<$ 0.001
Parameter	Category	%	*N*	%	*N*	P-Value[f]
Sex	male	44.74	51	42.29	192	0.637
	female	55.26	63	57.71	262	
Age Groups	18 to $<$ 30 years	5.26	6	11.45	52	$<$ 0.001
	30 to $<$ 40 years	12.28	14	25.55	116	
	40 to $<$ 50 years	14.91	17	23.79	108	
	50 to $<$ 65 years	42.98	49	23.79	108	
	$\geq$ 65 years	24.56	28	15.42	70	
Socio-Economic	lower class	22.81	26	33.26	151	$<$ 0.001
Status	lower middleclass	14.91	17	22.69	103	
	middleclass	5.26	6	10.79	49	
	upper middleclass	36.84	42	20.93	95	
	upper class	20.18	23	12.33	56	

[a] Mann-Whitney U test; [b] energy expenditure per day; [c] fatty acids in % of total fatty acid methyl esters in red blood cell membranes; [d] sum of eicosapentaenoic and docosahexaenoic acid; [e] given as geometric mean and 95 % CI; [f] Kruskal-Wallis test.

of obese participants exceeded that of the non-obese participants by 15 cm and 24 cm, the mean plasma IL-6 level of obese participants was also elevated. There was no significant difference in sex distribution, physical activity or dietary fatty acid intake between the

Table 3.2: Significant SNP–linoleic acid interactions on obesity risk, showing the adjusted[a] relative risk of obesity (OR, 95 % CI) per 1 mol-% increase in linoleic acid (main effect[a]: OR = 0.90, 95 % CI = [0.82, 0.99]) from erythrocyte membranes by allelic variants *(Jourdan et al., 2011)*.

Gene	SNP	Allele	Non-Obese (%)	Obese (%)	OR [95 % CI]	P_{int}[b]
IL-2	rs2069779	CC	85.8	86.7	0.93 [0.85, 1.03]	0.0310
		≥1 T allele	14.2	13.3	0.63 [0.42, 0.87]	
IL-2	rs2069762	TT	49.6	51.8	0.84 [0.73, 0.96]	0.0381
		≥1 G allele	50.4	48.2	0.96 [0.85, 1.10]	
IL-2 region 5'	rs4833248	GG	48.3	50.9	0.81 [0.70, 0.94]	0.0192
		≥1 A allele	51.7	49.1	0.96 [0.85, 1.10]	
IL-6	rs1800795	GG	33.6	35.4	0.98 [0.84, 1.14]	0.0341
		≥1 C allele	66.4	64.6	0.86 [0.76, 0.96]	
IL-6 region 3'	rs10242595	AA	49.2	50.0	0.81 [0.71, 0.93]	0.0229
		≥1 G allele	50.8	50.0	0.98 [0.87, 1.12]	
IL-18	rs3882891	AA	35.0	32.5	1.03 [0.88, 1.22]	0.0237
		≥1 C allele	65.0	67.5	0.83 [0.74, 0.94]	
LEPR	rs1805096	CC	37.5	36.8	1.01 [0.85, 1.20]	0.0084
		≥1 T allele	62.5	63.2	0.83 [0.74, 0.93]	

[a] adjusted for age, sex, physical activity, and socioeconomic status; [b] p-value of the likelihood ratio test (adjusted continuous interaction model).

Table 3.3: Significant SNP–arachidonic acid interactions on obesity risk, showing the adjusted[a] relative risk of obesity (OR, 95 % CI) per 1 mol-% increase in arachidonic acid (main effect[a]: OR = 0.97, 95 % CI = [0.94, 1.01]) from erythrocyte membranes by allelic variants *(Jourdan et al., 2011)*.

Gene	SNP	Allele	Non-Obese (%)	Obese (%)	OR [95 % CI]	P_{int}[b]
IL-2	rs2069779	CC	85.8	86.7	1.00 [0.95, 1.04]	0.0104
		≥1 T allele	14.2	13.3	0.83 [0.72, 0.94]	
IL-6	rs1800795	GG	33.6	35.4	1.01 [0.94, 1.08]	0.0315
		≥1 C allele	66.4	64.6	0.96 [0.91, 1.01]	
LEPR	rs1805096	CC	37.5	36.8	1.01 [0.94, 1.10]	0.0459
		≥1 T allele	62.5	63.2	0.95 [0.91, 1.00]	

[a] adjusted for age, sex, physical activity, and socioeconomic status; [b] p-value of the likelihood ratio test (adjusted continuous interaction model).

two groups. The LA, AA, and EPA&DHA compositions of erythrocyte membranes were higher for non-obese than obese participants but only the difference in LA content reached statistical significance. The following results are not corrected for multiple testing and therefore are only nominally significant at $\alpha = 5$ %. Table A1 in the appendix shows the distribution of the alleles within the two groups of obese and non-obese participants, the

Table 3.4: Significant SNP–EPA&DHA interactions on obesity risk, showing the adjusted[a] relative risk of obesity (OR, 95 % CI) per 1 mol-% increase in EPA&DHA (main effect[a]: OR = 0.95, 95 % CI = [0.89, 1.02]) from erythrocyte membranes by allelic variants *(Jourdan et al., 2011)*.

Gene	SNP	Allele	Non-Obese (%)	Obese (%)	OR [95 % CI]	P_{int}[b]
IL-2	rs2069779	CC	85.8	86.7	1.00 [0.93, 1.09]	0.0021
		≥1 T allele	14.2	13.3	0.66 [0.48, 0.85]	
IL-6	rs2069861	CC	80.4	86.8	1.00 [0.92, 1.08]	0.0219
		≥1 T allele	19.6	13.2	0.74 [0.57, 0.94]	
TNFRSF1B	rs3766730	CC	71.0	69.9	1.01 [0.93, 1.11]	0.0237
		≥1 T allele	29.0	30.1	0.86 [0.74, 0.99]	
TNFRSF1B	rs2275416	GG	67.9	62.8	1.02 [0.93, 1.11]	0.0341
		≥1 A allele	32.1	37.2	0.88 [0.77, 1.00]	
TNFRSF21 region 3'	rs9381530	TT	30.7	35.1	0.79 [0.68, 0.91]	0.0065
		≥1 G allele	69.3	64.9	1.03 [0.95, 1.13]	
TNFRSF21	rs2236039	AA	53.3	49.1	0.87 [0.78, 0.96]	0.0482
		≥1 G allele	46.7	50.9	1.06 [0.95, 1.17]	
ADIPOQ	rs2241766	TT	77.8	85.1	0.92 [0.85, 1.00]	0.004
		≥1 G allele	22.2	14.9	1.19 [0.96, 1.52]	
ADIPOQ	rs1063539	GG	72.7	80.5	0.92 [0.85, 1.00]	0.0316
		≥1 C allele	27.3	19.5	1.09 [0.92, 1.32]	

[a] adjusted for age, sex, physical activity, and socioeconomic status; [b] p-value of the likelihood ratio test (adjusted continuous interaction model).

p-values of the used test and the main effects of all analysed SNPs on the risk of obesity. Risk estimates were calculated for models with either three categories (homozygous wild type, heterozygous and homozygous mutant type) or two categories (homozygous wild type and one or more mutant allele carriers). The p-value of the continuous model is given as P_{trend}. A nominal p-value of less than 0.05 was reached by rs4719714 and rs12700386 (*IL-6* region 5'), rs2069849 (*IL-6*), rs1061628 (*TNFRSF1B*) and rs1116656 (*LEP* region 3'). The crude main effects for LA (OR = 0.90, 95 % CI = [0.83, 0.98]), AA (OR = 0.97, 95 % CI = [0.93, 1.01]) and EPA&DHA (OR = 0.96, 95 % CI = [0.89, 1.03]) in erythrocytes showed an indication of an inverse association with obesity, but only for LA, the statistical significance was reached. SNPs for which the interaction terms with PUFAs reached nominal statistical significance ($\alpha = 5\%$) were stratified by genotype (two categories: homozygote wild type and one or more mutant allele carriers), and risk estimates were calculated for the corresponding PUFAs within these strata (Tables 3.2 to 3.4). Concerning cytokine genes, we found several SNP–PUFA interactions in relation to obesity risk. For *IL-2*, the interaction term between rs2069779 and all three PUFAs as well as between rs2069762,

Table 3.5: Plasma IL-6 concentrations (pg/ml; geometric mean values and 95 % CI) by tertiles of linoleic acid, arachidonic acid, and EPA&DHA in erythrocyte membranes by allelic variants of *IL-6* SNPs: re1800795, rs10242595, and rs2069861 *(Jourdan et al., 2011).*

SNP	Allel	PUFA	Tertile	Obese	Non-Obese
rs1800795	GG	LA	1	3.04 [2.72, 3.40]	1.63 [1.53, 1.74]
			2	2.46 [2.20, 2.75]	1.40 [1.31, 1.49]
			3	1.59 [1.42, 1.77]	1.15 [1.08, 1.22]
	≥1 C allele		1	2.21 [1.98, 2.47]	1.63 [1.53, 1.74]
			2	2.96 [2.65, 3.30]	1.36 [1.27, 1.45]
			3	2.16 [1.93, 2.41]	1.23 [1.15, 1.31]
rs10242595	AA	LA	1	2.61 [2.33, 2.92]	1.56 [1.46, 1.66]
			2	3.31 [2.96, 3.70]	1.31 [1.23, 1.40]
			3	2.27 [2.03, 2.54]	1.21 [1.13, 1.29]
	≥1 G allele		1	2.24 [2.00, 2.50]	1.73 [1.63, 1.85]
			2	2.25 [2.01, 2.51]	1.50 [1.41, 1.60]
			3	1.71 [1.53, 1.92]	1.19 [1.12, 1.27]
rs1800795	GG	AA	1	2.78 [2.49, 3.11]	1.62 [1.52, 1.73]
			2	1.80 [1.61, 2.01]	1.21 [1.14, 1.29]
			3	2.50 [2.24, 2.79]	1.32 [1.24, 1.40]
	≥1 C allele		1	2.39 [2.14, 2.67]	1.42 [1.33, 1.51]
			2	2.59 [2.32, 2.90]	1.50 [1.41, 1.60]
			3	2.25 [2.01, 2.51]	1.25 [1.18, 1.33]
rs2069861	CC	EPA&DHA	1	2.55 [2.29, 2.85]	1.52 [1.42, 1.61]
			2	2.37 [2.13, 2.65]	1.37 [1.28, 1.46]
			3	2.20 [1.97, 2.45]	1.39 [1.30, 1.48]
	≥1 T allele		1	2.60 [2.33, 2.90]	1.19 [1.12, 1.27]
			2	1.65 [1.48, 1.84]	1.34 [1.25, 1.42]
			3	3.34 [2.99, 3.72]	1.18 [1.11, 1.26]

Tertiles LA: (I) 2.7-10.7, (II) 10.7-12.2, (III) 12.2-16.8 ; Tertiles AA: (I) 1.0-14.5, (II) 14.5-17.1, (III) 17.1-21.1 ; Tertiles EPA&DHA: (I) 0.00-4.8, (II) 4.8-7.1 (III)7.1-14.0.

rs4833248 (*IL-2* region 5') and LA were statistically significant. Each PUFA associated with rs2069779 had a decreasing effect on obesity risk for minor allele carriers (Figure 3.1). In this gene stratum, the risk decreased for each mol-% increase in erythrocyte membrane-bound PUFAs with OR of 0.63 (LA), 0.83 (AA) and 0.66 (EPA&DHA). For rs4833248 as well as rs2069762, homozygous wild-type carriers benefited from increased LA content in erythrocyte membranes. Analyses for *IL-6* revealed three SNPs: rs1800795, rs10242595, and rs2069861. The first two showed a significant interaction effect with LA with P_{int} = 0.0341 and 0.0315, respectively. For each percentage increase in erythrocyte membrane-bound LA, obesity risk decreased in carriers of at least one minor allele of rs1800795 with an OR of 0.86 (95 % CI = [0.76, 0.96]); a similar effect was found for the rs1800795–AA interaction (Figure 3.2). In the case of rs10242595, the relative risk

decreased for carriers of the homozygous wild-type alleles with increasing LA content (OR = 0.81, 95 % CI = [0.71, 0.93]). The interaction effect of rs2069861 and EPA&DHA was significant as well. Here, the obesity risk decreased with each mol-% increase of erythrocyte membrane-bound EPA&DHA for minor allele carriers (OR = 0.74, 95 % CI = [0.57, 0.94]). For *IL-18*, one SNP (rs3882891) interacted significantly with LA when analysing obesity risk. Minor allele carriers of this SNP had a reduced obesity risk with increasing LA content in erythrocyte membranes (OR = 0.84, 95 % CI = [0.75, 0.94], P_{int} = 0.0203). We also obtained evidence for SNP–EPA&DHA interaction effects of the *TNFRSF1B* gene. Participants carrying at least one minor allele of rs3766730 (OR = 0.86, 95 % CI = [0.75, 0.98], P_{int} = 0.0225) or rs2275416 (OR = 0.88, 95 % CI = [0.78, 0.99], P_{int} = 0.0455) had a lower obesity risk than homozygous wild-type carriers. In relation to obesity risk, two SNPs of *TNFRSF21* were shown to interact with EPA&DHA; rs9381530 (region 3') with an OR of 0.79 (95 % CI = [0.68, 0.91], P_{int} = 0.0065) and rs2236039 with an OR of 0.87 (95 % CI = [0.78, 0.96], P_{int} = 0.0482). In each case, obesity risk decreased with increasing PUFA content in participants carrying two major alleles.

Among the selected adipokine genes, few significant results were obtained. The interaction terms of two *ADIPOQ* SNPs (rs1063539 and rs2241766) and membrane EPA&DHA content were significantly associated with obesity risk. In homozygous wild-type carriers, obesity risk decreased with increasing EPA&DHA content (Table 3.4). Concerning a *LEPR* polymorphism (rs1805096), an inverse association with obesity risk existed in carriers of the minor allele, with an increasing erythrocyte membrane content of LA (OR = 0.83, 95 % CI = [0.74, 0.93], P_{int} = 0.0084; Table 3.2) or AA (OR = 0.95, 95 % CI = [0.91, 1.00], P_{int} = 0.0459; Table 3.3).

Table 3.5 gives the geometric means and the 95 % CI of plasma IL-6 stratified by *IL-6* SNPs rs1800795, rs10242595 and rs2069861 (homozygote wild type and one or more mutant alleles) and tertiles of LA, AA and EPA&DHA for obese and non-obese participants. The plasma IL-6 concentrations were generally higher in obese participants compared with non-obese participants (Table 3.1) and decreased with increasing PUFA content in erythrocyte membranes (tertiles). These results lend credit to the identified *IL-6* SNP–PUFA interactions and obesity risk derived from the statistical models.

3.1.3 Discussion

This project aimed at investigating the additional effect on obesity brought on by the interaction of selected genetic variants and PUFA content of erythrocyte membranes. Out

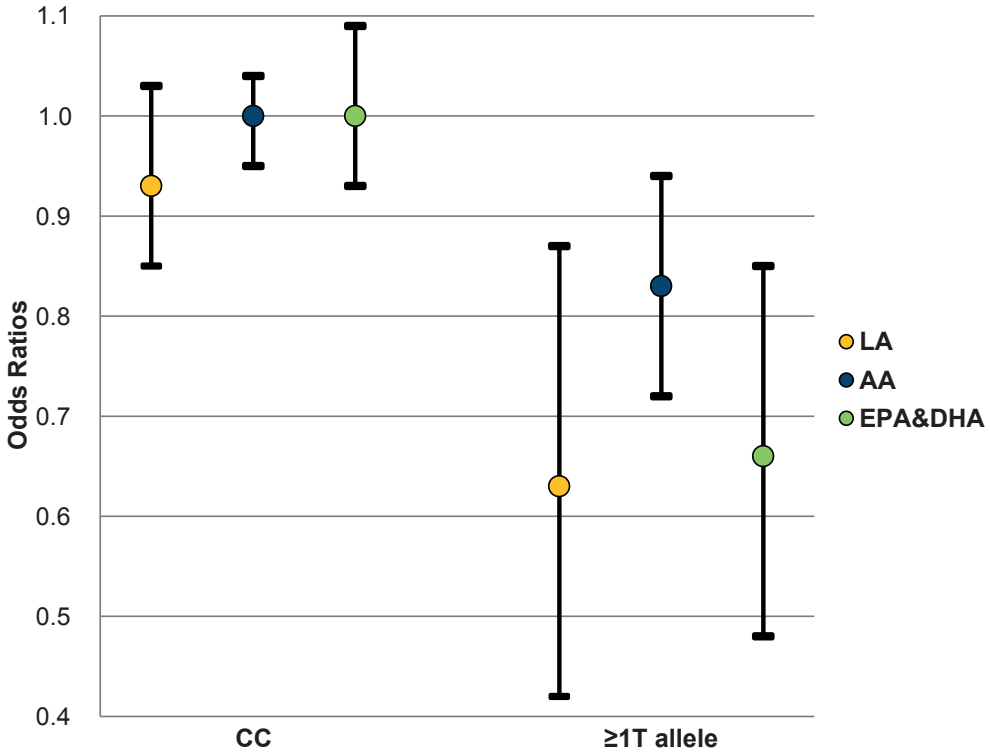

Figure 3.1: The effect of LA (P_{int} = 0.0310), AA (P_{int} = 0.0104) and EPA&DHA (P_{int} = 0.0022) on the risk of obesity, stratified by genotype of *IL-2* (rs2069779). Estimates are adjusted for age, sex, physical activity, and socioeconomic status *(Jourdan et al., 2011)*.

of the four different groups of genes, including cytokines, adipokines, neurotransmitters and transcription factors, we obtained significant interaction effects between the SNPs of *IL-2*, *IL-6*, *IL-18*, *TNFRSF1B*, *TNFRSF21*, *LEPR*, or *ADIPOQ* and PUFA content in erythrocyte membranes. We found a reduced obesity risk for minor allele carriers of most variants with high PUFA content in erythrocyte membranes, except for the SNPs of *TNFRSF21*, *ADIPOQ*, rs2069762 (*IL-2*), rs4833248 (*IL-2* region 5') and rs10242595 (*IL-6* region 3'). With the latter genes, participants, homozygote for the major allele, benefited from an increased PUFA content of erythrocyte membranes. In the case of *IL-6*, the analysed plasma IL-6 protein concentration supports the statistical findings.

PUFAs and Cytokines

Obesity has been described as a state of chronic low-grade inflammation (Engstrom et al., 2003; Festa et al., 2001). Thus, polymorphisms in different cytokines were included in the

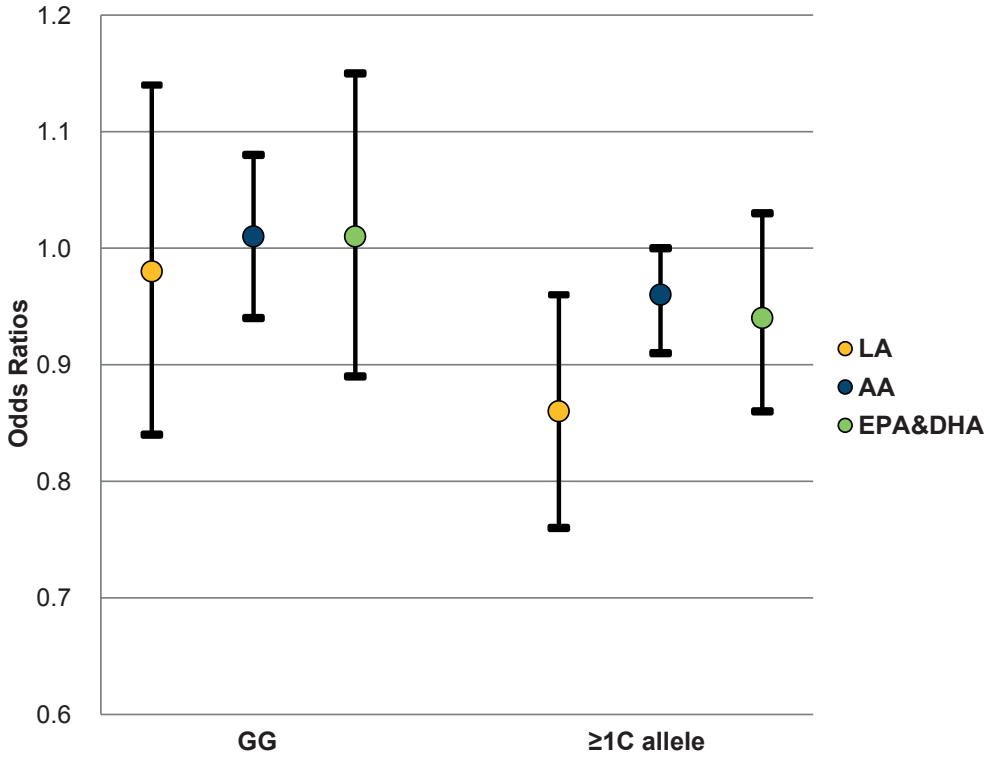

Figure 3.2: The effect of LA (P_{int} = 0.0341), AA (P_{int} = 0.0315) and EPA&DHA (P_{int} = 0.0878) on the risk of obesity, stratified by genotype of *IL-6* (rs1800795). Estimates are adjusted for age, sex, physical activity, and socioeconomic status *(Jourdan et al., 2011)*.

analyses of gene–PUFA interactions. Cytokines are a group of modulatory proteins which respond to various stimuli, thereby activating second messengers and signal transduction pathways within the cells (Smith & Humphries, 2009). Several cell studies and also dietary intervention studies have shown a reduced production of IL-2 in response to PUFAs (Merzouk et al., 2008; Verlengia et al., 2003; Alnajjar et al., 2006; von Schacky, 2007); however, the exact mechanism behind this phenomenon still remains unclear (Calder & Grimble, 2002; Gorjao et al., 2007). Here, obesity risk decreased with increasing PUFA content of the erythrocyte membranes, and thus confirms the expected direction. PUFA eicosanoid derivates, such as prostaglandin E2 (PGE_2), are involved in the modulation of the intensity and duration of inflammatory processes and suppress the production of IL-6 (Stulnig, 2003). Adipose tissue in human participants releases IL-6 and serum levels are positively correlated with body fat mass (Vozarova et al., 2001). Himmerich et al. (2006) confirmed this relation for the present population. *IL-6* gene transcription was found to be influenced in vitro by the

rs1800795 polymorphism within the promoter region (Fishman et al., 1998). The G allele of this SNP was described as to be more common in lean participants (Berthier et al., 2003); additionally, a lower BMI was measured in participants with the CC genotype (Kubaszek et al., 2003), which might eventually predispose to weight gain; this hypothesis has been supported by some studies but not confirmed in two meta-analyses of the association of this SNP with BMI (Huth et al., 2009; Qi et al., 2007). Our findings on SNP–PUFA interactions may provide an explanation for the diverging results since they consider the possible interplay between SNPs and the PUFA supply status. For the other *IL-6* SNP, rs10242595, the A variant was found to be significantly associated with decreased body fat mass in young adult men, a result which was replicated in two other population-based studies of elderly men (Andersson et al., 2010). The interaction effect between this SNP and PUFAs in this study is indicative towards the importance of this SNP for the development of obesity. Variations in the *IL-18* gene have been associated with IL-18 plasma concentrations and measures of obesity (Thompson et al., 2007). Obese participants show higher levels of IL-18 than lean participants (Skurk et al., 2005), and IL-18 has been associated with excess adiposity (Hung et al., 2005). Our *IL-18* variant is in complete LD with rs5744292, an *IL-18* SNP whose minor allele has been reported to be associated with lower circulating IL-18 levels and lower mRNA expression in immortalised lymphocytes (Barbaux et al., 2007; Tiret et al., 2005)). Furthermore, a suppressing effect of PGE_2 on the expression of *IL-18* has been shown in cell studies (Suk et al., 2001). The finding of an *IL-18*–PUFA interaction in the present study fits well with these data. Even though the production of TNF_α by monocytes and macrophages is also suppressed by PGE_2 (Stulnig, 2003), no significant interactions were detected. However, we found evidence for significant interaction effects for SNPs from its receptors, *TNFRSF1B* and *TNFRSF21*. Overall, all identified (significant) interactions between cytokine SNPs and PUFAs indicate an inverse association with obesity risk for minor allele carriers, with increasing PUFA content in erythrocyte membranes, except for SNPs of *TNFRSF21*, rs4833248 (*IL-2* region 5') and rs10242595 (*IL-6* region 3').

PUFAs and Adipokines

Besides its role for lipid storage, adipose tissue functions as an endocrine organ, regulating metabolism and different vital functions related, among others, to inflammation (Saltiel, 2001; Spiegelman & Flier, 2001). Thus, different adipokines have been included in this project. Adiponectin is exclusively secreted by adipose tissue and serum levels are inversely correlated with body fat mass (Arita et al., 1999). The mRNA expression is reduced in obese

individuals (Hu et al., 1996). Serum adiponectin levels are highly heritable (approximately 50 %) and are linked to the *ADIPOQ* gene locus (Chuang et al., 2004; Comuzzie et al., 2001; Vasseur et al., 2002). Different cell and dietary intervention studies found EPA&DHA to stimulate the expression of *ADIPOQ* and to increase plasma adiponectin levels (Itoh et al., 2007; Flachs et al., 2006; Yu et al., 2008); however, findings differ (Lorente-Cebrian et al., 2006). EPA&DHA might possibly up-regulate *ADIPOQ* by acting through *PPAR*γ, affecting the *ADIPOQ* promoter (Iwaki et al., 2003). The present results are in line with these findings and show a significantly decreased obesity risk for carriers of two major alleles of rs2241766 or rs1063539, with increasing EPA&DHA concentrations in erythrocyte membranes. Different animal, human and cell studies have shown an inverse effect of PUFAs on the *LEP* mRNA expression (Reseland et al., 2001; Phillips et al., 2010). The present analyses resulted in one significant interaction for a variant of the *LEPR* gene, which is in line with these findings.

Sensitivity Analyses

We see two major mechanisms of how PUFAs may in conjunction with genetic variants affect obesity risk: either via direct modification of gene transcription or by products of the eicosanoid pathway. To compare the direction of the different effects of PUFAs on the risk of obesity within the SNP strata of the significant interaction models, we also estimated the effects of the remaining PUFAs by the given SNP strata for which the interaction term with those SNPs was not significant (e.g., Figure 3.2). We observed quite similar effects (direction and estimates) over the different PUFAs in the various SNP strata (data not shown). A high erythrocyte membrane content of LA, AA, or EPA&DHA thereby did either show no association or an inverse association with obesity risk in each of the SNP strata. In mutually adjusted analyses, we have also not received any indication for changes of effects of *n-3* PUFA-adjusted *n-6* PUFAs and vice versa.

Strength and Limitations

A limitation of the first project is obviously the small sample size (n = 621). Studies of genetic associations with complex diseases need thousands of cases and controls (Colhoun et al., 2003); however, this requirement is not easily fulfilled with respect to the costly fatty acid analyses. The small number of cases and controls and consequently the limited statistical power strongly argue for a careful interpretation of the results and a replication in a second, larger and independent study. Because of the small sample size and the

resulting limited power, we did not correct for multiple testing. The observational nature of this project does not allow for interpreting causal associations, and we cannot rule out the possibility of reverse causation. However, we controlled for potential confounding by adjusting for sex, age, physical activity, and socioeconomic status. The genetic dataset of the BVS II was comprised in 2006 and was based on an extensive literature research for obesity candidate genes. This was shortly after the first GWAS and thus, in the meantime newly identified SNPs and genes associated with obesity are not part of the dataset.
The major strength of this project is the use of erythrocyte membranes to assess biologically available PUFAs at the cellular level and its association with genetic variants influencing the risk of obesity. With the utilisation of biomarkers as an objective metabolic correlate of dietary PUFA intake, misclassifications can be largely avoided. A further strength of the present study is its population-based design aiming at representativeness for the adult Bavarian population and the strict quality control in the analyses.

Conclusion

We conclude that PUFAs exert their effects rather via modification of gene transcription than through metabolites derived during eicosanoid synthesis, since the latter would have led to differential effects of *n-3* and *n-6* PUFAs. Further, it is important to mention that the frequency of these SNPs for which we observed interactive effects with PUFAs is fairly high, except for *IL-2* SNP (rs2069779). This implicates that a substantial part of the population would benefit from a high PUFA intake with respect to obesity risk.

3.2 Metabolomics and Fat Free Mass

3.2.1 Background

This project aimed at providing a comprehensive picture of fat free mass induced effects on the metabolite profile in blood samples of adults. The human serum metabolome is currently characterised in many studies using different analytic approaches (Psychogios et al., 2011), including the method applied here. To the best of our knowledge, the association of FFMI or fat free mass and serum metabolites was not explored before in an epidemiologic setting involving healthy participants. Rather, metabolomics signatures of exercise (before, during and afterwards) in human plasma were investigated showing that subjects who were in better shape exhibited more lipolysis during and after exercise than did the less fit subjects

Table 3.6: Characteristics (mean, SD, % or *N*) of male and female participants of the analysed samples of KORA S4 and KORA F4 *(Jourdan et al., 2012)*.

		KORA S4 ($n = 965$)				KORA F4 ($n = 890$)			
		Men ($n = 485$)		Women ($n = 480$)		Men ($n = 423$)		Women ($n = 467$)	
Parameter	Unit	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	years	63.2	5.5	63.3	5.3	53.8	12.0	54.7	12.5
Weight	kg	83.2	11.4	71.6	12.0	83.2	11.4	69.0	13.1
Height	cm	172.3	6.4	159.3	6.00	176.7	7.0	162.9	6.6
Body Mass Index	kg/m^2	28.0	3.6	28.2	4.7	26.6	3.3	26.0	4.7
Waist	cm	100.0	9.4	89.6	11.1	95.9	9.9	85.2	12.6
Hip	cm	104.7	6.5	107.2	9.9	104.2	6.2	104.2	9.4
Waist to Hip Ratio		1.0	0.1	0.8	0.1	0.9	0.1	0.8	0.1
Fat Free Mass[a]	kg	58.5	5.7	43.1	5.1	60.8	6.1	43.6	5.4
Body Fat Mass[b]	%	29.3	4.7	39.2	4.8	26.3	5.0	36.0	5.7
FFMI[a,b]	kg/m^2	19.7	1.7	17.0	1.9	19.6	1.6	16.5	1.8
BFMI[a,c]	kg/m^2	8.3	2.3	11.2	3.1	7.2	2.1	9.6	3.2
Parameter	Category	%	*N*	%	*N*	%	*N*	%	*N*
Body Mass Index	< 18.5	-	-	-	-	0.2	1	0.6	3
	18.5 to < 25	17.1	83	25.6	123	30.5	129	45.8	214
	25 to < 30	56.5	274	43.3	208	52.7	223	34.9	163
	≥ 30	26.2	127	30.6	147	16.6	70	18.6	87
Physical Activity[d]	active	38.76	188	46.7	224	59.8	253	61.2	286
	inactive	60.4	293	52.9	254	40.0	169	38.8	181
Age Groups	31 to 40 years	-	-	-	-	14.7	62	15.4	72
	41 to 50 years	-	-	-	-	29.6	125	24.2	113
	51 to 60 years	38.1	185	35.4	170	23.9	101	27.0	126
	61 to 70 years	48.5	235	52.1	250	22.0	93	21.2	99
	71 to 80 years	13.4	65	12.5	60	9.5	40	11.6	54
	≥ 81 years	-	-	-	-	0.5	2	0.6	3

[a] Parameter derived from the bioelectrical impedance analysis measurements which were only conducted in KORA S4; [b] Fat Free Mass Index; [c] Body Fat Mass Index; [d] Physical Activity (active: $>$ 1 h leisure time of sports per week on a regular basis; inactive: less than 1h per week).

(Lewis et al., 2010). Thus, we hypothesised that a sedentary lifestyle leads to derangements of skeletal muscle metabolism favouring, e.g., the development of obesity.

3.2.2 Results

Table 3.6 summarises the anthropometric data of the KORA S4 and KORA F4 participants. Selected statistically significant associations of FFMI with different metabolite concentrations for the KORA S4 population are given in Table 3.7. Different parameters such as the direction of the β-estimate derived from the adjusted linear models are given, as is the

agreement between the KORA S4 and KORA F4 results. The full list of statistically significant associations obtained in KORA S4 and KORA F4 are found in the Supplementary Tables B2 and B3, respectively. The GGMs established in KORA S4 and KORA F4 are displayed in Figure 3.4, 3.5, and B1, completing the results of the linear regression models by illustrating the underlying relationships between the metabolite concentrations.

Amino Acids

With higher FFMI, increasing serum concentrations of the branched-chain amino acids (BCAAs) valine, isoleucine, and leucine as well as of the sum of BCAAs were observed. Furthermore, other serum amino acids increased with higher FFMI, including the glucogenic amino acid alanine, and the aromatic amino acids tyrosine and phenylalanine. With respect to metabolite ratios, strong positive associations were found between FFMI and the ratios of isoleucine to glycine and leucine to glycine. In addition, the ratio of all BCAAs to all glucogenic amino acids (sum of alanine, glycine, and serine) was positively related to FFMI, supporting the notion of increasing BCAAs concentrations in relation to glucogenic amino acids in serum samples of participants with higher FFMI. Inspecting the GGM results (Figure 3.4), we also observe these strong correlations between BCAAs. Based on these results, we illustrated the association between the sum of BCAAs and quintiles of FFMI in Figure 3.3, and described the anthropometric characteristics of the KORA S4 participants by quintiles of BCAAs (Table 3.8). These findings are replicated in the KORA F4.

Acylcarnitines

Serum concentrations of free carnitine (C0) and short-chain odd-numbered acylcarnitines, such as propionylcarnitine (C3) and valerylcarnitine (C5), were found to be positively associated with FFMI while octadecanoylcarnitine (C18) decreased with increasing FFMI. This is also reflected in the results for the ratios of C18 to C0, C3, or C5. These findings in KORA S4 are supported by the KORA F4 results. The acylcarnitines form a separate group within the partial correlation networks and a particularly strong correlation exists between the metabolites C0 and C3.

Phosphatidylcholines

The group of phosphatidylcholines consists of different PC diacyl (aa), PC acyl-alkyl (ae), and lysoPC acyl (a) compounds. Numerous associations between FFMI and PCs or PC

Table 3.7: Selected metabolic traits significantly associated with FFMI[a] in a linear regression adjusted for age and sex in KORA S4 *(Jourdan et al., 2012)*.

Trait	Mean (µmol/l)	SD	Dir[b]	P-Value Adj.[c]	R^2 Adj.[d]	P-Gain[e]	F4[f]
Val	227.26	53.13	pos.	$4.75\text{x}10^{-16}$	0.16		*
Glu	80.13	32.04	pos.	$1.22\text{x}10^{-15}$	0.11		n.a.
Ile	72.14	20.22	pos.	$1.96\text{x}10^{-11}$	0.22		#
Leu	160.51	44.33	pos.	$2.57\text{x}10^{-08}$	0.18		#
Ala	417.99	101.40	pos.	$8.95\text{x}10^{-06}$	0.03		n.a.
Tyr	72.09	20.06	pos.	$4.77\text{x}10^{-10}$	0.06		*
Phe	76.73	17.19	pos.	$2.53\text{x}10^{-07}$	0.05		n.s.
Σ aromatic AAs	208.98	43.75	pos.	$3.37\text{x}10^{-09}$	0.07		*
Σ BCAAs	459.91	113.06	pos.	$2.07\text{x}10^{-13}$	0.19		*
Ile/Gly	0.29	0.11	pos.	$1.61\text{x}10^{-14}$	0.30	$1.22\text{x}10^{+03}$	#
Leu/Gly	0.65	0.25	pos.	$1.46\text{x}10^{-12}$	0.29	$1.75\text{x}10^{+04}$	#
Σ BCAAs / Σ glucogenic AAs	0.58	0.14	pos.	$1.49\text{x}10^{-08}$	0.26		*
C5	0.16	0.06	pos.	$3.49\text{x}10^{-05}$	0.17		*
C3	0.47	0.15	pos.	$4.85\text{x}10^{-05}$	0.13		*
C0	40.52	8.49	pos.	$1.19\text{x}10^{-02}$	0.13		*
C18	0.06	0.01	neg.	$3.96\text{x}10^{-02}$	0.10		n.s.
C18/C5	0.37	0.14	neg.	$1.44\text{x}10^{-09}$	0.08	$2.42\text{x}10^{+04}$	n.s.
C18/C3	0.13	0.05	neg.	$3.65\text{x}10^{-09}$	0.05	$1.33\text{x}10^{+04}$	n.s.
C18/C0	0.001	0.0004	neg.	$5.44\text{x}10^{-07}$	0.05	$2.19\text{x}10^{+04}$	n.s.
PC aa C38:3	57.77	14.01	pos.	$7.02\text{x}10^{-06}$	0.06		*
PC ae C42:3	0.85	0.19	neg.	$5.10\text{x}10^{-18}$	0.10		*
PC ae C36:2	15.33	3.88	neg.	$2.42\text{x}10^{-15}$	0.19		*
lysoPC a C18:2	28.46	9.04	neg.	$8.19\text{x}10^{-16}$	0.16		*
lysoPC a C18:1	21.61	6.10	neg.	$2.30\text{x}10^{-10}$	0.11		*
Σ PC ae	181.45	30.52	neg.	$1.38\text{x}10^{-04}$	0.10		*
Σ lysoPC	229.29	47.21	neg.	$4.36\text{x}10^{-04}$	0.07		*
PC aa C38:3/PC aa C42:6	97.71	21.87	pos.	$1.04\text{x}10^{-17}$	0.09	$6.73\text{x}10^{+11}$	*
PC aa C38:3/PC aa C42:0	111.66	41.58	pos.	$1.06\text{x}10^{-15}$	0.07	$3.68\text{x}10^{+06}$	*
PC aa C38:3/PC aa C42:2	297.65	96.51	pos.	$1.72\text{x}10^{-16}$	0.10	$1.69\text{x}10^{+09}$	*
lysoPC a C14:0/lysoPC a C18:2	0.24	0.08	pos.	$1.04\text{x}10^{-20}$	0.18	$7.88\text{x}10^{+04}$	n.s.
PC ae C36:4/PC ae C40:1	12.99	3.34	pos.	$1.70\text{x}10^{-07}$	0.04	$3.57\text{x}10^{+02}$	*
PC aa C38:3/lysoPC a C18:1	2.27	0.99	pos.	$3.37\text{x}10^{-20}$	0.19	$2.43\text{x}10^{+04}$	*
PC aa C38:3/lysoPC a C18:2	2.87	1.03	pos.	$1.38\text{x}10^{-19}$	0.17	$1.66\text{x}10^{+09}$	*
PC aa C38:3/PC ae C42:3	70.43	21.88	pos.	$3.12\text{x}10^{-26}$	0.12	$1.63\text{x}10^{+08}$	*
PC aa C38:3/PC ae C42:2	93.08	24.28	pos.	$3.73\text{x}10^{-23}$	0.11	$7.97\text{x}10^{+15}$	*
SM C16:0/SM C16:1	6.40	0.76	neg.	$1.52\text{x}10^{-11}$	0.29	$3.13\text{x}10^{+08}$	*
SM (OH) C16:1/SM C18:1	0.31	0.06	neg.	$3.51\text{x}10^{-10}$	0.05	$4.94\text{x}10^{+07}$	*
SM C16:0/SM C18:1	9.36	1.83	neg.	$5.71\text{x}10^{-08}$	0.24	$8.33\text{x}10^{+04}$	*
SM (OH) C16:1/SM C18:0	0.16	0.03	neg.	$3.28\text{x}10^{-10}$	0.10	$5.27\text{x}10^{+07}$	*
SM (OH) C22:2/SM C18:1	1.00	0.19	neg.	$4.14\text{x}10^{-07}$	0.05	$2.93\text{x}10^{+05}$	*

[a] Fat Free Mass Index; [b] direction of the association (positive or negative); [c] for multiple testing adjusted p-value; [d] adjusted R^2 of the linear model; [e] p-gain, fold decrease in the p-value of association for the pair of metabolites, compared to the lowest of two p-values for the single metabolites; [f] confirmed in KORA F4, * for significance and direction; # confirmed for xLeu in KORA F4, n.a. metabolite was not available in KORA F4, n.s. not significant; AAs amino acids; Σ aromatic amino acids is the sum of tyrosine, phenylalanine, and tryptophan; Σ BCAAs is the sum of valine, isoleucine, and leucine; Σ glucogenic amino acids is the sum of alanine, glycine, and serine.

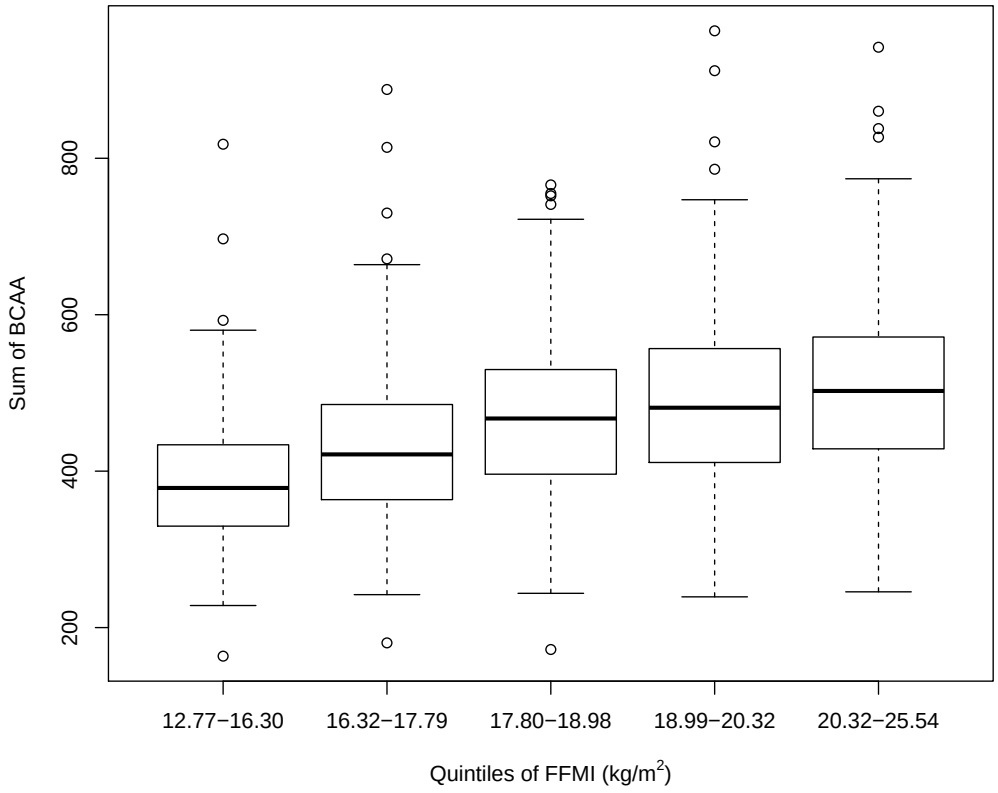

Figure 3.3: Boxplot of serum BCAA concentrations (µmol/l), by quintiles of FFMI, for the KORA S4 population. *(Jourdan et al., 2012).*

ratios could be observed. An increase in FFMI was associated with (i) a higher serum concentration of PC aa in relation to PC ae, (ii) a decrease in chain length of the fatty acid residues, and (iii) a decrease in saturation (i.e., a higher number of double bonds) of the fatty acid moieties. Significant results for single PC compounds were all negatively associated with FFMI, such as PC ae C42:3 or PC ae C36:2, lysoPC a C18:2 or lysoPC a C18:1; the only exception is PC aa C38:3 which increased with higher FFMI. Ratios within subgroups (aa/aa, ae/ae, lyso/lyso) demonstrated that increasing FFMI is associated with a shift towards shorter fatty acids and fatty acids with more double bonds. Examples are ratios of PC aa C38:3/PC aa C42:6, PC aa C38:3/PC aa C42:2, PC aa C38:3/PC aa C42:0, PC ae C36:4/PC ae C40:1 or lysoPC a C14:0/lysoPC a C18:2. This is most likely a consequence of the associations observed for the single compounds (e.g., PC aa C38:3 increased and lysoPC a C18:1 decreased with increasing FFMI). Ratios of PC aa

Table 3.8: Different characteristics (mean, SD, %, or *N*) of the KORA S4 sample stratified by quintiles of the BCAAs[a] serum concentration *(Jourdan et al., 2012).*

	Quintiles of the sum of BCAA (µmol/l)									
	1 (163.5-363.7)		2 (364.1-418)		3 (418.2-476.9)		4 (477-542.2)		5 (542.3-963)	
Parameter	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	63.1	5.4	63.3	5.4	63.5	5.6	63.6	5.4	62.9	5.3
Weight	69.5	11.8	75.5	12.7	76.1	11.2	81.6	12.4	84.3	11.9
Height	161.4	7.5	164.7	8.7	165.8	9.1	168.9	8.8	168.5	8.4
Body Mass Index	26.6	4.1	27.9	4.3	27.8	4.0	28.6	3.8	29.8	4.2
Fat Free Mass (kg)	44.1	7.3	49.4	9.1	50.2	8.7	54.8	8.8	55.7	8.1
Body Fat Mass (%)	36.1	6.3	34.4	6.9	34.0	7.2	32.7	6.8	33.7	6.7
FFMI[b]	16.9	2.0	18.1	2.3	18.2	2.1	19.1	1.9	19.6	1.9
BFMI[c]	9.8	2.9	9.7	3.1	9.6	3.2	9.5	3.0	10.3	3.2
FFM/BFM[d]	1.9	0.8	2.1	0.7	2.1	0.7	2.2	0.7	2.1	0.7
Parameter	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*
Male	19.7	38	42.5	82	49.7	96	67.9	131	71.5	138
Female	80.3	155	57.5	111	50.3	97	32.1	62	28.5	55
Physical activity[e]	47.2	91	35.8	69	52.3	101	40.9	79	37.3	72

[a] BCAAs is the sum of valine, isoleucine, and leucine; [b] Fat Free Mass Index; [c] Body Fat Mass Index; [d] Fat Free Mass divided by Body Fat Mass; [e] Physical Activity (active: $>$ 1 h leisure time of sports per week on a regular basis; inactive: less than 1h sports per week).

to PC ae were significantly associated with FFMI, such as PC aa C38:3/PC ae C42:3 or PC aa C38:3/PC ae 42:2. There are three large groups of PCs which were identified in the network analyses (Figure 3.5). PC aa C38:3 is the centre of the largest cluster which includes mainly PC aa and shorter PC ae; the second cluster is very similar to the former. The third cluster consists of mostly long-chain PCs. These findings are also supported by the results obtained in the KORA F4 sample.

Sphingomyelins

With higher FFMI an increased concentration of sphingomyelins (SM) as compared to hydroxysphingomyelins (SM (OH)) was observed. This is reflected e.g., by the ratios of SM (OH) C16:1/SM C18:1, SM (OH) C16:1/SM C18:0 or SM (OH) C22:2/SM C18:1. Also, the results of sphingomyelin ratios, such as SM C16:0/SM C16:1 or SM 16:0/SM C18:1, demonstrate a decrease in saturation of the fatty acids with increasing FFMI. The same associations are found in KORA F4. The GGM results show that almost all sphingomyelin are interrelated and the strong relationship between SM (OH) C16:1 and SM (OH) C14:1 is present in both GGMs (Figure 3.5 and Figure B1).

Table 3.9: Selected metabolic traits significantly associated with FFMI[a] in a linear regression model adjusted for age, and sex for the non-obese (BMI < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) participants in the KORA S4 sample *(Jourdan et al., 2012)*.

	Obese (n = 274)			Non-Obese (n = 691)		
Trait	Beta	Adj. P-Value[b]	Adj.[c] R^2	Beta	Adj. P-Value[b]	Adj.[c] R^2
Val	0.08	1.00	0.03	0.14	$1.70\text{x}10^{-04}$	0.17
Ile	0.06	1.00	0.12	0.13	$3.94\text{x}10^{-04}$	0.25
Leu	0.04	1.00	0.08	0.13	$3.77\text{x}10^{-04}$	0.22
Ala	0.02	1.00	0.00	0.12	0.0409	0.02
Tyr	0.04	1.00	0.00	0.14	$2.09\text{x}10^{-03}$	0.05
Phe	0.06	1.00	0.00	0.10	0.2377	0.04
Σ aromatic AAs	0.05	1.00	0.02	0.12	0.014	0.06
Σ BCAAs	0.06	1.00	0.07	0.15	$5.10\text{x}10^{-05}$	0.21
Ile/Gly	0.03	1.00	0.26	0.13	$2.42\text{x}10^{-04}$	0.30
Leu/Gly	0.02	1.00	0.22	0.13	$9.29\text{x}10^{-05}$	0.30
Σ BCAAs/Σ glucogenic AAs	0.05	1.00	0.15	0.10	0.0353	0.30
C5	0.06	1.00	0.13	0.14	$1.34\text{x}10^{-04}$	0.19
C3	0.06	1.00	0.06	0.13	$2.52\text{x}10^{-03}$	0.16
C0	0.06	1.00	0.08	0.09	0.2550	0.16
PC aa C38.3	0.00	1.00	0.02	0.08	1.00	0.04
PC ae C42.3	-0.14	0.3100	0.04	-0.16	$7.30\text{x}10^{-05}$	0.06
PC ae C36.2	-0.07	1.00	0.13	-0.09	0.4180	0.17
lysoPC a C18.1	-0.08	1.00	0.08	-0.07	1.00	0.05
lysoPC a C18.2	-0.14	0.2100	0.13	-0.07	1.00	0.08
Σ PC ae	-0.04	1.00	0.05	-0.05	1.00	0.09
Σ lysoPC	-0.04	1.00	0.06	-0.02	1.00	0.04
PC aa C38:3/PC aa C42:6	0.03	1.00	0.01	0.18	$2.69\text{x}10^{-06}$	0.05
PC aa C38:3/PC aa C42:2	0.05	1.00	0.03	0.14	$7.49\text{x}10^{-04}$	0.05
lysoPC a C14:0/lysoPC a C18:2	0.18	0.0030	0.17	0.10	0.1130	0.09
PC aa C38:3/lysoPC a C18:1	0.07	1.00	0.11	0.11	0.0377	0.10
PC aa C38:3/lysoPC a C18:2	0.10	1.00	0.13	0.10	0.1580	0.11
PC aa C38:3/PC ae C42:3	0.10	1.00	0.01	0.18	$8.77\text{x}10^{-07}$	0.05
PC aa C38:3/PC ae C36:2	0.06	1.00	0.04	0.14	$1.48\text{x}10^{-03}$	0.06
PC aa C38:3/PC ae C42:2	0.07	1.00	0.00	0.17	$1.02\text{x}10^{-05}$	0.04
SM C16:0/SM C16:1	-0.02	1.00	0.23	-0.06	1.00	0.27
SM (OH) C16:1/SM C 18:1	0.01	1.00	0.01	-0.08	1.00	0.02
SM C 16:0/SM C 18:1	-0.02	1.00	0.17	-0.06	1.00	0.23
SM (OH) C16:1/SM C 18:0	0.02	1.00	0.17	-0.10	0.1700	0.05
SM (OH) C22:2/SM C 18:1	0.00	1.00	0.05	-0.07	1.00	0.01

[a] Fat Free Mass Index; [b] for multiple testing adjusted p-value; [c] adjusted R^2 of the linear model; Σ AAs amino acids; Σ aromatic amino acids is the sum of tyrosine, phenylalanine, and tryptophan; Σ BCAAs is the sum of valine, isoleucine, and leucine; Σ glucogenic amino acids is the sum of alanine, glycine, and serine.

Appendicular Skeletal Muscle Mass Index

For both, KORA S4 and KORA F4, the results for the appendicular skeletal muscle mass index were largely comparable to the results with FFMI (data not shown). However, the p-values in the linear regression models did not decrease and also the adjusted R^2 did not improve as compared to the FFMI based results. Therefore, FFMI remained as primary explanatory variable.

Stratifications

In stratified analyses, very similar results could be observed for men and women. With respect to physical activity, there was only a slight difference between both groups (active versus inactive participants) for the associations with the acylcarnitine metabolites. Most of the statistically significant associations between FFMI and the acylcarnitines found for the entire group and the physically active group were not present in the inactive group. Regarding age ($>$ 65 years versus $\leq$ 65 years; KORA S4), there were no distinct differences between groups. With respect to the associations between FFMI and the metabolites in obese and non-obese participants in KORA S4 we did observe significant differences. Most associations described for the whole population and also noted for the non-obese subgroup are not present in obese participants (Table 3.9).

Genetic Analyses

No significant associations were found between the selected genetic variants (Supplementary Table B4) and the serum metabolite concentrations (KORA S4 or KORA F4).

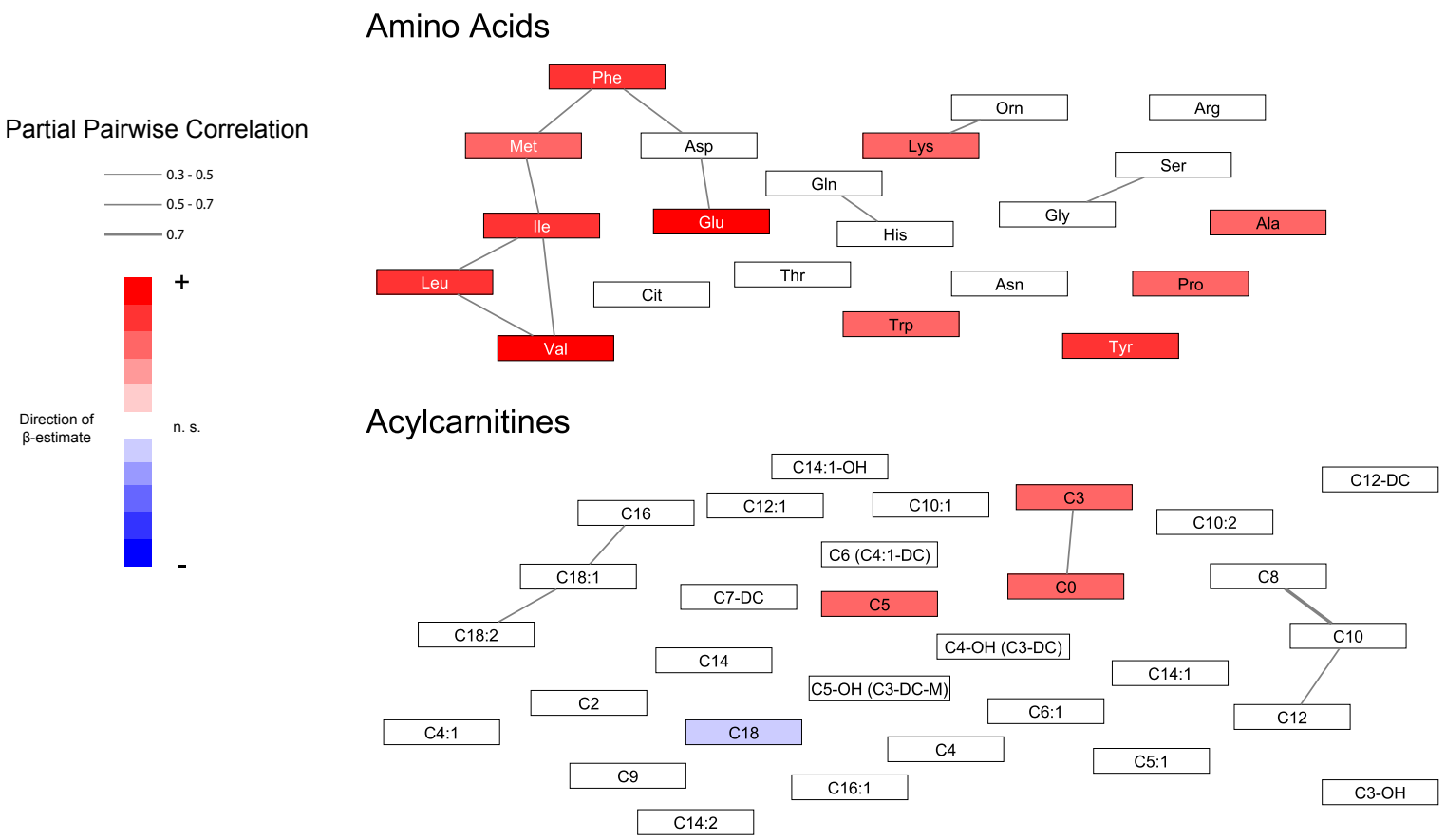

Figure 3.4: Gaussian graphical model of serum amino acids and acylcarnitine metabolite concentrations in KORA S4. Each node represents a metabolite, whereas edges represent significant partial correlations. Nodes were coloured according to the β-estimate and the p-value from the linear models (red = positive association with FFMI; blue = negative association with FFMI; white = not significant association with FFMI) *(Jourdan et al., 2012)*.

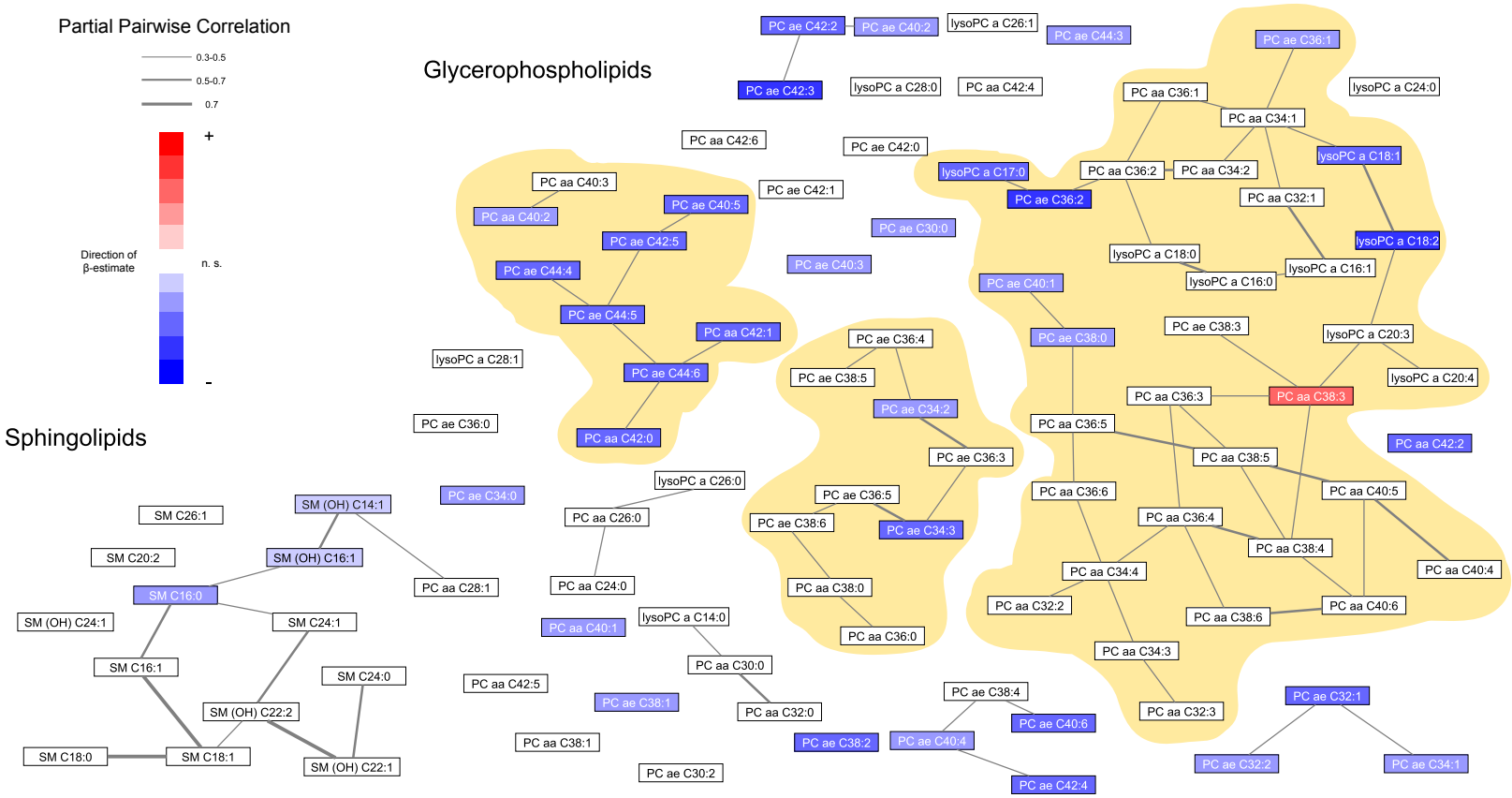

Figure 3.5: Gaussian graphical model of serum glycerophospholipids and sphingolipid metabolite concentrations in KORA S4. Each node represents a metabolite, whereas edges represent significant partial correlations. Nodes were coloured according to the β-estimate and the p-value from the linear models (red = positive association with FFMI; blue = negative association with FFMI; white = not significant association with FFMI). Yellow highlights the large clusters within the glycerophospholipid metabolites *(Jourdan et al., 2012)*.

3.2.3 Discussion

In this population-based study, strong associations between FFMI and serum metabolite concentrations were found in KORA S4 and reproduced in KORA F4. With higher FFMI, BCAA serum concentrations and the ratio of BCAAs to glucogenic amino acids increased. Free carnitine levels were also positively associated with FFMI, and for the various PCs we found a decrease in chain length and/or saturation of the fatty acid residues in combination with higher concentrations of PC aa in expense of PC ae and lysoPC. In obese participants of KORA S4, however, these associations were lacking.

Sedentary Lifestyle leads to Derangements in Skeletal Muscle Metabolism

As described in 3.2.1 we hypothesised that a sedentary lifestyle leads to derangements in skeletal muscle metabolism thereby favouring the development of obesity and metabolic diseases. The fact that we observed a lack of associations between FFMI and serum metabolites in obese participants at baseline (KORA S4) fits well to this hypothesis. As observed by Lewis et al. (2010), a decreased capability to stimulate lipid oxidation during exercise could be reflected in the missing associations between FFMI and the various lipid metabolites in obese participants. For the non-obese participants, we find evidence for an enhanced β-oxidation with higher FFMI which is reflected in the carnitine and PC metabolite results.

BCAAs and Muscle Metabolism

In contrast to a study with physical activity intervention, it was not clear how strong the associations between FFMI and serum concentrations of amino acids, acylcarnitines, glycerophospholipids, and sphingolipids could be in a cross-sectional study with collection of serum samples after short-term fasting of at least eight hours. However, our results fit well to biological pathways that are related to skeletal muscle metabolism, namely amino acid metabolism and fatty acid metabolism (reflected by acylcarnitines and glycerophospholipids). BCAAs are described as preferred substrates for muscle tissue, and BCAA supplementation can suppress protein degradation (Tom & Nair, 2006). During short-term fasting, glucose released from glycogen stores of the liver is provided as fuel for tissues that need glucose, e.g., the brain. Muscle protein degradation provides amino acids that are used by the liver for gluconeogenesis (Layman & Walker, 2006), with alanine being the most important one. BCAAs are a major source of nitrogen for muscle synthesis of glucogenic amino acids such

as alanine (Ruderman, 1975; Layman, 2003). This has been shown in studies with 1 to 3 days of starvation. Levels of BCAAs rise in fasting state parallel to an increased protein degradation. In this state, the only source of BCAAs is appearance from protein degradation, which is a key process for maintenance of protein quality and repair process of tissues. Thus, during overnight fasting, BCAA serum concentrations are increased proportional to the muscle mass of the body. Furthermore, alanine concentration levels rise with increasing protein degradation during starving (Tom & Nair, 2006). Thus, our findings of increasing serum concentrations of BCAAs and alanine that are strongly associated with FFMI are in line with the expectations.

Acycarnitines reflect Upregulation of β-Oxidation

Several other studies reported that acylcarnitines are also found in circulation (Psychogios et al., 2011). Acylcarnitines are intra-cellularly synthesised for the transport of fatty acids into the mitochondria for β-oxidation. In the present analyses an increase of acylcarnitine concentrations could be observed which argues for an upregulated β-oxidation of fatty acids in participants with higher muscle mass. One explanation for the origin of propionylcarnitine is oxidative degradation (β-oxidation, γ-oxidation) of BCAAs, releasing propionylcarnitine units. Another source of propionyl residues may be the intestinal production by gut microbiota; however a relationship with plasma propionylcarnitine or FFMI is not established.

Possibly altered Activity of ELOVL or FADS

Our phospholipid results point towards a decrease in chain length and degree of saturation of the lipid side chains. The concentrations of lysoPC and PC ae decrease with increasing FFMI and PC aa C38:3 is the only PC positively associated with higher FFMI. Considering the GGM results, PC aa C38:3 is central in one cluster of PC metabolites, while the other cluster consists of long-chain PCs. Overall, our results implicate that FFMI is associated with lower plasma concentrations of very long-chain PCs (GGM cluster 2), while the concentration of PC aa C38:3 increased. Thus, a higher FFMI may indicate a higher activity of enzymes involved in fatty acid oxidation, especially in the oxidation of very long-chain fatty acids. In addition, an altered activity of enzymes involved in chain elongation (ELOVL) or desaturation (FADS) could contribute to these findings. Earlier studies using metabolomics and genetic data demonstrated that genetic effects (mediated by the expression of enzymes) are reflected in the serum metabolic profile, lending credibility to the approach of identifying enzyme activities by means of serum metabolites or metabolite ratios (Illig et al., 2010;

Gieger et al., 2008). The shift from PC ae and lysoPC towards PC aa could also be explained by modifications in expression or activity of relevant enzymes (Illig et al., 2010). However, our analyses between SNPs associated with anthropometric characteristics and metabolite variables did not reveal any significant results.

Greater Muscle Mass might affect SCD

In addition, a higher FFMI was associated with an increased concentration of sphingomyelins as compared to hydroxysphingomyelins. Recently, Wang-Sattler et al. (2008) reported a reduced concentration of sphingomyelins and an increased concentration of hydroxysphingomyelins in smokers. This finding was explained as a consequence of smoking on the activity of the peroxisomal enzyme alkylglycerone phosphate synthase (alkyl-DHAP). Following this argumentation, FFMI is probably associated with an increase of the activity of alkyl-DHAP. The negative association of the SM C16:0/SM C16:1 ratio with FFMI might be explained by regulatory processes in the fatty acid biosynthesis pathway. In particular, stearoyl-CoA desaturase (SCD), which catalyses the desaturation of C16 and C18 fatty acids, might be a target enzyme/gene affected by greater muscle mass and/or activity.

Sensitivity Analyses

For the current analysis, subjects with a diagnosis of diabetes or hypertension or medication for both diseases were excluded. However, obese subjects are more likely to develop derangements in glucose or lipid metabolism as compared to normal-weight subjects which are in a subclinical state and have not led to a clinical diagnosis yet. An analysis of serum glucose (hexose) and triacylglycerol indicated significantly different means between non-obese and obese subjects. In non-obese subjects, mean $\pm$ standard deviation serum glucose concentration was 5.18 $\pm$ 0.76 mmol/l and mean serum triacylglycerol concentration was 1.4 $\pm$ 0.81 mmol/l; the corresponding values in obese subjects were 5.6 $\pm$ 1.11 mmol/l and 1.70 $\pm$ 1.05 mmol/l, respectively. However, the higher glucose and triacylglycerol concentrations in obese do not indicate a catabolic status and thus are not sufficient to explain the missing association between FFMI and serum metabolites.

Stratified Analyses

Stratified analyses by gender, age, and physical activity were conducted in order to detect potential confounders and effect modifiers. Similar results were found for men and women

separately. P-values increased, as the sample size within the strata (slightly more for men) was smaller. However there was no improvement of the model fit, represented by the adjusted R^2. In addition, the FFMI is independent of height (Kyle et al., 2003a) thus taking one difference between men and women into account. Furthermore, analysing the whole sample increases the power and we were able to cover a wider range of the FFMI. With respect to physical activity, slight differences were found for the acylcarnitine metabolite group. These effects were no longer present within the inactive participants. However, as physical activity and FFMI are correlated and FFMI covers the long-term sports effect as representative of the muscle mass, physical activity was not included as a covariate in the main analyses.

Strength and Limitations

The participants of our studies represent random samples of the underlying population. In such a population with a heterogeneous metabolic makeup influenced by different environmental factors, genetic predispositions, and lifestyles, the interpretation of metabolic profiling is quite ambitious (Suhre et al., 2010). The metabolite concentrations which are reported in the present paper were identified by means of two slightly different AbIsolute*IDQ*^{TM} kits p150 and p180. These two kits are not identical (190 different metabolites were measured with an overlap of 141) and the measurement method of the amino acids slightly differs. However, this technology allows the automated quantification of hundreds of metabolites for many samples at a time which is very helpful for future studies (Altmaier et al., 2011). Furthermore, the side chain composition of the different PCs, lysoPCs, sphingomyelins and acylcarnitines carries many information on the different fatty acid pools in the human body, such as *n-3* and *n-6* PUFAs or saturated and mono-saturated short and medium-chain fatty acids (Wenk, 2005). Thus, the kit is well oriented to map out the human lipidome and therefore particular for the purpose of this project.

The BIA measurements did only take place in KORA S4. For the analyses of associations between FFMI and the metabolite concentrations in KORA F4 only the results of the BIA measurements at baseline examination (KORA S4) were available. Assuming that the participants' body composition is fairly stable in weight-stable subjects, the KORA F4 based analyses were restricted to the weight-stable subjects in order to account for this.

No significant associations were detected between the different SNPs and metabolite variables. However, at the time of our analyses only one GWAS with lean body mass as phenotype has been published.

The GGMs present low levels of linkage between the metabolites which is in line with findings from Krumsiek et al. (2011) who demonstrated that GGMs omit indirect correlations. Nevertheless, the GGMs complete the linear regression results with the underlying relationships between the metabolites.

Conclusion

We found strong associations between serum amino acids, acylcarnitines, and glycerophospholipids with the FFMI in a population-based sample. These findings were stable as they could be reproduced in a follow-up study of this population. Most interestingly, such associations were largely missing in obese subjects. The latter finding supports the hypothesis that a sedentary lifestyle associated with accumulation of fat tissue may be accompanied by a derangement in skeletal muscle metabolism, especially a limited inducibility of fatty acid oxidation.

3.3 Metabolomics and Thyroid Hormones

3.3.1 Background

Thyroid hormones are responsible for the proper function of nearly all organ systems (Brix et al., 2011) and disturbances are associated with major health problems. For example, the non-treatment of hyperthyroidism bears a high risk of death from cardiovascular disease (Boelaert & Franklyn, 2005). The circulating concentrations of TSH, FT4 and FT3 have a strong heritable component and are supposed to be controlled by multiple genes (Panicker et al., 2010). However, in case of FT4 these genes are still unknown. So far, one GWAS has been conducted but with little success (Panicker et al., 2010). In this project, we therefore decided not to focus on the genetics, but to focus on the thyroid hormone effects on the actual metabolism with a scope on euthyroid participants. We hypothesised that the effects of FT4 and TSH on substrate oxidation and the activity of involved enzymes are reflected in serum metabolite concentrations. Therefore, we took a targeted quantitative metabolomics approach to identify FT4 and TSH triggered pathways.

3.3.2 Results

Table 3.10 summarises the characteristics of all euthyroid KORA F4 participants and the weight-stable subsample. On average, men and women were 51 $\pm$ 12 years old and had a

Table 3.10: Characteristics (mean, SD, % or *N*) of male and female participants in the analysed samples of KORA F4 sample and the weight-stable[a] subset.

		All (n = 1496)				Weight-Stable[a] (n = 621)			
		Men (n = 792)		Women (n = 677)		Men (n = 343)		Women (n =278)	
Parameter	Unit	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	years	50.9	12.1	51.0	12.4	53.3	12.1	54.1	12.7
Weight	kg	85.3	13.0	69.8	13.1	83.3	11.5	67.9	12.5
Height	cm	177.1	6.9	162.9	6.7	176.7	7.0	162.4	6.4
Body-Mass-Index	kg/m^2	27.2	3.7	26.4	5.0	26.7	3.3	25.8	4.7
Waist	cm	97.2	11.4	85.3	12.2	95.9	10.1	84.1	12.2
Hip	cm	105.6	8.1	104.9	9.9	104.3	6.3	103.6	9.4
Waist-to-Hip Ratio		0.9	0.1	0.8	0.1	0.9	0.1	0.8	0.1
FT4	pmol/l	13.5	1.7	13.5	1.6	13.4	1.6	13.6	1.6
TSH	mIU/l	1.4	0.7	1.5	0.7	1.4	0.6	1.5	0.7
Fat Free Mass[b]	kg	60.9	6.1	43.3	5.2	60.8	6.1	43.2	5.2
Body Fat Mass[b]	%	26.3	5.0	35.6	5.7	26.4	4.9	35.6	5.6
FFMI[b,c]	kg/m^2	19.6	1.6	16.4	1.8	19.6	1.6	16.4	1.8
BFMI[b,d]	kg/m^2	7.2	2.2	9.5	3.2	7.21	2.1	9.4	3.2
Parameter	Category	%	*N*	%	*N*	%	*N*	%	*N*
Body-Mass-Index	<18.5	0.13	1	0.1	3	0.3	1	0.4	1
	18.5 to < 25	28.3	224	28.3	321	30.6	105	50.7	141
	25 to < 30	52.5	416	52.5	217	51.6	177	32.7	91
	$\geq$ 30	19.1	151	19.1	135	17.5	60	16.2	45
Physical Activity[e]	active	58.0	459	58.0	379	60.4	207	60.4	168
	inactive	42.1	333	42.1	298	39.7	136	39.6	110
Age Groups	31 to 40 years	23.2	184	25.0	169	18.4	51	15.2	52
	41 to 50 years	30.6	242	30.0	203	23.4	65	31.8	109
	51 to 60 years	23.0	182	23.0	156	26.6	74	23.3	80
	61 to 70 years	15.5	123	12.9	87	20.14	56	19.8	68
	71 to 80 years	7.5	59	8.7	59	10.4	29	9.3	32
	$\geq$ 81 years	0.3	2	0.4	3	1.1	3	0.6	2

[a] weight-stable subjects of KORA F4, whose weight gain or loss did not exceed more than 0.5% per year since their body weight was measured in KORA S4 (on average seven years prior F4 examination); [b] Parameters derived from the BIA-measurements which were only conducted in KORA S4; [c] fat free mass index; [d] body fat mass index; [e] Physical Activity (active: >1h sport per week on a regular basis; inactive: less than 1h sport per week).

BMI of 27 $\pm$ 4 kg/m^2 and 26 $\pm$ 5 kg/m^2, respectively. About 19 % of men and women were classified as obese. Mean serum TSH and FT4 concentrations were 1.40 $\pm$ 0.65 mIU/l and 13.45 $\pm$ 1.67 pmol/l in men and 1.51 $\pm$ 0.71 mIU/l and 13.54 $\pm$ 1.62 pmol/l in women. Comparing serum FT4 and TSH hormone concentrations across different categories of age, sex, BMI, and physical activity for all KORA F4 participants and the two subsets, weight-stable and obese participants, we hardly detected any differences (Table 3.11 and 3.12). Applying ANOVA and pairwise t-tests, mean FT4 values of all KORA F4 participants

Table 3.11: Mean and SD of FT4 hormone concentration (pmol/l) across different strata of age, BMI (kg/m^2), sex or physical activity for the KORA F4 participants (n = 1469), the weight-stable[a] subset (n = 621) and the obese participants (BMI $\geq$ 30 kg/m^2; n = 286).

		KORA F4 (n = 1469)			Weight-Stable[a] (n = 621)			Obese Subset (n = 286)		
Parameter	Category	Mean	SD		Mean	SD		Mean	SD	
Age	31 to 40 years	13.34	1.59		13.43	1.59		13.00	1.54	
	41 to 50 years	13.23	1.61		13.10	1.64		13.34	1.64	
	51 to 60 years	13.41	1.54		13.34	1.35		13.34	1.45	
	61 to 70 years	13.88	1.67	*	13.80	1.60	*of 2	13.95	1.70	*of 1
	71 to 80 years	14.45	1.72	*	14.43	1.70	*of 1-3	14.49	1.85	*of 1-3
	$\geq$ 81 years	14.22	2.05		14.22	2.05		15.45	3.18	
Body Mass	$<$ 18.5	16.65	1.04	*	16.90	1.41	*			
Index	18.5 to $<$ 25	13.50	1.62		13.49	1.66				
	25 to $<$ 30	13.43	1.63		13.49	1.50				
	$\geq$ 30	13.56	1.69		13.46	1.72				
Physical	active	13.45	1.57	#	13.54	1.54	#	13.50	1.54	
Activity[b]	inactive	13.55	1.73		13.41	1.71		13.60	1.80	

[a] weight-stable subjects of KORA F4, whose weight gain or loss did not exceed more than 0.5% per year since their body weight was measured in KORA S4 (on average seven years prior KORA F4 examination); [b] Physical Activity (active: >1h sport per week on a regular basis; inactive: less than 1h sport per week); * pairwise t-test was significant; # leven test resulted in rejection of equal variances.

for the age strata 61 to 70 years and 71 to 80 years were significantly different to the other strata. Also the mean FT4 value in the BMI category <18.5 was significantly higher as compared to the other BMI categories. No differences among categories were found for the TSH concentrations (Table 3.12).

After correction for multiple testing we obtained 152 statistically significant associations between various serum metabolite concentrations, metabolite ratios, and FT4. Significant associations between metabolites and TSH concentrations were entirely lacking. Selected statistically significant associations of FT4 with different metabolite concentrations for the KORA F4 population are shown in Table 3.13. Different parameters such as the direction of the beta estimate derived from the adjusted linear model are given, as well as the adjusted p-value, the adjusted R^2 and the p-gain. The full list of all obtained statistically significant associations can be found in Supplementary Table C2.

FT4 and Acylcarnitines

For a series of different serum acylcarnitines, statistically significant associations with serum FT4 concentrations were detected, and all of them showed a positive direction (of the

Table 3.12: Mean and SD of TSH hormone concentration (mIU/l) across different strata of age, BMI (kg/m^2), sex or physical activity for the KORA F4 participants (n = 1469), the weight-stable[a] subset (n = 621) and the obese participants (BMI $\geq$ 30 kg/m^2; n = 286).

		KORA F4 (n = 1469)		Weight-Stable[a] (n = 621)		Obese Subset (n = 286)	
Parameter	Category	Mean	SD	Mean	SD	Mean	SD
Age	31 to 40 years	1.54	0.67	1.52	0.54	1.44	0.66
	41 to 50 years	1.47	0.67	1.46	0.68	1.54	0.58
	51 to 60 years	1.40	0.70	1.42	0.71	1.48	0.61
	61 to 70 years	1.42	0.64	1.35	0.63	1.60	0.69
	71 to 80 years	1.33	0.70	1.25	0.66	1.48	0.80
	$\geq$ 81	0.91	0.59	0.91	0.59	0.43	0.01
Body Mass Index	$<$ 18.5	1.23	0.59	1.23	0.89		
	18.5 to $<$ 25	1.46	0.73	1.41	0.71		
	25 to $<$ 30	1.41	0.65	1.36	0.58		
	$\geq$ 30	1.51	0.65	1.55	0.70		
Physical Activity	active	1.44	0.69	1.38	0.65	1.49	0.61
	inactive	1.45	0.67	1.47	0.67	1.52	0.69

[a] weight-stable subjects of KORA F4, whose weight gain or loss did not exceed more than 0.5% per year since their body weight was measured in KORA S4 (on average seven years prior KORA F4 examination); [b] Physical Activity (active: >1h sport per week on a regular basis; inactive: less than 1h sport per week).

β-estimate), strongly indicating an overall elevated β-oxidation of fatty acids with higher serum FT4 concentration. For acetylcarnitine (C2) as the quantitatively most important serum acylcarnitine the adjusted p-value was 3.23x10^{-10}. Similarly strong associations were detected for single acylcarnitine concentrations such as C18:1, C16:1, C18:2, the sums of all acylcarnitines, long-chain acylcarnitines, even-numbered acylcarnitines, and acylcarnitines carrying monounsaturated or polyunsaturated fatty acids. Special ratios, such as C2 by C0 or the sum of C2 and C3 by C0 were suggested as valid measures of β-oxidation of fatty acids (Pande, 1975; Roschinger et al., 2000) and they were both positively associated with FT4 hormone concentrations in our project (Table 3.13, Figure 3.6). The activity of carnitine palmitoyltransferase I, reflected by the ratio of (C16 + C18) by C0 as described by the manufacturer of the metabolite analysis kit, increased with higher FT4 hormone concentrations. These results are strongly representative of the effects that higher FT4 concentrations exert on fatty acid oxidation.

FT4 and Phosphatidylcholines

The group of phosphatidylcholines consists of different PC diacyl (aa), PC acyl-alkyl (ae), and lysoPC acyl (a) compounds. Numerous associations between FT4 and PCs or PC ratios

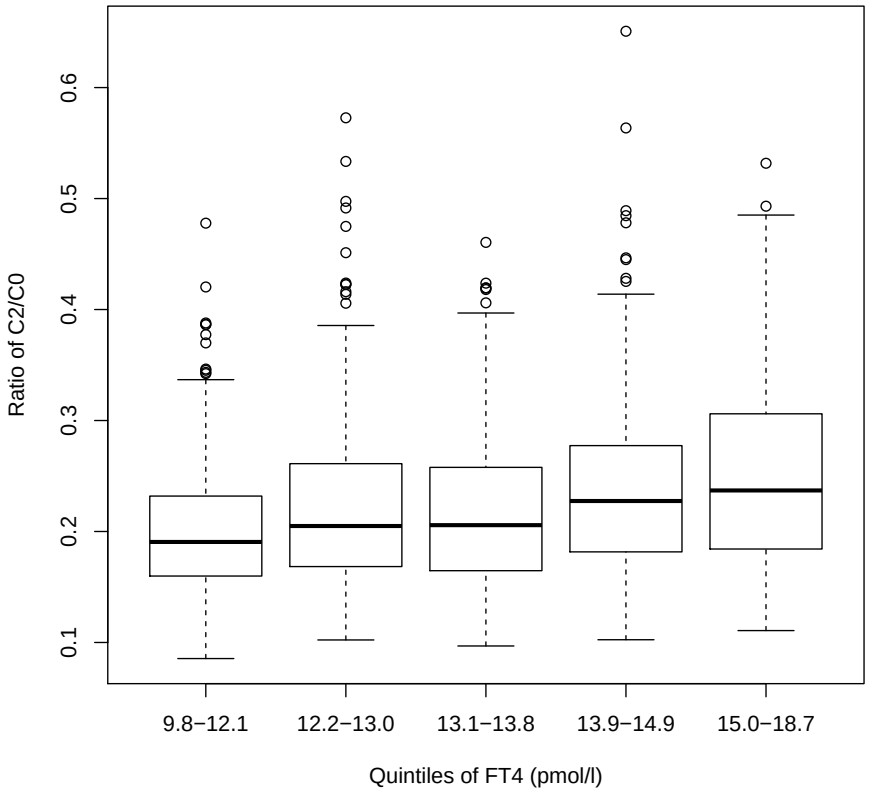

Figure 3.6: Boxplot of serum C2/C0 concentrations by quintiles of the FT4 (pmol/l), for the KORA F4 population

were observed. Generally, an increase in FT4 levels was associated with lower concentrations of PCs. This was reflected by the sum of all PCs, and the different sums of PCs containing saturated, monounsaturated, polyunsaturated, or short-chain fatty acides. These results are in line with the associations found for the sums of PC aa, PC ae, or lysoPC with FT4 concentrations. Furthermore, single PCs such as PC aa C34:4, PC aa 36:1, PC ae C40:1, PC ae C40:0, lysoPC a C14:0, or lysoPC a C16:1 were all inversely associated with increasing serum FT4 concentrations. Regarding metabolite ratios, we received some indication for an increase in saturation and chain length for PC aa by PC aa ratios, such as PC aa C36:6 by PC aa C42:0, PC aa C36:5 by PC aa C42:0 or PC aa 36:0 by PC aa C38:0 with elevated FT4 levels. For PC ae by PC ae ratios, an increase in desaturation and chain length with higher FT4 concentrations was observed, e.g., PC ae C42:2 by PC ae C42.5, PC ae C40:1 by PC ae C40:5 or PC ae C38:2 by PC ae C42:5.

Table 3.13: Selected metabolic traits significantly associated with FT4 in a linear regression model adjusted for age, sex, BMI, and batch in the KORA F4 sample.

Trait	Mean (µmol/l)	SD	Dir.[a]	P-Value Adj.[b]	R^2 Adj.[c]	P-Gain[d]
Σ AC	10.81	3.24	pos.	9.02×10^{-11}	0.14	
Σ even. AC	9.97	3.16	pos.	9.35×10^{-11}	0.14	
Σ long. AC	0.40	0.09	pos.	9.56×10^{-11}	0.21	
Σ med. AC	1.12	0.36	pos.	2.82×10^{-06}	0.14	
Σ mono AC	1.73	0.46	pos.	1.92×10^{-08}	0.16	
Σ poly AC	8.32	2.85	pos.	1.74×10^{-10}	0.13	
C18:1	0.13	0.04	pos.	5.15×10^{-14}	0.18	
C16:1	0.04	0.01	pos.	4.29×10^{-11}	0.17	
C2	7.86	2.77	pos.	3.23×10^{-10}	0.13	
C14:2	0.03	0.01	pos.	3.58×10^{-10}	0.14	
C18:2	0.05	0.01	pos.	7.09×10^{-07}	0.18	
C12:1	0.14	0.05	pos.	1.10×10^{-06}	0.12	
C12	0.13	0.05	pos.	1.70×10^{-06}	0.12	
C10	0.34	0.16	pos.	3.72×10^{-05}	0.10	
C10:1	0.16	0.06	pos.	2.72×10^{-04}	0.14	
C14:1	0.14	0.05	pos.	1.59×10^{-02}	0.25	
C8	0.21	0.09	pos.	2.55×10^{-02}	0.10	
C2/C0	0.23	0.08	pos.	2.18×10^{-10}	0.15	
(C2+C3)/C0	0.24	0.08	pos.	1.19×10^{-10}	0.14	
CPT1: (C16+C18)/C0	0.001	0.001	pos.	2.35×10^{-02}	0.07	
Σ PCs	1985.90	355.32	neg.	3.66×10^{-11}	0.14	
Σ mono PCs	348.23	86.27	neg.	1.08×10^{-10}	0.07	
Σ poly PCs	1593.43	279.51	neg.	9.44×10^{-10}	0.15	
Σ sat. PCs	44.23	7.91	neg.	2.83×10^{-06}	0.12	
Σ short. PCs	759.58	161.54	neg.	3.58×10^{-11}	0.25	
PC aa						
Σ PC aa	1788.09	333.40	neg.	8.32×10^{-12}	0.14	
Σ long. PC aa	47.14	12.35	neg.	1.24×10^{-02}	0.07	
Σ mono PC aa	323.62	83.10	neg.	1.25×10^{-10}	0.07	
Σ poly PC aa	1436.75	261.65	neg.	2.23×10^{-10}	0.15	
Σ sat. PC aa	27.72	5.60	neg.	9.50×10^{-06}	0.11	
Σ short. PC aa	721.28	156.91	neg.	2.97×10^{-11}	0.25	
PC aa C34:4	2.26	0.83	neg.	2.08×10^{-16}	0.07	
PC aa C36:1	53.44	13.59	neg.	1.23×10^{-14}	0.10	
PC ae						
Σ mono PC ae	24.61	5.00	neg.	7.52×10^{-04}	0.17	
Σ sat. PC ae	16.51	2.81	neg.	8.24×10^{-05}	0.12	
Σ short. PC ae	38.30	8.25	neg.	9.24×10^{-03}	0.19	
PC ae C40:1	1.69	0.40	neg.	1.84×10^{-10}	0.08	
PC ae C40:0	10.27	1.63	neg.	8.27×10^{-03}	0.11	
lysoPC a						
Σ lysoPCs	191.41	40.73	neg.	6.92×10^{-05}	0.19	
Σ sat. lysoPCs	127.77	26.44	neg.	2.33×10^{-03}	0.14	
Σ unsat. lysoPCs	63.64	17.36	neg.	2.95×10^{-05}	0.23	
lysoPC a C14:0	3.23	0.84	neg.	2.84×10^{-06}	0.04	

Trait	Mean (µmol/l)	SD	Dir.[a]	P-Value Adj.[b]	R^2 Adj.[c]	P-Gain[d]
lysoPC a C16:1	2.92	1.00	neg.	$2.19\text{x}10^{-05}$	0.06	
PC aa C36:6/ PC aa C42:0	1.95	0.80	neg.	$1.45\text{x}10^{-15}$	0.06	$5.08\text{x}10^{+05}$
PC aa C36:5/ PC aa C42:0	51.17	24.93	neg.	$5.52\text{x}10^{-14}$	0.10	$4.10\text{x}10^{+04}$
PC aa C36.0/ PC aa.C38.0	0.83	0.13	neg.	$2.79\text{x}10^{-09}$	0.04	$1.51\text{x}10^{+08}$
PC ae C42:2/ PC ae C42:5	0.29	0.06	neg.	$1.23\text{x}10^{-19}$	0.07	$4.37\text{x}10^{+12}$
PC ae C40:1/ PC ae C40:5	0.48	0.10	neg.	$1.97\text{x}10^{-17}$	0.09	$9.35\text{x}10^{+06}$
PC ae C38:2/ PC ae C42:5	0.92	0.22	neg.	$3.80\text{x}10^{-16}$	0.08	$9.04\text{x}10^{+06}$

[a] direction of the association (positive or negative); [b] for multiple testing adjusted p-value; [c] adjusted R^2 of the linear model; [d] p-gain, fold decrease in the p-value of association for the pair of metabolites, compared to the lowest of two p values for the single metabolites; AC, acylcarnitines; CPT1, carnitine palmitoyltransferase I; even., even numbered; long., long-chain; med., medium-chain; short, short-chain; sat., saturated; unsat., unsaturated.

Subanalyses

Weight-Stable Subsample. Restricting our sample to the weight-stable subset and adjusting for FFMI instead of BMI resulted in a substantial loss of significant associations with FT4 as compared to the results in the entire sample (Supplementary Table S3). Although β-estimates are similar in both analyses, statistical power was lower due to the smaller size of the weight-stable group. Still, long-chain acylcarnitines, the sums of long-chain acylcarnitines and of monounsaturated acylcarnitines were significantly positively associated with FT4 levels in this subsample. The significant associations between single PC concentrations and FT4 were similar to the results of the entire sample. However, significant associations with PC ratios are largely missing, indicating loss of statistical power as a consequence of the reduced sample size. Adjusting the linear models for BMI instead of FFMI in the weight-stable subsample resulted in almost the same significant associations with FT4, suggesting no distinct effect of the more precise adjustment for lean body mass.

Physical Activity. The acylcarnitine results for physically inactive participants paralleled the results in the whole sample, showing an enhanced oxidation activity with no preference of acylcarnitine type. The results for the active participants varied slightly (Supplementary Table C4). Here, the positive associations with most sums of acylcarnitines were also present, but regarding individual compounds, only C18:1, C14:2, C18:2 and C2 were still positively associated with elevated FT4 hormone concentrations. Testing for differences of the estimated coefficients between groups revealed no statistical significance. The associations between PCs and FT4 levels in active and inactive participants were in line with the results for the entire study population. For the inactive participants, however, most associations regarding metabolite ratios were missing.

Males versus Females. The acylcarnitine results for men were very much comparable to the results in the whole sample while the results for the female participants varied slightly (Supplementary Table C5). Here, the positive associations with the sums of acylcarnitines were still present, but regarding the single concentrations, only C18:1, C14:2 and C18:2 are positively associated with elevated FT4 hormone concentrations. Testing for differences of the estimated coefficients between men and women revealed no statistical significance. The associations between PCs and FT4 levels in men and women were in line with the results for the entire study population.

Obese versus Non-Obese. The associations with FT4 levels found for the entire population and the non-obese participants were similar for both, the acylcarnitine and the PC concentrations (see Supplementary Table C6). In the obese group, many significant associations identified in the entire group were lacking which is likely due to sample size reasons. This is supported by the results of the β-estimates which were largely comparable in size and direction to those obtained in the entire group or the non-obese participants, although not reaching statistical significance (data not shown). Still, significant associations were identified for long-chain acylcarnitines with FT4 in the group of obese participants.

Influence of Liver, Kidney, or Inflammation Parameters. Almost all identified associations between FT4 and different metabolite variables were independent of parameters such as glutamate pyruvate transaminase, glutamic oxaloacetic transaminase, gamma-glutamyl transpeptidase, cystatin C, albumin, creatinine, C-reactive protein, or white blood cell count, indicating liver or kidney insufficiency or underlying inflammation. Only the associations between FT4 and PC aa C38:5, PC aa C40:4, PC aa C40:5, PC aa C42:6, PC ae C40:0, and PC ae C42:1 were influenced by gamma-glutamyl transpeptidase, and the association between FT4 and lysoPC a C18:2 was affected by C-reactive protein.

3.3.3 Discussion

In this population-based study, after overnight fasting, strong associations between serum FT4 and serum metabolite concentrations were found. With higher FT4 levels, the concentration of acylcarnitines as well as the ratio of C2 by C0 increased, indicating an overall increase of β-oxidation of fatty acids. In addition, the inverse associations between FT4 and PC metabolites are reflective of a uniform decline in serum PC concentrations. These results were supported by the associations found in stratified analyses and strengthened

by their independency of different liver, kidney, and inflammation parameters, indicative for liver or kidney insufficiency, or underlying inflammation. In euthyroid adults, TSH concentrations were not associated with serum metabolites. Also, no effect of FT4 on serum amino acids concentrations was found.

Possible Direct Effects of FT4 on the Mitochondrial Level

Knowledge of how thyroid hormones exert their effects has further increased since the successful molecular cloning of nuclear thyroid hormone receptors in the mid 90's (Yen, 2001; Flamant et al., 2007; Wagner et al., 1995; Ribeiro et al., 1998). Most of the physiological effects of thyroid hormones are exerted through thyroid hormone receptor complexes and the response elements of regulatory regions of target genes (Brix et al., 2011; Biondi, 2012a). Nevertheless, not all thyroid hormone effects are attributable to nuclear mediated pathways (Moreno et al., 2008) and an increasing number of non-genetic effects such as the transportation of ions, e.g., calcium, sodium, and potassium across plasma membranes or glucose and amino acids have been described lately (Biondi et al., 2002; Fazio et al., 2004). From a clinical point of view, it is clear that minor changes in thyroid hormone concentrations cause distinct metabolic effects (Kim, 2008). In a recent microarray study by Clement et al. (2002) on the transcriptome of the vastus lateralis, a daily dosage of 75 µg of T4 was administered to healthy male volunteers with the result of 22 genes involved in mitochondrial energy metabolism being up-regulated. At the cellular level, T4 is converted to T3, and T3 is considered the active hormone. It is evident that intracellular T3 concentrations do not necessarily correspond to blood T3 concentrations. Although serum FT3 concentrations were measured in our study as well, the applied analytic method did not fulfil the strict quality control criteria in the end (Thienpont et al., 2010). Thus, FT3 data could not be used in this project. However, our results and the findings of the microarray study argue for an independent effect of FT4 on the mitochondrial level.

β-Oxidation increases with FT4

In a human experimental setting, it has recently been described that all plasma acylcarnitines (except for C3, C4, and C5) showed a strong increase in times of elevated β-oxidation, e.g., during fasting and or exercise (Krug et al., 2012). Concomitantly, plasma free carnitine (C0) decreases. In this project blood samples from all participants were drawn in fasting state, i.e., after overnight fast (minimum of 8 hours). Thus, all study participants were in a catabolic metabolic state which is characterised by low plasma insulin concentrations, increased

plasma concentrations of non-esterified fatty acids and ketone bodies, and an enhanced gluconeogenesis. Under this fasting condition, our results strongly indicate elevated β-oxidation with increasing plasma FT4 concentrations. Results from single acylcarnitine concentrations, sums of different acylcarnitine groups, as well as the ratio of C2 by C0 support this conclusion (Pande, 1975; Roschinger et al., 2000). The observed decreasing serum PC concentrations with higher FT4 levels are probably the consequence of this enhanced lipid oxidation, and therefore underline our hypothesis.

No Effect of FT4 on Gluconeogenesis

Krug et al. (2012) further demonstrated that plasma concentrations of specific amino acids, especially branched-chain amino acids, increased during fasting status, indicating enhanced gluconeogenesis. Although, a strong relationship between branched-chain amino acid serum concentrations and fat free mass in fasted state has been described for the present population (3.2), we did not observe significant associations between serum amino acid concentrations and FT4 levels in this project. Thus, we conclude that FT4 does not affect gluconeogenesis in euthyroid and fasting subjects. This finding affirms the notion that we do not simply see the effects of fasting status in our study but a specific effect attributable to the thyroid hormone FT4 which is characterised by enhanced transport of fatty acids in form of carnitine acylesters to the mitochondrion and subsequent β-oxidation. To the best of our knowledge no study directly comparable to ours has been performed so far. Most recent studies using transcriptomics or proteomics techniques investigated effects of T3 administration. In these studies effects of T3 on proteins of gluconeogenic pathways have been described; a review is given by Silvestri et al. (2011).

Independency of FT4 and β-Oxidation Association

For treatment of obesity, T3 and T4 in varying doses and duration have been administered to euthyroid obese subjects during caloric deprivation to enhance weight loss and a systematic review on this issue is given by Kaptein et al. (2009). The authors summarised that available studies are insufficient to draw conclusions on beneficial or adverse effects of T3 or T4 administration; however, because of possible side-effect they do not advise on treatment of obesity with T4 or T3 (Kaptein et al., 2009). The results of the subanalyses presented here did not suggest specific differences by fat free mass (analysis in weight-stable subjects) or between obese and non-obese subjects. Also, subanalyses by sex and physical activity provided largely similar results across subgroups. Thus, we conclude that the positive

association between FT4 and β-oxidation of fatty acids after overnight fast is not dependent on lean body mass, body fat mass, sex, or habitual physical activity. In other words, we gained no indication for obesity being a consequence of altered fatty acid oxidation in fasting status as related to serum FT4 concentrations in euthyroid subjects. Further, no impact of liver or kidney insufficiency or underlying inflammation on the associations between FT4 and β-oxidation could be observed. This supports the stability of our results and argues for an independent effect of FT4.

Strength and Limitations

The human serum metabolome is currently characterised in many studies using different analytic approaches (Psychogios et al., 2011), including the method applied here. To the best of our knowledge, the association of FT4, TSH, and serum metabolites was not explored before in a population-based setting. The participants of our study represent a random sample of the underlying population. In such a population with a heterogeneous metabolic makeup influenced by different environmental factors, genetic predispositions, and lifestyles, the interpretation of metabolic profiling is quite ambitious (Suhre, Meisinger et al. 2010). The metabolite concentrations which are reported in the present paper were identified by means of the Absolute*IDQ*^{TM} p150 kit. This technology allows the automated quantification of many metabolites with a focus on amino acids, acylcarnitines, and PCs for many samples at a time (Wenk, 2005; Altmaier et al., 2011). Thus, the kit is well suitable to assess a suggested impact of thyroid hormones on energy metabolism, especially lipid metabolism. The BIA measurements did only take place in KORA S4. For the analyses of associations with FT4 and the metabolite concentrations in the linear models with the FFMI instead of the BMI as adjustment variable only the results of the BIA measurements at baseline examination (KORA S4) were available. Assuming that the participants' body composition is fairly stable in weight-stable subjects, those analyses were restricted to the weight-stable subjects in order to account for this.

Conclusion

Our results indicate that in a euthyroid population after overnight fast, serum FT4 concentrations are strongly linked to serum acylcarnitines and PCs, indicating enhanced transport of fatty acids to the mitochondrion and subsequent β-oxidation. These findings were stable as they could be largely reproduced in different subsets of the population.

4 Future Prospects

In this thesis three projects are presented exploring different aspects of body composition, metabolism, and energy balance, and their interplay which are co-determining the health status of human beings. These factors are themselves influenced by a multitude of environmental factors and genetics. The projects in this thesis are utilising genetics and metabolomics data for analysing gene–diet interactions and serum metabolite patterns related to variation in fat free mass as proxy for skeletal muscle mass or thyroid hormones.

In the first project, we concluded that a large portion of the population would benefit from a high PUFA intake with respect to obesity risk. Nevertheless, the study was not sufficiently powered for the analyses of interaction effects. Hence, a replication of our results in a larger prospective study is warranted. However, until today there has not been a comparable project (Vliet-Ostaptchouk et al., 2012). Conventional analyses of fatty acids as, e.g., described in this thesis are expensive and time consuming. A possible further exploration of this topic could be on the basis of a GWAS in combination with a metabolomics approach. A prerequisite would be the identification and validation of metabolomics pattern indicative for the intake of specific fatty acids, such as PUFAs. Then, a GWAS could be conducted analysing the interaction effects between the SNPs and those identified sets of metabolites with respect to obesity risk. Studies with genome wide data and metabolomics often are large in size and thus more suitable for the analyses of interaction effects.

The second project incorporated metabolomics as well as genetics. We received an extensive picture of the fat free mass related metabolic makeup of adults and the interrelation between the metabolites. The genetic approach aimed at identifying significant associations between different metabolites and SNPs described to be associated with anthropometric measurements. The idea was to incorporate the genetic background and therewith sharpen the picture of fat free mass induced effects. Unfortunately, no significant association was found for the selected SNPs. However, stratified analyses supported our hypothesis that the excessive accumulation of body fat tissue may be accompanied by a derangement in skeletal muscle metabolism, especially a limited inducibility of fatty acid oxidation. Lifestyle factors

favouring the development of obesity, especially low physical activity over a longer time period, may be causally related to this modified skeletal muscle metabolism. Further large prospective studies have to explore in more detail the interrelationships between lifestyle factors and derangements of muscle mass metabolism. From a public health perspective, it would be important to know whether this metabolic status is reversible and how much of regular physical activity is necessary to avoid such derangement.

In the third project, we identified a set of metabolites which indicates an overall enhanced transport to the mitrochondria and β-oxidation of fatty acids with higher FT4 concentrations in fasted euthyroid adults. No associations were found for TSH. The results for FT4 were quite stable throughout stratified analyses and no differences between obese versus non-obese subjects were identified. However, the situation might be different in an anabolic status or during phases of increased energy expenditure. Studies considering these aspects should be performed as well and additionally in different populations with abnormal thyroid hormone concentrations (subclinical derangements, thyroid diseases). The number of participants with hormone concentrations above or below the normal range was too small in our study to perform statistically meaningful subanalyses.

The results described in this thesis give a taste of the values, possibilities and potentials of "new" data obtained by means of "omics" techniques and the possible combination of different "omics" approaches such as genomics and metabolomics. Ideas for meaningful follow-up projects are described and suggested above. However, there are many research opportunities and projects, either in the field of gene–diet interactions or in applying metabolomics data in observational and intervention studies. Also, obesity is only one of the important chronic diseases which have to be addressed. This thesis with the incorporation of gene–environment interactions and the utilisation of metabolomics data shows promising perspectives in the development of new measures to prevent, early detect or treat metabolic diseases and other chronic diseases.

Bibliography

Ahima, R. S., Flier, J. S. (2000). Adipose tissue as an endocrine organ. *Trends Endocrinol Metab*, 11(8): 327–32.

Allison, D. B., Faith, M. S., Heo, M., Kotler, D. P. (1997). Hypothesis concerning the U-shaped relation between body mass index and mortality. *Am J Epidemiol*, 146(4): 339–49.

Alnajjar, A., Chabane Sari, D., Abuharfeil, N., Hudaib, M., Aburjai, T. (2006). Effect of n-3 and n-6 polyunsaturated fatty acids on lymphocyte proliferation, interleukin production and phospholipid fatty acids composition in type 2 diabetic and healthy subjects in Jordan people. *Prostaglandins Leukot Essent Fatty Acids*, 74(6): 347–56.

Altmaier, E., Kastenmuller, G., Romisch-Margl, W., Thorand, B., Weinberger, K. M., Adamski, J., Illig, T., Doring, A., Suhre, K. (2009). Variation in the human lipidome associated with coffee consumption as revealed by quantitative targeted metabolomics. *Mol Nutr Food Res*, 53(11): 1357–65.

Altmaier, E., Kastenmuller, G., Romisch-Margl, W., Thorand, B., Weinberger, K. M., Illig, T., Adamski, J., Doring, A., Suhre, K. (2011). Questionnaire-based self-reported nutrition habits associate with serum metabolism as revealed by quantitative targeted metabolomics. *Eur J Epidemiol*, 26(2): 145–56.

Altmaier, E., Ramsay, S. L., Graber, A., Mewes, H. W., Weinberger, K. M., Suhre, K. (2008). Bioinformatics analysis of targeted metabolomics – uncovering old and new tales of diabetic mice under medication. *Endocrinology*, 149(7): 3478–89.

Andersson, N., Strandberg, L., Nilsson, S., Adamovic, S., Karlsson, M. K., Ljunggren, O., Mellstrom, D., Lane, N. E., Zmuda, J. M., Nielsen, C., Orwoll, E., Lorentzon, M., Ohlsson, C., Jansson, J. O. (2010). A variant near the interleukin-6 gene is associated with fat mass in Caucasian men. *Int J Obes (Lond)*, 34(6): 1011–9.

Arab, L., Akbar, J. (2002). Biomarkers and the measurement of fatty acids. *Public Health Nutr*, 5(6A): 865–71.

Arita, Y., Kihara, S., Ouchi, N., Takahashi, M., Maeda, K., Miyagawa, J., Hotta, K., Shimomura, I., Nakamura, T., Miyaoka, K., Kuriyama, H., Nishida, M., Yamashita, S., Okubo, K., Matsubara, K., Muraguchi, M., Ohmoto, Y., Funahashi, T., Matsuzawa, Y. (1999). Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun*, 257(1): 79–83.

Assfalg, M., Bertini, I., Colangiuli, D., Luchinat, C., Schafer, H., Schutz, B., Spraul, M. (2008). Evidence of different metabolic phenotypes in humans. *Proc Natl Acad Sci U S A*, 105(5): 1420–4.

Atwood, L. D., Heard-Costa, N. L., Cupples, L. A., Jaquish, C. E., Wilson, P. W., D'Agostino, R. B. (2002). Genomewide linkage analysis of body mass index across 28 years of the Framingham Heart Study. *Am J Hum Genet*, 71(5): 1044–50.

Barbaux, S., Poirier, O., Godefroy, T., Kleinert, H., Blankenberg, S., Cambien, F., Tiret, L. (2007). Differential haplotypic expression of the interleukin-18 gene. *Eur J Hum Genet*, 15(8): 856–63.

Bauer, M., Goetz, T., Glenn, T., Whybrow, P. C. (2008). The thyroid-brain interaction in thyroid disorders and mood disorders. *J Neuroendocrinol*, 20(10): 1101–14.

Beechy, L., Galpern, J., Petrone, A., Das, S. K. (2012). Assessment tools in obesity – psychological measures, diet, activity, and body composition. *Physiol Behav*, 107(1): 154–71.

Bell, C. G., Walley, A. J., Froguel, P. (2005). The genetics of human obesity. *Nat Rev Genet*, 6(3): 221–34.

Berthier, M. T., Paradis, A. M., Tchernof, A., Bergeron, J., Prud'homme, D., Despres, J. P., Vohl, M. C. (2003). The interleukin 6-174G/C polymorphism is associated with indices of obesity in men. *J Hum Genet*, 48(1): 14–9.

Biondi, B. (2012a). Mechanisms in endocrinology: Heart failure and thyroid dysfunction. *Eur J Endocrinol*, 167(5): 609–18.

Biondi, B. (2012b). Natural history, diagnosis and management of subclinical thyroid dysfunction. *Best Pract Res Clin Endocrinol Metab*, 26(4): 431–46.

Biondi, B., Palmieri, E. A., Lombardi, G., Fazio, S. (2002). Subclinical hypothyroidism and cardiac function. *Thyroid*, 12(6): 505–10.

Boelaert, K., Franklyn, J. A. (2005). Thyroid hormone in health and disease. *J Endocrinol*, 187(1): 1–15.

Bouchard, C. (1991). Current understanding of the etiology of obesity: genetic and nongenetic factors. *Am J Clin Nutr*, 53(6 Suppl): 1561S–1565S.

Brabant, G., Beck-Peccoz, P., Jarzab, B., Laurberg, P., Orgiazzi, J., Szabolcs, I., Weetman, A. P., Wiersinga, W. M. (2006). Is there a need to redefine the upper normal limit of TSH? *Eur J Endocrinol*, 154(5): 633–7.

Brix, K., Fuhrer, D., Biebermann, H. (2011). Molecules important for thyroid hormone synthesis and action - known facts and future perspectives. *Thyroid Res*, 4 Suppl 1: S9.

Butte, W. (1983). Rapid method for the determination of fatty acid profiles from fats and oils using trimethylsulphonium hydroxide for transesterification. *J Chromatogr A*, 261: 142–145.

Calder, P. C., Grimble, R. F. (2002). Polyunsaturated fatty acids, inflammation and immunity. *Eur J Clin Nutr*, 56 Suppl 3: S14–9.

Cheng, S. Y., Leonard, J. L., Davis, P. J. (2010). Molecular aspects of thyroid hormone actions. *Endocr Rev*, 31(2): 139–70.

Chuang, L. M., Chiu, Y. F., Sheu, W. H., Hung, Y. J., Ho, L. T., Grove, J., Rodriguez, B., Quertermous, T., Chen, Y. D., Hsiung, C. A., Tai, T. Y. (2004). Biethnic comparisons of autosomal genomic scan for loci linked to plasma adiponectin in populations of Chinese and Japanese origin. *J Clin Endocrinol Metab*, 89(11): 5772–8.

Clement, K., Viguerie, N., Diehn, M., Alizadeh, A., Barbe, P., Thalamas, C., Storey, J. D., Brown, P. O., Barsh, G. S., Langin, D. (2002). In vivo regulation of human skeletal muscle gene expression by thyroid hormone. *Genome Res*, 12(2): 281–91.

Colhoun, H. M., McKeigue, P. M., Davey Smith, G. (2003). Problems of reporting genetic associations with complex outcomes. *Lancet*, 361(9360): 865–72.

Comuzzie, A. G., Funahashi, T., Sonnenberg, G., Martin, L. J., Jacob, H. J., Black, A. E., Maas, D., Takahashi, M., Kihara, S., Tanaka, S., Matsuzawa, Y., Blangero, J., Cohen,

D., Kissebah, A. (2001). The genetic basis of plasma variation in adiponectin, a global endophenotype for obesity and the metabolic syndrome. *J Clin Endocrinol Metab*, 86(9): 4321–5.

Demers, L. M., Spencer, C. A. (2003). *Laboratory Support for the Diagnosis and Monitoring of Thyroid Disease. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines.* National Academy of Clinical Biochemistry, Washington, DC.

Dulloo, A. G., Jacquet, J., Solinas, G., Montani, J. P., Schutz, Y. (2010). Body composition phenotypes in pathways to obesity and the metabolic syndrome. *Int J Obes (Lond)*, 34 Suppl 2: S4–17.

Dumas, M. E., Wilder, S. P., Bihoreau, M. T., Barton, R. H., Fearnside, J. F., Argoud, K., D'Amato, L., Wallis, R. H., Blancher, C., Keun, H. C., Baunsgaard, D., Scott, J., Sidelmann, U. G., Nicholson, J. K., Gauguier, D. (2007). Direct quantitative trait locus mapping of mammalian metabolic phenotypes in diabetic and normoglycemic rat models. *Nat Genet*, 39(5): 666–72.

Duren, D. L., Sherwood, R. J., Czerwinski, S. A., Lee, M., Choh, A. C., Siervogel, R. M., Cameron Chumlea, W. (2008). Body composition methods: comparisons and interpretation. *J Diabetes Sci Technol*, 2(6): 1139–46.

Engstrom, G., Hedblad, B., Stavenow, L., Lind, P., Janzon, L., Lindgarde, F. (2003). Inflammation-sensitive plasma proteins are associated with future weight gain. *Diabetes*, 52(8): 2097–101.

Fazio, S., Palmieri, E. A., Lombardi, G., Biondi, B. (2004). Effects of thyroid hormone on the cardiovascular system. *Recent Prog Horm Res*, 59: 31–50.

Festa, A., D'Agostino, J., R., Williams, K., Karter, A. J., Mayer-Davis, E. J., Tracy, R. P., Haffner, S. M. (2001). The relation of body fat mass and distribution to markers of chronic inflammation. *Int J Obes Relat Metab Disord*, 25(10): 1407–15.

Fiehn, O. (2002). Metabolomics – the link between genotypes and phenotypes. *Plant Mol Biol*, 48(1-2): 155–71.

Fischer, S. (1986). Analysis of cardiovascular eicosanoids in man with special reference to HPLC. *Chromatographia*, 22(7): 416–420.

Fishman, D., Faulds, G., Jeffery, R., Mohamed-Ali, V., Yudkin, J. S., Humphries, S., Woo, P. (1998). The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. *J Clin Invest*, 102(7): 1369–76.

Flachs, P., Mohamed-Ali, V., Horakova, O., Rossmeisl, M., Hosseinzadeh-Attar, M. J., Hensler, M., Ruzickova, J., Kopecky, J. (2006). Polyunsaturated fatty acids of marine origin induce adiponectin in mice fed a high-fat diet. *Diabetologia*, 49(2): 394–7.

Flamant, F., Gauthier, K., Samarut, J. (2007). Thyroid hormones signaling is getting more complex: STORMs are coming. *Mol Endocrinol*, 21(2): 321–33.

Folch, J., Lees, M., Sloane Stanley, G. H. (1957). A simple method for the isolation and purification of total lipides from animal tissues. *J Biol Chem*, 226(1): 497–509.

Fox, S. I. (1999). *Human Physiology*. WBC/McGraw-Hill College (Boston).

Fruhbeck, G., Gomez-Ambrosi, J., Muruzabal, F. J., Burrell, M. A. (2001). The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation. *Am J Physiol Endocrinol Metab*, 280(6): E827–47.

Galic, S., Oakhill, J. S., Steinberg, G. R. (2010). Adipose tissue as an endocrine organ. *Mol Cell Endocrinol*, 316(2): 129–39.

Gieger, C., Geistlinger, L., Altmaier, E., Hrabe de Angelis, M., Kronenberg, F., Meitinger, T., Mewes, H. W., Wichmann, H. E., Weinberger, K. M., Adamski, J., Illig, T., Suhre, K. (2008). Genetics meets metabolomics: a genome-wide association study of metabolite profiles in human serum. *PLoS Genet*, 4(11): e1000282.

Golik, A., Weissgarten, J., Evans, S., Cohen, N., Averbukh, Z., Zaidenstein, R., Cotariu, D., Modai, D. (1996). Erythrocyte Na+, K+ and Ca2+, Mg(2+)-ATPase activities in hypertensives on angiotensin-converting enzyme inhibitors. *Clin Biochem*, 29(3): 249–54.

Gorjao, R., Hirabara, S. M., de Lima, T. M., Cury-Boaventura, M. F., Curi, R. (2007). Regulation of interleukin-2 signaling by fatty acids in human lymphocytes. *J Lipid Res*, 48(9): 2009–19.

Grant, G. H., Butt, W. R. (1970). Immunochemical methods in clinical chemistry. *Adv Clin Chem*, 13: 383–466.

Harris, W. S., Lu, G., Rambjor, G. S., Walen, A. I., Ontko, J. A., Cheng, Q., Windsor, S. L. (1997). Influence of n-3 fatty acid supplementation on the endogenous activities of plasma lipases. *Am J Clin Nutr*, 66(2): 254–60.

Heid, I. M., Jackson, A. U., Randall, J. C., Winkler, T. W., Qi, L., Steinthorsdottir, V., Thorleifsson, G., Zillikens, M. C., Speliotes, E. K., Magi, R., Workalemahu, T., White, C. C., Bouatia-Naji, N., Harris, T. B., Berndt, S. I., Ingelsson, E., Willer, C. J., Weedon, M. N., Luan, J., Vedantam, S., Esko, T., Kilpelainen, T. O., Kutalik, Z., Li, S., Monda, K. L., Dixon, A. L., Holmes, C. C., Kaplan, L. M., Liang, L., Min, J. L., Moffatt, M. F., Molony, C., Nicholson, G., Schadt, E. E., Zondervan, K. T., Feitosa, M. F., Ferreira, T., Lango Allen, H., Weyant, R. J., Wheeler, E., Wood, A. R., Estrada, K., Goddard, M. E., Lettre, G., Mangino, M., Nyholt, D. R., Purcell, S., Smith, A. V., Visscher, P. M., Yang, J., McCarroll, S. A., Nemesh, J., Voight, B. F., Absher, D., Amin, N., Aspelund, T., Coin, L., Glazer, N. L., Hayward, C., Heard-Costa, N. L., Hottenga, J. J., Johansson, A., Johnson, T., Kaakinen, M., Kapur, K., Ketkar, S., Knowles, J. W., Kraft, P., Kraja, A. T., Lamina, C., Leitzmann, M. F., McKnight, B., Morris, A. P., Ong, K. K., Perry, J. R., Peters, M. J., Polasek, O., Prokopenko, I., Rayner, N. W., Ripatti, S., Rivadeneira, F., Robertson, N. R., Sanna, S., Sovio, U., Surakka, I., Teumer, A., van Wingerden, S., Vitart, V., Zhao, J. H., Cavalcanti-Proenca, C., Chines, P. S., Fisher, E., Kulzer, J. R., Lecoeur, C., Narisu, N., Sandholt, C., Scott, L. J., Silander, K., Stark, K., Tammesoo, M. L., et al. (2010). Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. *Nat Genet*, 42(11): 949–60.

Heymsfield, S. B., Smith, R., Aulet, M., Bensen, B., Lichtman, S., Wang, J., Pierson, J., R. N. (1990). Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. *Am J Clin Nutr*, 52(2): 214–8.

Himmerich, H., Fulda, S., Linseisen, J., Seiler, H., Wolfram, G., Himmerich, S., Gedrich, K., Pollmacher, T. (2006). TNF-alpha, soluble TNF receptor and interleukin-6 plasma levels in the general population. *Eur Cytokine Netw*, 17(3): 196–201.

Hoff, S., Seiler, H., Heinrich, J., Kompauer, I., Nieters, A., Becker, N., Nagel, G., Gedrich, K., Karg, G., Wolfram, G., Linseisen, J. (2005). Allergic sensitisation and allergic rhinitis are associated with n-3 polyunsaturated fatty acids in the diet and in red blood cell membranes. *Eur J Clin Nutr*, 59(9): 1071–80.

Holle, R., Happich, M., Lowel, H., Wichmann, H. E. (2005). KORA – a research platform for population based health research. *Gesundheitswesen*, 67 Suppl 1: S19–25.

Hu, E., Liang, P., Spiegelman, B. M. (1996). ADIPOQ is a novel adipose-specific gene dysregulated in obesity. *J Biol Chem*, 271(18): 10697–703.

Hung, J., McQuillan, B. M., Chapman, C. M., Thompson, P. L., Beilby, J. P. (2005). Elevated interleukin-18 levels are associated with the metabolic syndrome independent of obesity and insulin resistance. *Arterioscler Thromb Vasc Biol*, 25(6): 1268–73.

Huth, C., Illig, T., Herder, C., Gieger, C., Grallert, H., Vollmert, C., Rathmann, W., Hamid, Y. H., Pedersen, O., Hansen, T., Thorand, B., Meisinger, C., Doring, A., Klopp, N., Gohlke, H., Lieb, W., Hengstenberg, C., Lyssenko, V., Groop, L., Ireland, H., Stephens, J. W., Wernstedt Asterholm, I., Jansson, J. O., Boeing, H., Mohlig, M., Stringham, H. M., Boehnke, M., Tuomilehto, J., Fernandez-Real, J. M., Lopez-Bermejo, A., Gallart, L., Vendrell, J., Humphries, S. E., Kronenberg, F., Wichmann, H. E., Heid, I. M. (2009). Joint analysis of individual participants' data from 17 studies on the association of the IL6 variant -174G>C with circulating glucose levels, interleukin-6 levels, and body mass index. *Ann Med*, 41(2): 128–38.

Illig, T., Gieger, C., Zhai, G., Romisch-Margl, W., Wang-Sattler, R., Prehn, C., Altmaier, E., Kastenmuller, G., Kato, B. S., Mewes, H. W., Meitinger, T., de Angelis, M. H., Kronenberg, F., Soranzo, N., Wichmann, H. E., Spector, T. D., Adamski, J., Suhre, K. (2010). A genome-wide perspective of genetic variation in human metabolism. *Nat Genet*, 42(2): 137–41.

Itoh, M., Suganami, T., Satoh, N., Tanimoto-Koyama, K., Yuan, X., Tanaka, M., Kawano, H., Yano, T., Aoe, S., Takeya, M., Shimatsu, A., Kuzuya, H., Kamei, Y., Ogawa, Y. (2007). Increased adiponectin secretion by highly purified eicosapentaenoic acid in rodent models of obesity and human obese subjects. *Arterioscler Thromb Vasc Biol*, 27(9): 1918–25.

Iwaki, M., Matsuda, M., Maeda, N., Funahashi, T., Matsuzawa, Y., Makishima, M., Shimomura, I. (2003). Induction of adiponectin, a fat-derived antidiabetic and antiatherogenic factor, by nuclear receptors. *Diabetes*, 52(7): 1655–63.

James, W. P., Ferro-Luzzi, A., Waterlow, J. C. (1988). Definition of chronic energy deficiency in adults. Report of a working party of the international dietary energy consultative group. *Eur J Clin Nutr*, 42(12): 969–81.

Jourdan, C., Kloiber, S., Nieters, A., Seiler, H., Himmerich, H., Kohli, M. A., Lucae, S., Wolfram, G., Gieger, C., Wichmann, H. E., Linseisen, J. (2011). Gene–PUFA interactions and obesity risk. *Br J Nutr*, 106(8): 1263–72.

Jourdan, C., Petersen, A. K., Gieger, C., Döring, A., Illig, T., Wang-Sattler, R., Meisinger, C., Peters, A., Adamski, J., Prehn, C., Suhre, K., Altmaier, E., Kastenmuller, G., Romisch-Margl, W., Theis, F. J., Krumsiek, J., Wichmann, H. E., Linseisen, J. (2012). Body fat free mass is associated with the serum metabolite profile in a population-based study. *PLoS One*, 7(6): e40009.

Jump, D. B. (2004). Fatty acid regulation of gene transcription. *Crit Rev Clin Lab Sci*, 41(1): 41–78.

Kaptein, E. M., Beale, E., Chan, L. S. (2009). Thyroid hormone therapy for obesity and nonthyroidal illnesses: a systematic review. *J Clin Endocrinol Metab*, 94(10): 3663–75.

Kekwick, R. A. (1939). The electrophoretic analysis of normal human serum. *Biochem J*, 33(7): 1122–9.

Kershaw, E. E., Flier, J. S. (2004). Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab*, 89(6): 2548–56.

Keys, A., Fidanza, F., Karvonen, M. J., Kimura, N., Taylor, H. L. (1972). Indices of relative weight and obesity. *J Chronic Dis*, 25(6): 329–43.

Kim, B. (2008). Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate. *Thyroid*, 18(2): 141–4.

Knudsen, N., Jorgensen, T., Rasmussen, S., Christiansen, E., Perrild, H. (1999). The prevalence of thyroid dysfunction in a population with borderline iodine deficiency. *Clin Endocrinol (Oxf)*, 51(3): 361–7.

Krug, S., Kastenmuller, G., Stuckler, F., Rist, M. J., Skurk, T., Sailer, M., Raffler, J., Romisch-Margl, W., Adamski, J., Prehn, C., Frank, T., Engel, K. H., Hofmann, T., Luy, B., Zimmermann, R., Moritz, F., Schmitt-Kopplin, P., Krumsiek, J., Kremer, W., Huber,

F., Oeh, U., Theis, F. J., Szymczak, W., Hauner, H., Suhre, K., Daniel, H. (2012). The dynamic range of the human metabolome revealed by challenges. *FASEB J*, 26(6): 2607–19.

Krumsiek, J., Suhre, K., Illig, T., Adamski, J., Theis, F. J. (2011). Gaussian graphical modeling reconstructs pathway reactions from high-throughput metabolomics data. *BMC Syst Biol*, 5: 21.

Kubaszek, A., Pihlajamaki, J., Punnonen, K., Karhapaa, P., Vauhkonen, I., Laakso, M. (2003). The C-174G promoter polymorphism of the IL-6 gene affects energy expenditure and insulin sensitivity. *Diabetes*, 52(2): 558–61.

Kyle, U. G., Genton, L., Hans, D., Pichard, C. (2003a). Validation of a bioelectrical impedance analysis equation to predict appendicular skeletal muscle mass (ASMM). *Clin Nutr*, 22(6): 537–43.

Kyle, U. G., Genton, L., Karsegard, L., Slosman, D. O., Pichard, C. (2001). Single prediction equation for bioelectrical impedance analysis in adults aged 20 – 94 years. *Nutrition*, 17(3): 248–53.

Kyle, U. G., Schutz, Y., Dupertuis, Y. M., Pichard, C. (2003b). Body composition interpretation. Contributions of the fat-free mass index and the body fat mass index. *Nutrition*, 19(7-8): 597–604.

Layman, D. K. (2003). The role of leucine in weight loss diets and glucose homeostasis. *J Nutr*, 133(1): 261S–267S.

Layman, D. K., Walker, D. A. (2006). Potential importance of leucine in treatment of obesity and the metabolic syndrome. *J Nutr*, 136(1 Suppl): 319S–23S.

Lee, S. Y., Gallagher, D. (2008). Assessment methods in human body composition. *Curr Opin Clin Nutr Metab Care*, 11(5): 566–72.

Lewis, G. D., Farrell, L., Wood, M. J., Martinovic, M., Arany, Z., Rowe, G. C., Souza, A., Cheng, S., McCabe, E. L., Yang, E., Shi, X., Deo, R., Roth, F. P., Asnani, A., Rhee, E. P., Systrom, D. M., Semigran, M. J., Vasan, R. S., Carr, S. A., Wang, T. J., Sabatine, M. S., Clish, C. B., Gerszten, R. E. (2010). Metabolic signatures of exercise in human plasma. *Sci Transl Med*, 2(33): 33ra37.

Linseisen, J., Schulze, M. B., Saadatian-Elahi, M., Kroke, A., Miller, A. B., Boeing, H. (2003). Quantity and quality of dietary fat, carbohydrate, and fiber intake in the German EPIC cohorts. *Ann Nutr Metab*, 47(1): 37–46.

Liu, X. G., Tan, L. J., Lei, S. F., Liu, Y. J., Shen, H., Wang, L., Yan, H., Guo, Y. F., Xiong, D. H., Chen, X. D., Pan, F., Yang, T. L., Zhang, Y. P., Guo, Y., Tang, N. L., Zhu, X. Z., Deng, H. Y., Levy, S., Recker, R. R., Papasian, C. J., Deng, H. W. (2009). Genome-wide association and replication studies identified TRHR as an important gene for lean body mass. *Am J Hum Genet*, 84(3): 418–23.

Lorente-Cebrian, S., Perez-Matute, P., Martinez, J. A., Marti, A., Moreno-Aliaga, M. J. (2006). Effects of eicosapentaenoic acid (EPA) on adiponectin gene expression and secretion in primary cultured rat adipocytes. *J Physiol Biochem*, 62(2): 61–9.

Maes, H. H., Neale, M. C., Eaves, L. J. (1997). Genetic and environmental factors in relative body weight and human adiposity. *Behav Genet*, 27(4): 325–51.

Max Rubner-Institut – Bundesforschungsanstalt für Ernährung und Lebensmittel (2008). Nationale Verzehrsstudie II: Ergebnisbericht, Teil 1 einschließlich Ergänzungsband und Schichtindex [online]. `http://www.was-esse-ich.de/uploads/media/NVS_II_Abschlussbericht_Teil_1_mit_Ergaenzungsbericht.pdf`. Last accessed September 10th 2012.

Meisinger, C., Lowel, H., Heier, M., Kandler, U., Doring, A. (2007). Association of sports activities in leisure time and incident myocardial infarction in middle-aged men and women from the general population: the MONICA/KORA Augsburg cohort study. *Eur J Cardiovasc Prev Rehabil*, 14(6): 788–92.

Merzouk, S. A., Saker, M., Reguig, K. B., Soulimane, N., Merzouk, H., Guermouche, B., Berrouiguet, A. Y., Hichami, A., Narce, M., Khan, N. A. (2008). N-3 polyunsaturated fatty acids modulate in-vitro T cell function in type I diabetic patients. *Lipids*, 43(6): 485–97.

Moreno, M., de Lange, P., Lombardi, A., Silvestri, E., Lanni, A., Goglia, F. (2008). Metabolic effects of thyroid hormone derivatives. *Thyroid*, 18(2): 239–53.

Newell, A., Zlot, A., Silvey, K., Arail, K. (2007). Addressing the obesity epidemic: a genomics perspective. *Prev Chronic Dis*, 4(2): A31.

Nieters, A., Becker, N., Linseisen, J. (2002). Polymorphisms in candidate obesity genes and their interaction with dietary intake of n-6 polyunsaturated fatty acids affect obesity risk in a sub-sample of the EPIC-Heidelberg cohort. *Eur J Nutr*, 41(5): 210–21.

Nimptsch, K., Berg-Beckhoff, G., Linseisen, J. (2010). Effect of dietary fatty acid intake on prospective weight change in the Heidelberg cohort of the European prospective investigation into cancer and nutrition. *Public Health Nutr*, 13(10): 1636–46.

Obregon, M. J. (2008). Thyroid hormone and adipocyte differentiation. *Thyroid*, 18(2): 185–95.

Pande, S. V. (1975). A mitochondrial carnitine acylcarnitine translocase system. *Proc Natl Acad Sci U S A*, 72(3): 883–7.

Panicker, V., Wilson, S. G., Walsh, J. P., Richards, J. B., Brown, S. J., Beilby, J. P., Bremner, A. P., Surdulescu, G. L., Qweitin, E., Gillham-Nasenya, I., Soranzo, N., Lim, E. M., Fletcher, S. J., Spector, T. D. (2010). A locus on chromosome 1p36 is associated with thyrotropin and thyroid function as identified by genome-wide association study. *Am J Hum Genet*, 87(3): 430–5.

Paternoster, R., Brame, R., Mazerolle, P., Piquero, A. (1998). Using the correct statistical test for the equality of regression coefficients. *Criminology*, 36(4): 859–866.

Pedersen, B. K. (2009). The diseasome of physical inactivity – and the role of myokines in muscle–fat cross talk. *J Physiol*, 587(Pt 23): 5559–68.

Pedersen, B. K. (2011). Muscles and their myokines. *J Exp Biol*, 214(Pt 2): 337–46.

Pedersen, B. K., Febbraio, M. A. (2008). Muscle as an endocrine organ: focus on muscle-derived interleukin-6. *Physiol Rev*, 88(4): 1379–406.

Peeters, A., Beckers, S., Verrijken, A., Mertens, I., Van Gaal, L., Van Hul, W. (2009). Possible role for ENPP1 polymorphism in obesity but not for INSIG2 and PLIN variants. *Endocrine*, 36(1): 103–9.

Pegorier, J. P., Le May, C., Girard, J. (2004). Control of gene expression by fatty acids. *J Nutr*, 134(9): 2444S–2449S.

Petersen, A. K., Krumsiek, J., Wagele, B., Theis, F. J., Wichmann, H. E., Gieger, C., Suhre, K. (2012). On the hypothesis-free testing of metabolite ratios in genome-wide and metabolome-wide association studies. *BMC Bioinformatics*, 13(1): 120.

Phillips, C. M., Goumidi, L., Bertrais, S., Field, M. R., Ordovas, J. M., Cupples, L. A., Defoort, C., Lovegrove, J. A., Drevon, C. A., Blaak, E. E., Gibney, M. J., Kiec-Wilk, B., Karlstrom, B., Lopez-Miranda, J., McManus, R., Hercberg, S., Lairon, D., Planells, R., Roche, H. M. (2010). Leptin receptor polymorphisms interact with polyunsaturated fatty acids to augment risk of insulin resistance and metabolic syndrome in adults. *J Nutr*, 140(2): 238–44.

Pischon, T., Boeing, H., Hoffmann, K., Bergmann, M., Schulze, M. B., Overvad, K., van der Schouw, Y. T., Spencer, E., Moons, K. G., Tjonneland, A., Halkjaer, J., Jensen, M. K., Stegger, J., Clavel-Chapelon, F., Boutron-Ruault, M. C., Chajes, V., Linseisen, J., Kaaks, R., Trichopoulou, A., Trichopoulos, D., Bamia, C., Sieri, S., Palli, D., Tumino, R., Vineis, P., Panico, S., Peeters, P. H., May, A. M., Bueno-de Mesquita, H. B., van Duijnhoven, F. J., Hallmans, G., Weinehall, L., Manjer, J., Hedblad, B., Lund, E., Agudo, A., Arriola, L., Barricarte, A., Navarro, C., Martinez, C., Quiros, J. R., Key, T., Bingham, S., Khaw, K. T., Boffetta, P., Jenab, M., Ferrari, P., Riboli, E. (2008). General and abdominal adiposity and risk of death in Europe. *N Engl J Med*, 359(20): 2105–20.

Psychogios, N., Hau, D. D., Peng, J., Guo, A. C., Mandal, R., Bouatra, S., Sinelnikov, I., Krishnamurthy, R., Eisner, R., Gautam, B., Young, N., Xia, J., Knox, C., Dong, E., Huang, P., Hollander, Z., Pedersen, T. L., Smith, S. R., Bamforth, F., Greiner, R., McManus, B., Newman, J. W., Goodfriend, T., Wishart, D. S. (2011). The human serum metabolome. *PLoS One*, 6(2): e16957.

Qi, L., Zhang, C., van Dam, R. M., Hu, F. B. (2007). Interleukin-6 genetic variability and adiposity: associations in two prospective cohorts and systematic review in 26,944 individuals. *J Clin Endocrinol Metab*, 92(9): 3618–25.

Reinehr, T. (2010). Obesity and thyroid function. *Mol Cell Endocrinol*, 316(2): 165–71.

Reseland, J. E., Haugen, F., Hollung, K., Solvoll, K., Halvorsen, B., Brude, I. R., Nenseter, M. S., Christiansen, E. N., Drevon, C. A. (2001). Reduction of leptin gene expression by dietary polyunsaturated fatty acids. *J Lipid Res*, 42(5): 743–50.

Ribeiro, R. C., Apriletti, J. W., Wagner, R. L., West, B. L., Feng, W., Huber, R., Kushner, P. J., Nilsson, S., Scanlan, T., Fletterick, R. J., Schaufele, F., Baxter, J. D. (1998). Mechanisms of thyroid hormone action: insights from X-ray crystallographic and functional studies. *Recent Prog Horm Res*, 53: 351–92; discussion 392–4.

Römisch-Margl, W., Prehn, C., Bogumil, R., Röhring, C., Suhre, K., Adamski, J. (2012). Procedure for tissue sample preparation and metabolite extraction for high-throughput targeted metabolomics. *Metabolomics*, 8: 133–142.

Roschinger, W., Muntau, A. C., Duran, M., Dorland, L., L, I. J., Wanders, R. J., Roscher, A. A. (2000). Carnitine-acylcarnitine translocase deficiency: metabolic consequences of an impaired mitochondrial carnitine cycle. *Clin Chim Acta*, 298(1-2): 55–68.

Ruderman, N. B. (1975). Muscle amino acid metabolism and gluconeogenesis. *Annu Rev Med*, 26: 245–58.

Rush, E. C., Chandu, V., Plank, L. D. (2006). Prediction of fat-free mass by bioimpedance analysis in migrant Asian Indian men and women: a cross validation study. *Int J Obes (Lond)*, 30(7): 1125–31.

Salsberry, P. J., Reagan, P. B. (2010). Effects of heritability, shared environment, and nonshared intrauterine conditions on child and adolescent BMI. *Obesity (Silver Spring)*, 18(9): 1775–80.

Saltiel, A. R. (2001). You are what you secrete. *Nat Med*, 7(8): 887–8.

Sampath, H., Ntambi, J. M. (2004). Polyunsaturated fatty acid regulation of gene expression. *Nutr Rev*, 62(9): 333–9.

Schaller, N., Seiler, H., Himmerich, S., Karg, G., Gedrich, K., Wolfram, G., Linseisen, J. (2005). Estimated physical activity in Bavaria, Germany, and its implications for obesity risk: results from the BVS-II Study. *Int J Behav Nutr Phys Act*, 2: 6.

Schutz, Y., Kyle, U. U., Pichard, C. (2002). Fat-free mass index and fat mass index percentiles in Caucasians aged 18-98 y. *Int J Obes Relat Metab Disord*, 26(7): 953–60.

Segal, K. R., Dunaif, A., Gutin, B., Albu, J., Nyman, A., Pi-Sunyer, F. X. (1987). Body composition, not body weight, is related to cardiovascular disease risk factors and sex hormone levels in men. *J Clin Invest*, 80(4): 1050–5.

Siiteri, P. K. (1987). Adipose tissue as a source of hormones. *Am J Clin Nutr*, 45(1 Suppl): 277–82.

Silvestri, E., Lombardi, A., de Lange, P., Glinni, D., Senese, R., Cioffi, F., Lanni, A., Goglia, F., Moreno, M. (2011). Studies of complex biological systems with applications to molecular medicine: the need to integrate transcriptomic and proteomic approaches. *J Biomed Biotechnol*, 2011: 810242.

Skurk, T., Kolb, H., Muller-Scholze, S., Rohrig, K., Hauner, H., Herder, C. (2005). The proatherogenic cytokine interleukin-18 is secreted by human adipocytes. *Eur J Endocrinol*, 152(6): 863–8.

Slimani, N., Deharveng, G., Charrondiere, R. U., van Kappel, A. L., Ocke, M. C., Welch, A., Lagiou, A., van Liere, M., Agudo, A., Pala, V., Brandstetter, B., Andren, C., Stripp, C., van Staveren, W. A., Riboli, E. (1999). Structure of the standardized computerized 24-h diet recall interview used as reference method in the 22 centers participating in the EPIC project. European prospective investigation into cancer and nutrition. *Comput Methods Programs Biomed*, 58(3): 251–66.

Slimani, N., Ferrari, P., Ocke, M., Welch, A., Boeing, H., Liere, M., Pala, V., Amiano, P., Lagiou, A., Mattisson, I., Stripp, C., Engeset, D., Charrondiere, R., Buzzard, M., Staveren, W., Riboli, E. (2000). Standardization of the 24-hour diet recall calibration method used in the European prospective investigation into cancer and nutrition (EPIC): general concepts and preliminary results. *Eur J Clin Nutr*, 54(12): 900–17.

Smith, A. J., Humphries, S. E. (2009). Cytokine and cytokine receptor gene polymorphisms and their functionality. *Cytokine Growth Factor Rev*, 20(1): 43–59.

Speliotes, E. K., Willer, C. J., Berndt, S. I., Monda, K. L., Thorleifsson, G., Jackson, A. U., Lango Allen, H., Lindgren, C. M., Luan, J., Magi, R., Randall, J. C., Vedantam, S., Winkler, T. W., Qi, L., Workalemahu, T., Heid, I. M., Steinthorsdottir, V., Stringham, H. M., Weedon, M. N., Wheeler, E., Wood, A. R., Ferreira, T., Weyant, R. J., Segre, A. V., Estrada, K., Liang, L., Nemesh, J., Park, J. H., Gustafsson, S., Kilpelainen, T. O., Yang, J., Bouatia-Naji, N., Esko, T., Feitosa, M. F., Kutalik, Z., Mangino, M., Raychaudhuri, S., Scherag, A., Smith, A. V., Welch, R., Zhao, J. H., Aben, K. K., Absher, D. M., Amin, N., Dixon, A. L., Fisher, E., Glazer, N. L., Goddard, M. E., Heard-Costa, N. L., Hoesel, V., Hottenga, J. J., Johansson, A., Johnson, T., Ketkar, S., Lamina, C.,

Li, S., Moffatt, M. F., Myers, R. H., Narisu, N., Perry, J. R., Peters, M. J., Preuss, M., Ripatti, S., Rivadeneira, F., Sandholt, C., Scott, L. J., Timpson, N. J., Tyrer, J. P., van Wingerden, S., Watanabe, R. M., White, C. C., Wiklund, F., Barlassina, C., Chasman, D. I., Cooper, M. N., Jansson, J. O., Lawrence, R. W., Pellikka, N., Prokopenko, I., Shi, J., Thiering, E., Alavere, H., Alibrandi, M. T., Almgren, P., Arnold, A. M., Aspelund, T., Atwood, L. D., Balkau, B., Balmforth, A. J., Bennett, A. J., Ben-Shlomo, Y., Bergman, R. N., Bergmann, S., Biebermann, H., Blakemore, A. I., Boes, T., Bonnycastle, L. L., Bornstein, S. R., Brown, M. J., Buchanan, T. A., et al. (2010). Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*, 42(11): 937–48.

Spiegelman, B. M., Flier, J. S. (2001). Obesity and the regulation of energy balance. *Cell*, 104(4): 531–43.

Storlien, L. H., Huang, X. F., Lin, S., Xin, X., Wang, H. Q., Else, P. L. (2001). Dietary fat subtypes and obesity. *World Rev Nutr Diet*, 88: 148–54.

Storlien, L. H., Hulbert, A. J., Else, P. L. (1998). Polyunsaturated fatty acids, membrane function and metabolic diseases such as diabetes and obesity. *Curr Opin Clin Nutr Metab Care*, 1(6): 559–63.

Stulnig, T. M. (2003). Immunomodulation by polyunsaturated fatty acids: mechanisms and effects. *Int Arch Allergy Immunol*, 132(4): 310–21.

Suhre, K., Meisinger, C., Doring, A., Altmaier, E., Belcredi, P., Gieger, C., Chang, D., Milburn, M. V., Gall, W. E., Weinberger, K. M., Mewes, H. W., Hrabe de Angelis, M., Wichmann, H. E., Kronenberg, F., Adamski, J., Illig, T. (2010). Metabolic footprint of diabetes: a multiplatform metabolomics study in an epidemiological setting. *PLoS One*, 5(11): e13953.

Suk, K., Yeou Kim, S., Kim, H. (2001). Regulation of IL-18 production by IFN gamma and PGE2 in mouse microglial cells: involvement of Nf-kB pathway in the regulatory processes. *Immunol Lett*, 77(2): 79–85.

Surks, M. I., Ortiz, E., Daniels, G. H., Sawin, C. T., Col, N. F., Cobin, R. H., Franklyn, J. A., Hershman, J. M., Burman, K. D., Denke, M. A., Gorman, C., Cooper, R. S., Weissman, N. J. (2004). Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA*, 291(2): 228–38.

Tarim, O. (2011). Thyroid hormones and growth in health and disease. *J Clin Res Pediatr Endocrinol*, 3(2): 51–5.

Thienpont, L. M., Van Uytfanghe, K., Beastall, G., Faix, J. D., Ieiri, T., Miller, W. G., Nelson, J. C., Ronin, C., Ross, H. A., Thijssen, J. H., Toussaint, B., Tests, I. W. G. o. S. o. T. F. (2010). Report of the IFCC working group for standardization of thyroid function tests; part 2: free thyroxine and free triiodothyronine. *Clin Chem*, 56(6): 912–20.

Thompson, S. R., Sanders, J., Stephens, J. W., Miller, G. J., Humphries, S. E. (2007). A common interleukin 18 haplotype is associated with higher body mass index in subjects with diabetes and coronary heart disease. *Metabolism*, 56(5): 662–9.

Thorleifsson, G., Walters, G. B., Gudbjartsson, D. F., Steinthorsdottir, V., Sulem, P., Helgadottir, A., Styrkarsdottir, U., Gretarsdottir, S., Thorlacius, S., Jonsdottir, I., Jonsdottir, T., Olafsdottir, E. J., Olafsdottir, G. H., Jonsson, T., Jonsson, F., Borch-Johnsen, K., Hansen, T., Andersen, G., Jorgensen, T., Lauritzen, T., Aben, K. K., Verbeek, A. L., Roeleveld, N., Kampman, E., Yanek, L. R., Becker, L. C., Tryggvadottir, L., Rafnar, T., Becker, D. M., Gulcher, J., Kiemeney, L. A., Pedersen, O., Kong, A., Thorsteinsdottir, U., Stefansson, K. (2009). Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat Genet*, 41(1): 18–24.

Tiret, L., Godefroy, T., Lubos, E., Nicaud, V., Tregouet, D. A., Barbaux, S., Schnabel, R., Bickel, C., Espinola-Klein, C., Poirier, O., Perret, C., Munzel, T., Rupprecht, H. J., Lackner, K., Cambien, F., Blankenberg, S. (2005). Genetic analysis of the interleukin-18 system highlights the role of the interleukin-18 gene in cardiovascular disease. *Circulation*, 112(5): 643–50.

Tom, A., Nair, K. S. (2006). Assessment of branched-chain amino acid status and potential for biomarkers. *J Nutr*, 136(1 Suppl): 324S–30S.

U. S. Department of Health and Human Services and Food and Drug Administration and Center for Drug Evaluation and Research (CDER) and Center for Veterinary Medicine (CVM) (May 2001). Guidance for industry - bioanalytical method validation.

Vasseur, F., Helbecque, N., Dina, C., Lobbens, S., Delannoy, V., Gaget, S., Boutin, P., Vaxillaire, M., Lepretre, F., Dupont, S., Hara, K., Clement, K., Bihain, B., Kadowaki, T., Froguel, P. (2002). Single-nucleotide polymorphism haplotypes in the both proximal promoter and exon 3 of the APM1 gene modulate adipocyte-secreted adiponectin hormone

levels and contribute to the genetic risk for type 2 diabetes in French Caucasians. *Hum Mol Genet*, 11(21): 2607–14.

Verlengia, R., Gorjao, R., Kanunfre, C. C., Bordin, S., de Lima, T. M., Curi, R. (2003). Effect of arachidonic acid on proliferation, cytokines production and pleiotropic genes expression in Jurkat cells – a comparison with oleic acid. *Life Sci*, 73(23): 2939–51.

Vinayavekhin, N., Saghatelian, A. (2009). Regulation of alkyl-dihydrothiazole-carboxylates (ATCs) by iron and the pyochelin gene cluster in pseudomonas aeruginosa. *ACS Chem Biol*, 4(8): 617–23.

Vliet-Ostaptchouk, J., Snieder, H., Lagou, V. (2012). Gene-lifestyle interactions in obesity. *Current Nutrition Reports*, 1: 184–196.

von Schacky, C. (2007). N-3 PUFA in CVD: influence of cytokine polymorphism. *Proc Nutr Soc*, 66(2): 166–70.

Voss, S., Charrondiere, U. R., Slimani, N., Kroke, A., Riboli, E., Wahrendorf, J., Boeing, H. (1998). [EPIC-SOFT a european computer program for 24-hour dietary protocols]. *Z Ernahrungswiss*, 37(3): 227–33.

Vozarova, B., Weyer, C., Hanson, K., Tataranni, P. A., Bogardus, C., Pratley, R. E. (2001). Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion. *Obes Res*, 9(7): 414–7.

Wagner, R. L., Apriletti, J. W., McGrath, M. E., West, B. L., Baxter, J. D., Fletterick, R. J. (1995). A structural role for hormone in the thyroid hormone receptor. *Nature*, 378(6558): 690–7.

Wang, Z. M., Pierson, J., R. N., Heymsfield, S. B. (1992). The five-level model: a new approach to organizing body-composition research. *Am J Clin Nutr*, 56(1): 19–28.

Wang-Sattler, R., Yu, Y., Mittelstrass, K., Lattka, E., Altmaier, E., Gieger, C., Ladwig, K. H., Dahmen, N., Weinberger, K. M., Hao, P., Liu, L., Li, Y., Wichmann, H. E., Adamski, J., Suhre, K., Illig, T. (2008). Metabolic profiling reveals distinct variations linked to nicotine consumption in humans – first results from the KORA study. *PLoS One*, 3(12): e3863.

Watson, A. D. (2006). Thematic review series: systems biology approaches to metabolic and cardiovascular disorders. Lipidomics: a global approach to lipid analysis in biological systems. *J Lipid Res*, 47(10): 2101–11.

Wenk, M. R. (2005). The emerging field of lipidomics. *Nat Rev Drug Discov*, 4(7): 594–610.

Wigginton, J. E., Cutler, D. J., Abecasis, G. R. (2005). A note on exact tests of HARDY–Weinberg equilibrium. *Am J Hum Genet*, 76(5): 887–93.

Willer, C. J., Speliotes, E. K., Loos, R. J., Li, S., Lindgren, C. M., Heid, I. M., Berndt, S. I., Elliott, A. L., Jackson, A. U., Lamina, C., Lettre, G., Lim, N., Lyon, H. N., McCarroll, S. A., Papadakis, K., Qi, L., Randall, J. C., Roccasecca, R. M., Sanna, S., Scheet, P., Weedon, M. N., Wheeler, E., Zhao, J. H., Jacobs, L. C., Prokopenko, I., Soranzo, N., Tanaka, T., Timpson, N. J., Almgren, P., Bennett, A., Bergman, R. N., Bingham, S. A., Bonnycastle, L. L., Brown, M., Burtt, N. P., Chines, P., Coin, L., Collins, F. S., Connell, J. M., Cooper, C., Smith, G. D., Dennison, E. M., Deodhar, P., Elliott, P., Erdos, M. R., Estrada, K., Evans, D. M., Gianniny, L., Gieger, C., Gillson, C. J., Guiducci, C., Hackett, R., Hadley, D., Hall, A. S., Havulinna, A. S., Hebebrand, J., Hofman, A., Isomaa, B., Jacobs, K. B., Johnson, T., Jousilahti, P., Jovanovic, Z., Khaw, K. T., Kraft, P., Kuokkanen, M., Kuusisto, J., Laitinen, J., Lakatta, E. G., Luan, J., Luben, R. N., Mangino, M., McArdle, W. L., Meitinger, T., Mulas, A., Munroe, P. B., Narisu, N., Ness, A. R., Northstone, K., O'Rahilly, S., Purmann, C., Rees, M. G., Ridderstrale, M., Ring, S. M., Rivadeneira, F., Ruokonen, A., Sandhu, M. S., Saramies, J., Scott, L. J., Scuteri, A., Silander, K., Sims, M. A., Song, K., Stephens, J., Stevens, S., Stringham, H. M., Tung, Y. C., Valle, T. T., Van Duijn, C. M., Vimaleswaran, K. S., Vollenweider, P., et al. (2009). Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet*, 41(1): 25–34.

Williams, G. R., Bassett, J. H. (2011). Deiodinases: the balance of thyroid hormone: local control of thyroid hormone action: role of type 2 deiodinase. *J Endocrinol*, 209(3): 261–72.

Winkler, J., Stolzenberg, H. (1999). [Social class index in the Federal Health Survey]. *Gesundheitswesen*, 61 Spec No: S178–83.

World Health Organization (1995). Physical status: the use and interpretation of anthropometry. Report of a WHO expert committee. *World Health Organ Tech Rep Ser*, 854: 1–452.

World Health Organization (2000). Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*, 894: i–xii, 1–253.

World Health Organization (2012). Obesity and overweight: Fact sheet no. 311. `http://www.who.int/mediacentre/factsheets/fs311/en/`. Last accessed September 10th 2012.

Wren, J. J., Szczepanowksa, A. D. (1964). Chromatography of lipids in presence of an antioxidant, 4-methyl-2,6-di-tert.-butylphenol. *J Chromatogr A*, 14: 387–404.

Yen, P. M. (2001). Physiological and molecular basis of thyroid hormone action. *Physiol Rev*, 81(3): 1097–142.

Yu, Y. H., Lin, E. C., Wu, S. C., Cheng, W. T., Mersmann, H. J., Wang, P. H., Ding, S. T. (2008). Docosahexaenoic acid regulates adipogenic genes in myoblasts via porcine peroxisome proliferator-activated receptor gamma. *J Anim Sci*, 86(12): 3385–92.

Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L., Friedman, J. M. (1994). Positional cloning of the mouse obese gene and its human homologue. *Nature*, 372(6505): 425–32.

Appendix

A Supplementary Material - Gene–PUFA Interactions and Obesity Risk

Table A1: Genotype distribution and crude main effects of the different SNPs on the risk of obesity in the BVS II study *(Jourdan et al., 2011)*.

Gene	SNP	MAF[a]	Allele	Obese	Non-Obese	P-value[b]	OR [95% CI]	P-trend[c]
IL-2 region 5'	rs4833248	0.30	GG	50.90	48.30	0.8876	1.00	0.6606
			AG	40.90	43.10		0.90 [0.58-1.39]	
			AA	8.20	8.60		0.91 [0.39-1.91]	
IL-2	rs2069779	0.07	CC	86.70	85.80	0.8649	1.00	0.7599
			CT	13.30	14.00		0.93 [0.49-1.65]	
			TT	0.00	0.20			
IL-2	rs2069778	0.16	CC	69.40	71.00	0.923	1.00	0.7846
			CT	28.80	27.00		1.09 [0.68-1.72]	
			TT	1.80	2.00		0.93 [0.14-3.69]	
IL-2	rs2069763	0.35	GG	38.90	43.20	0.0835	1.00	0.8331
			GT	54.00	43.90		1.37 [0.89-2.12]	
			TT	7.10	12.90		0.61 [0.25-1.31]	
IL-2	rs2069762	0.29	TT	51.80	49.60	0.9149	1.00	0.7005
			GT	40.20	42.00		0.91 [0.59-1.41]	
			GG	8.00	8.40		0.91 [0.40-1.92]	
IL-6 region 5'	rs1880241	0.50	AA	30.70	26.00	0.5736	1.00	0.3146
			AG	45.60	47.30		0.82 [0.50-1.33]	
			GG	23.70	26.70		0.75 [0.43-1.32]	
IL-6 region 5'	rs4719714	0.22	AA	59.80	61.60	0.0284	1.00	0.2056
			AT	30.40	34.60		0.90 [0.57-1.42]	
			TT	9.80	3.80		2.68 [1.17-5.94]	
IL-6 region 5'	rs12700386	0.19	CC	76.30	63.40	0.0327	1.00	0.0184
			CG	20.20	31.80		0.53 [0.31-0.86]	
			GG	3.50	4.90		0.60 [0.17-1.62]	
IL-6	rs1800797	0.42	GG	35.10	33.60	0.9132	1.00	0.6772
			AG	47.40	47.30		0.96 [0.61-1.52]	
			AA	17.50	19.10		0.88 [0.48-1.58]	
IL-6	rs1800795	0.43	GG	35.40	33.60	0.8814	1.00	0.6257
			CG	46.90	46.80		0.95 [0.60-1.52]	
			CC	17.70	19.60		0.86 [0.46-1.54]	
IL-6	rs2069840	0.35	CC	46.90	43.00	0.4942	1.00	0.8148
			CG	38.10	44.10		0.79 [0.50-1.24]	
			GG	15.00	12.90		1.07 [0.56-1.96]	
IL-6	rs2069861	0.10	CC	86.80	80.40	0.1825	1.00	0.2004
			CT	11.40	18.40		0.62 [0.33-1.10]	
			TT	1.80	1.10			
IL-6	rs2069833	0.43	TT	35.10	32.90	0.8205	1.00	0.5411
			CT	48.20	48.10		0.94 [0.60-1.49]	
			CC	16.70	19.00		0.82 [0.44-1.49]	
IL-6 region 3'	rs10242595	0.30	AA	50.00	49.20	0.6341	1.00	0.7851
			AG	37.50	41.00		0.90 [0.57-1.40]	
			GG	12.50	9.80		1.26 [0.63-2.40]	
IL-10 region 5'	rs17015767	0.19	GG	70.20	65.90	0.6464	1.00	0.5015
			CG	24.60	29.00		0.80 [0.49-1.27]	
			CC	5.30	5.10		0.97 [0.35-2.31]	

Gene	SNP	MAF[a]	Allele	Obese	Non-Obese	P-value[b]	OR [95% CI]	P-trend[c]
IL-10 region 5'	rs3122605	0.16	AA	63.20	72.10	0.1351	1.00	0.0477
			AG	33.30	26.20		1.45 [0.92-2.26]	
			GG	3.50	1.80		2.26 [0.59-7.37]	
IL-10	rs3024498	0.22	AA	66.70	60.70	0.4964	1.00	0.306
			AG	28.10	33.60		0.76 [0.48-1.20]	
			GG	5.30	5.70		0.84 [0.30-1.98]	
IL-10	rs1554286	0.20	CC	59.60	63.70	0.5686	1.00	0.5872
			CT	37.70	32.70		1.23 [0.80-1.89]	
			TT	2.60	3.50		0.79 [0.18-2.47]	
IL-10	rs3021094	0.10	AA	84.20	79.90	0.3698	1.00	0.2204
			AC	15.80	19.00		0.74 [0.42-1.27]	
			CC	0.00	1.10			
IL-10	rs1800896	0.44	AA	25.40	31.30	0.3532	1.00	0.5466
			AG	57.90	50.60		1.41 [0.87-2.31]	
			GG	16.70	18.20		1.13 [0.59-2.12]	
IL-10 region 3'	rs3024505	0.16	CC	63.20	70.40	0.1416	1.00	0.0783
			CT	33.30	28.30		1.31 [0.84-2.03]	
			TT	3.50	1.30		2.94 [0.74-10.57]	
IL-18	rs3882891	0.42	AA	32.50	35.00	0.7613	1.00	0.8617
			AC	50.90	47.00		1.17 [0.74-1.86]	
			CC	16.70	18.00		1.00 [0.53-1.83]	
IL-18	rs5744280	0.33	CC	45.10	43.80	0.9581	1.00	0.8547
			CT	45.10	46.70		0.94 [0.61-1.45]	
			TT	9.70	9.60		0.98 [0.45-1.98]	
IL-18	rs549908	0.30	TT	44.20	49.10	0.6455	1.00	0.367
			GT	46.00	42.40		1.20 [0.78-1.86]	
			GG	9.70	8.50		1.27 [0.59-2.59]	
IL-18	rs5744256	0.26	TT	54.00	54.70	0.9818	1.00	0.9464
			CT	39.80	38.90		1.04 [0.67-1.59]	
			CC	6.20	6.40		0.97 [0.38-2.21]	
IL-18	rs360722	0.11	CC	82.50	77.50	0.5139	1.00	0.2638
			CT	16.70	21.40		0.73 [0.42-1.22]	
			TT	0.90	1.10			
IL-18	rs795467	0.27	GG	51.80	53.10	0.9414	1.00	0.7426
			AG	40.40	39.80		1.04 [0.67-1.60]	
			AA	7.90	7.10		1.14 [0.49-2.44]	
IL-18	rs1946519	0.39	CC	38.10	36.70	0.7115	1.00	0.5333
			AC	48.70	46.90		1.00 [0.64-1.57]	
			AA	13.30	16.40		0.78 [0.40-1.46]	
TNF-α	rs3093662	0.07	AA	87.60	85.90	0.8051	1.00	0.5965
			AG	12.40	13.90		0.86 [0.45-1.55]	
			GG	0.00	0.20			
TNF-α	rs3093668	0.05	GG	92.90	90.00	0.5996	1.00	0.329
			CG	7.10	9.70		0.69 [0.29-1.43]	
			CC	0.00	0.20			
TNFRSF1A	rs4149579	0.06	GG	90.40	88.30	0.6836	1.00	0.4742
			AG	9.60	11.30		0.81 [0.39-1.54]	
			AA	0.00	0.40			

Gene	SNP	MAF[a]	Allele	Obese	Non-Obese	P-value[b]	OR [95% CI]	P-trend[c]
TNFRSF1A	rs4149577	0.48	TT	28.10	24.30	0.4424	1.00	0.216
			CT	55.30	54.10		0.88 [0.55-1.44]	
			CC	16.70	21.60		0.67 [0.35-1.24]	
TNFRSF1A	rs4149576	0.45	GG	24.60	31.20	0.354	1.00	0.3468
			AG	55.30	48.90		1.44 [0.88-2.38]	
			AA	20.20	19.90		1.29 [0.69-2.37]	
TNFRSF1A	rs4149570	0.39	GG	43.40	34.40	0.2057	1.00	0.1269
			GT	44.20	51.40		0.68 [0.44-1.06]	
			TT	12.40	14.20		0.69 [0.35-1.31]	
TNFRSF1B	rs652625	0.05	AA	88.60	91.20	0.3895	1.00	0.5686
			AT	11.40	8.20		1.33 [0.66-2.51]	
			TT	0.00	0.70			
TNFRSF1B	rs496888	0.32	AA	49.10	46.70	0.7928	1.00	0.5235
			AG	41.20	41.60		0.94 [0.61-1.45]	
			GG	9.60	11.70		0.78 [0.37-1.55]	
TNFRSF1B	rs3766730	0.16	CC	69.90	71.00	0.1012	1.00	0.4355
			CT	25.70	27.70		0.94 [0.58-1.49]	
			TT	4.40	1.30		3.38 [0.95-11.48]	
TNFRSF1B	rs1061622	0.21	TT	61.10	62.90	0.1445	1.00	0.3269
			GT	31.90	34.00		0.97 [0.61-1.50]	
			GG	7.10	3.10		2.36 [0.91-5.74]	
TNFRSF1B	rs2275416	0.18	GG	62.80	67.90	0.2342	1.00	0.1668
			AG	31.90	29.70		1.16 [0.73-1.81]	
			AA	5.30	2.50		2.34 [0.78-6.36]	
TNFRSF1B	rs235219	0.10	GG	82.10	81.40	0.9817	1.00	0.8626
			AG	17.00	17.70		0.95 [0.54-1.60]	
			AA	0.90	0.90			
TNFRSF1B	rs1061624	0.41	GG	42.90	38.20	0.6605	1.00	0.4479
			AG	37.50	40.80		0.82 [0.51-1.30]	
			AA	19.60	21.00		0.83 [0.47-1.45]	
TNFRSF1B	rs1061628	0.40	CC	32.10	36.40	0.0219	1.00	0.5483
			CT	58.90	46.10		1.45 [0.92-2.29]	
			TT	8.90	17.50		0.58 [0.26-1.18]	
TNFRSF21	rs9473029	0.05	GG	92.00	90.10	0.6198	1.00	0.4332
			CG	8.00	9.30		0.78 [0.35-1.59]	
			CC	0.00	0.70			
TNFRSF21	rs2236039	0.28	AA	49.10	53.30	0.6287	1.00	0.6086
			AG	43.00	38.10		1.23 [0.80-1.89]	
			GG	7.90	8.60		0.99 [0.43-2.09]	
TNFRSF21	rs2295266	0.19	CC	61.90	66.40	0.6331	1.00	0.4735
			CG	34.50	29.90		1.24 [0.79-1.92]	
			GG	3.50	3.80		1.01 [0.28-2.83]	
TNFRSF21	rs714373	0.36	AA	44.70	40.30	0.649	1.00	0.5459
			AG	41.20	45.80		0.81 [0.52-1.26]	
			GG	14.00	13.90		0.91 [0.47-1.67]	
TNFRSF21	rs9473045	0.34	GG	45.10	43.00	0.7653	1.00	0.9333
			AG	41.60	45.20		0.88 [0.56-1.36]	
			AA	13.30	11.80		1.08 [0.55-2.03]	

Gene	SNP	MAF[a]	Allele	Obese	Non-Obese	P-value[b]	OR [95% CI]	P-trend[c]
TNFRSF21	rs16875844	0.08	GG	81.60	86.30	0.3809	1.00	0.274
			AG	17.50	12.60		1.42 [0.81-2.42]	
			AA	0.90	1.10			
TNFRSF21	rs2017424	0.48	CC	29.80	27.60	0.5536	1.00	0.8808
			CG	43.90	49.40		0.82 [0.51-1.34]	
			GG	26.30	23.00		1.06 [0.61-1.85]	
TNFRSF21	rs6458555	0.34	GG	44.20	46.80	0.8817	1.00	0.6226
			AG	41.60	40.10		1.10 [0.70-1.71]	
			AA	14.20	13.10		1.14 [0.59-2.12]	
TNFRSF21 region 3'	rs9381530	0.43	TT	35.10	30.70	0.6516	1.00	0.3818
			GT	49.10	51.70		0.83 [0.53-1.32]	
			GG	15.80	17.70		0.78 [0.41-1.44]	
NPY region 5'	rs16480	0.32	TT	56.30	52.90	0.3693	1.00	0.2632
			CT	30.40	28.00		1.02 [0.63-1.62]	
			CC	13.40	19.10		0.66 [0.35-1.19]	
NPY	rs16148	0.34	TT	43.40	43.50	0.3535	1.00	0.5282
			CT	48.70	43.90		1.11 [0.72-1.72]	
			CC	8.00	12.60		0.64 [0.28-1.32]	
NPY	rs16141	0.49	AA	25.00	23.60	0.6322	1.00	0.78
			AC	50.00	54.80		0.86 [0.52-1.45]	
			CC	25.00	21.60		1.09 [0.60-1.98]	
NPY	rs9785023	0.50	AA	23.70	23.20	0.7098	1.00	0.6878
			AG	50.90	54.60		0.91 [0.55-1.54]	
			GG	25.40	22.10		1.13 [0.62-2.04]	
NPY	rs16138	0.26	GG	56.10	53.00	0.4733	1.00	0.3394
			CG	40.40	40.60		0.94 [0.61-1.43]	
			CC	3.50	6.40		0.52 [0.15-1.37]	
NPY	rs16135	0.07	CC	90.40	84.70	0.2342	1.00	0.099
			CT	9.60	14.40		0.59 [0.29-1.11]	
			TT	0.00	0.90			
NPY	rs16131	0.15	AA	68.40	73.70	0.4935	1.00	0.2354
			AG	28.10	23.80		1.27 [0.79-2.01]	
			GG	3.50	2.40		1.56 [0.42-4.69]	
NPY	rs16475	0.11	TT	86.70	86.50	0.498	1.00	0.7838
			CT	2.70	4.90		0.54 [0.13-1.61]	
			CC	10.60	8.60		1.22 [0.59-2.36]	
NPY region 3'	rs2023890	0.22	TT	57.70	61.70	0.3871	1.00	0.2594
			CT	35.10	34.10		1.10 [0.70-1.71]	
			CC	7.20	4.20		1.82 [0.72-4.22]	
NPY region 3'	rs16472	0.08	CC	84.70	83.30	0.7242	1.00	0.724
			CT	15.30	16.70		0.90 [0.49-1.57]	
NPY region 3'	rs17374047	0.15	AA	73.20	70.80	0.6333	1.00	0.4807
			AG	25.90	27.00		0.93 [0.57-1.47]	
			GG	0.90	2.20		0.39 [0.02-2.08]	
NPY region 3'	rs16468	0.40	CC	33.00	33.90	0.8188	1.00	0.8685
			AC	54.50	51.70		1.08 [0.69-1.72]	
			AA	12.50	14.50		0.88 [0.44-1.72]	

Gene	SNP	MAF[a]	Allele	Obese	Non-Obese	P-value[b]	OR [95% CI]	P-trend[c]
NPY region 3'	rs16110	0.50	GG	26.50	23.70	0.8191	1.00	0.6479
			CG	50.40	52.80		0.85 [0.52-1.42]	
			CC	23.00	23.50		0.87 [0.48-1.58]	
NPY1R region 5'	rs4234955	0.23	AA	59.30	60.10	0.1041	1.00	0.3521
			AG	31.00	35.20		0.89 [0.56-1.40]	
			GG	9.70	4.70		2.11 [0.94-4.51]	
NPY1R region 5'	rs4691076	0.23	CC	58.40	59.00	0.2458	1.00	0.4733
			CT	32.70	36.10		0.91 [0.58-1.42]	
			TT	8.80	4.90		1.83 [0.80-3.96]	
NPY1R	rs9764	0.27	TT	53.60	50.60	0.8303	1.00	0.6456
			TC	42.00	45.20		0.88 [0.57-1.34]	
			CC	4.50	4.30		0.99 [0.32-2.57]	
NPY1R	rs4691075	0.11	TT	78.60	80.10	0.3085	1.00	0.4762
			CT	18.80	19.00		1.10 [0.65-1.80]	
			CC	2.70	0.90			
NPY1R	rs7687423	0.35	GG	40.40	41.30	0.9668	1.00	0.9305
			AG	48.20	46.90		1.05 [0.68-1.64]	
			AA	11.40	11.80		0.99 [0.48-1.93]	
NPY1R	rs12507653	0.30	AA	53.10	47.90	0.6132	1.00	0.3763
			AT	38.10	42.40		0.81 [0.52-1.25]	
			TT	8.80	9.80		0.82 [0.37-1.66]	
NPY5R	rs4632602	0.10	TT	74.60	82.10	0.1896	1.00	0.0779
			CT	24.60	17.20		1.57 [0.95-2.52]	
			CC	0.90	0.70			
NPY5R	rs7678265	0.08	CC	85.00	85.20	0.969	1.00	0.9122
			CT	14.20	14.20		1.02 [0.56-1.78]	
			TT	0.90	0.70			
NPY5R	rs11100494	0.08	CC	89.40	82.90	0.169	1.00	0.0692
			AC	10.60	15.70		0.58 [0.29-1.06]	
			AA	0.00	1.30			
NPY5R region 3'	rs6536721	0.34	GG	47.80	43.50	0.2032	1.00	0.9922
			AG	36.30	44.80		0.74 [0.47-1.15]	
			AA	15.90	11.70		1.24 [0.66-2.26]	
POMC region 5'	rs874401	0.18	CC	73.70	65.60	0.1012	1.00	0.2296
			CT	22.80	32.50		0.63 [0.38-1.00]	
			TT	3.50	2.00		1.57 [0.42-4.96]	
POMC	rs6713532	0.21	TT	69.90	60.00	0.1127	1.00	0.1282
			CT	24.80	35.10		0.61 [0.37-0.96]	
			CC	5.30	4.90		0.94 [0.34-2.26]	
POMC	rs934778	0.30	TT	50.40	46.80	0.6555	1.00	0.699
			CT	40.70	45.50		0.83 [0.54-1.28]	
			CC	8.80	7.80		1.06 [0.47-2.19]	
MC4R region 5'	rs8097783	0.06	GG	89.50	87.60	0.7778	1.00	0.5455
			AG	10.50	12.20		0.83 [0.41-1.56]	
			AA	0.00	0.20			
MC4R region 5'	rs8091237	0.23	CC	54.90	59.70	0.5989	1.00	0.4611
			CG	39.80	34.70		1.25 [0.81-1.92]	
			GG	5.30	5.50		1.05 [0.38-2.50]	

Gene	SNP	MAF[a]	Allele	Obese	Non-Obese	P-value[b]	OR [95% CI]	P-trend[c]
MC4R region 5'	rs1943225	0.26	TT	53.10	58.30	0.3252	1.00	0.6525
			GT	39.80	32.60		1.34 [0.86-2.07]	
			GG	7.10	9.20		0.85 [0.35-1.82]	
MC4R region 5'	rs7228573	0.31	CC	45.90	47.50	0.503	1.00	0.825
			CT	47.70	43.20		1.14 [0.74-1.76]	
			TT	6.30	9.30		0.70 [0.27-1.56]	
MC4R region 5'	rs1943228	0.22	AA	56.90	61.40	0.4261	1.00	0.6171
			AG	40.40	34.30		1.27 [0.82-1.96]	
			GG	2.80	4.30		0.70 [0.16-2.13]	
MC4R	rs8087522	0.32	GG	42.50	45.20	0.5264	1.00	0.9645
			AG	50.40	45.20		1.19 [0.77-1.83]	
			AA	7.10	9.50		0.79 [0.33-1.71]	
MC4R region 3'	rs17066829	0.35	TT	41.60	42.90	0.7242	1.00	0.9011
			AT	47.80	44.20		1.11 [0.72-1.73]	
			AA	10.60	12.80		0.85 [0.41-1.67]	
MC4R region 3'	rs1943226	0.10	TT	85.00	80.50	0.3931	1.00	0.2191
			GT	15.00	18.60		0.73 [0.40-1.26]	
			GG	0.00	0.90			
PPY	rs231471	0.44	AA	39.50	29.90	0.0621	1.00	0.3392
			AG	38.60	50.60		0.58 [0.36-0.92]	
			GG	21.90	19.50		0.85 [0.48-1.48]	
PPY	rs1642603	0.34	CC	46.00	43.40	0.7247	1.00	0.4614
			CT	43.40	43.40		0.94 [0.61-1.46]	
			TT	10.60	13.30		0.75 [0.36-1.46]	
PYY region 5'	rs17611995	0.18	CC	66.70	68.10	0.8208	1.00	0.9245
			AC	29.80	27.40		1.11 [0.70-1.74]	
			AA	3.50	4.40		0.81 [0.23-2.22]	
PYY region 5'	rs497847	0.07	AA	87.60	86.70	0.5218	1.00	0.9523
			AG	11.50	13.10		0.92 [0.48-1.68]	
			GG	0.90	0.20			
PYY	rs9907468	0.10	CC	81.40	80.10	0.5998	1.00	0.6236
			CT	18.60	19.00		0.92 [0.53-1.54]	
			TT	0.00	0.90			
PYY	rs918242	0.34	TT	43.80	43.00	0.8146	1.00	0.6827
			CT	46.40	45.00		1.01 [0.65-1.57]	
			CC	9.80	12.00		0.81 [0.38-1.61]	
PYY	rs1684668	0.24	CC	58.40	57.40	0.9807	1.00	0.8464
			CT	36.30	37.10		0.96 [0.62-1.48]	
			TT	5.30	5.50		0.95 [0.34-2.26]	
PYY	rs1859223	0.15	CC	71.10	71.70	0.7638	1.00	0.9592
			CG	28.10	26.50		1.03 [0.65-1.61]	
			GG	0.90	1.80			
PYY region 3'	rs1662754	0.47	AA	23.90	28.40	0.2685	1.00	0.95
			AT	58.40	49.90		1.39 [0.85-2.32]	
			TT	17.70	21.70		0.97 [0.51-1.82]	
PYY region 3'	rs8079623	0.13	CC	74.60	76.10	0.9068	1.00	0.6876
			CG	23.70	22.60		1.09 [0.67-1.73]	
			GG	1.80	1.30			

Gene	SNP	MAF[a]	Allele	Obese	Non-Obese	P-value[b]	OR [95% CI]	P-trend[c]
LEP	rs2167270	0.40	GG	36.00	36.20	0.8447	1.00	0.738
			AG	45.60	47.60		0.97 [0.61-1.53]	
			AA	18.40	16.20		1.14 [0.62-2.05]	
LEP	rs2278815	0.46	AA	27.20	32.20	0.5427	1.00	0.2784
			AG	47.40	45.60		1.23 [0.76-2.03]	
			GG	25.40	22.10		1.36 [0.77-2.40]	
LEP	rs11763517	0.47	CC	29.80	28.20	0.7577	1.00	0.945
			CT	46.50	50.30		0.87 [0.54-1.42]	
			TT	23.70	21.50		1.04 [0.58-1.84]	
LEP	rs7795794	0.05	GG	89.50	91.40	0.1278	1.00	0.3672
			AG	9.60	8.60		1.25 [0.61-2.40]	
			AA	0.90	0.00			
LEP	rs10954173	0.40	GG	36.00	36.10	0.6991	1.00	0.6587
			AG	44.70	47.80		0.94 [0.59-1.49]	
			AA	19.30	16.20		1.20 [0.66-2.14]	
LEP region 3'	rs10954176	0.47	TT	24.60	30.60	0.1173	1.00	0.8758
			CT	55.30	44.40		1.55 [0.95-2.57]	
			CC	20.20	25.00		1.00 [0.54-1.84]	
LEP region 3'	rs1116656	0.46	GG	27.20	30.80	0.0144	1.00	0.3721
			AG	59.60	45.80		1.48 [0.92-2.40]	
			AA	13.20	23.40		0.64 [0.32-1.22]	
LEPR	rs3790433	0.25	GG	50.90	58.10	0.3229	1.00	0.1334
			AG	40.40	35.80		1.29 [0.83-1.98]	
			AA	8.80	6.20		1.62 [0.71-3.42]	
LEPR	rs4655811	0.34	GG	44.60	42.30	0.8564	1.00	0.5812
			CG	45.50	46.50		0.93 [0.60-1.44]	
			CC	9.80	11.30		0.82 [0.38-1.65]	
LEPR	rs1327120	0.41	GG	32.50	32.70	0.5787	1.00	0.6174
			AG	55.30	51.30		1.08 [0.69-1.72]	
			AA	12.30	16.00		0.77 [0.38-1.49]	
LEPR	rs1327116	0.27	CC	50.40	52.10	0.7634	1.00	0.5888
			AC	42.50	42.60		1.03 [0.67-1.58]	
			AA	7.10	5.30		1.37 [0.55-3.10]	
LEPR	rs1782763	0.05	TT	89.30	91.30	0.5182	1.00	0.5185
			CT	10.70	8.70		1.25 [0.61-2.41]	
LEPR	rs6673324	0.48	AA	21.10	26.00	0.542	1.00	0.4375
			AG	57.00	52.70		1.34 [0.81-2.28]	
			GG	21.90	21.30		1.27 [0.68-2.37]	
LEPR	rs3790428	0.28	CC	50.90	49.00	0.6817	1.00	0.9737
			AC	42.10	45.70		0.89 [0.58-1.36]	
			AA	7.00	5.30		1.26 [0.51-2.85]	
LEPR	rs1137101	0.46	AA	29.80	26.40	0.367	1.00	0.1988
			AG	55.30	53.00		0.92 [0.58-1.49]	
			GG	14.90	20.60		0.64 [0.33-1.20]	
LEPR	rs4655537	0.33	GG	41.20	43.70	0.8253	1.00	0.5467
			AG	48.20	47.30		1.08 [0.70-1.68]	
			AA	10.50	9.00		1.24 [0.59-2.50]	

Gene	SNP	MAF[a]	Allele	Obese	Non-Obese	P-value[b]	OR [95% CI]	P-trend[c]
LEPR	rs3790419	0.22	AA	65.80	60.00	0.5004	1.00	0.3475
			AG	28.90	34.70		0.76 [0.48-1.19]	
			GG	5.30	5.30		0.90 [0.32-2.15]	
LEPR	rs8179183	0.20	GG	62.70	65.40	0.6831	1.00	0.8065
			CG	33.60	29.80		1.17 [0.74-1.83]	
			CC	3.60	4.80		0.79 [0.23-2.16]	
LEPR	rs1938484	0.19	CC	69.30	64.70	0.5503	1.00	0.2901
			AC	28.90	32.20		0.84 [0.53-1.31]	
			AA	1.80	3.10		0.53 [0.08-1.94]	
LEPR	rs1805096	0.39	CC	36.80	37.50	0.9541	1.00	0.9855
			CT	48.20	46.70		1.05 [0.67-1.66]	
			TT	14.90	15.70		0.97 [0.50-1.79]	
ADIPOQ region 5'	rs1648707	0.34	AA	45.90	43.10	0.7352	1.00	0.818
			AC	41.40	45.50		0.85 [0.55-1.33]	
			CC	12.60	11.40		1.04 [0.52-1.98]	
ADIPOQ region 5'	rs10937273	0.44	GG	30.10	31.60	0.9484	1.00	0.7506
			AG	50.40	49.80		1.06 [0.66-1.72]	
			AA	19.50	18.60		1.10 [0.59-1.99]	
ADIPOQ	rs16861194	0.07	AA	89.50	86.70	0.5573	1.00	0.3562
			AG	10.50	12.60		0.77 [0.38-1.43]	
			GG	0.00	0.70			
ADIPOQ	rs822391	0.21	TT	63.20	61.90	0.7309	1.00	0.6241
			CT	33.30	32.70		1.00 [0.64-1.54]	
			CC	3.50	5.30		0.65 [0.19-1.74]	
ADIPOQ	rs16861210	0.09	GG	83.30	83.40	0.9751	1.00	0.9711
			AG	15.80	15.50		1.01 [0.57-1.71]	
			AA	0.90	1.10			
ADIPOQ	rs822395	0.35	AA	47.40	41.40	0.3662	1.00	0.1607
			AC	43.00	44.90		0.84 [0.54-1.29]	
			CC	9.60	13.70		0.61 [0.29-1.21]	
ADIPOQ	rs822396	0.19	AA	68.50	65.20	0.7134	1.00	0.4385
			AG	28.80	30.70		0.89 [0.56-1.41]	
			GG	2.70	4.10		0.63 [0.15-1.93]	
ADIPOQ	rs12495941	0.35	GG	41.20	43.20	0.8475	1.00	0.5893
			GT	44.70	44.60		1.05 [0.68-1.64]	
			TT	14.00	12.20		1.21 [0.62-2.26]	
ADIPOQ	rs17366568	0.12	GG	78.90	77.00	0.9051	1.00	0.6962
			AG	19.30	21.20		0.89 [0.52-1.47]	
			AA	1.80	1.80		0.97 [0.14-3.95]	
ADIPOQ	rs2241766	0.11	TT	85.10	77.80	0.2306	1.00	0.1049
			GT	14.00	21.10		0.62 [0.34-1.05]	
			GG	0.90	1.10			
ADIPOQ	rs1501299	0.28	CC	51.80	51.70	0.9954	1.00	0.9557
			AC	40.40	40.20		1.00 [0.65-1.54]	
			AA	7.90	8.20		0.96 [0.42-2.03]	
ADIPOQ	rs3821799	0.45	CC	37.70	28.50	0.1589	1.00	0.1004
			CT	43.90	50.10		0.66 [0.42-1.05]	
			TT	18.40	21.40		0.65 [0.36-1.15]	

Gene	SNP	MAF[a]	Allele	Obese	Non-Obese	P-value[b]	OR [95% CI]	P-trend[c]
ADIPOQ	rs17366743	0.11	TT	84.10	81.70	0.8112	1.00	0.6611
			CT	11.50	13.80		0.81 [0.41-1.49]	
			CC	4.40	4.50		0.97 [0.31-2.46]	
ADIPOQ	rs6773957	0.39	GG	42.10	36.80	0.5817	1.00	0.3651
			AG	43.90	47.90		0.80 [0.51-1.25]	
			AA	14.00	15.30		0.80 [0.42-1.48]	
ADIPOQ	rs1063539	0.13	GG	80.50	72.70	0.1881	1.00	0.0755
			CG	19.50	26.60		0.64 [0.38-1.06]	
			CC	0.00	0.70			
RETN region 5'	rs2081075	0.27	GG	59.30	54.40	0.5533	1.00	0.5421
			AG	31.00	36.40		0.78 [0.49-1.22]	
			AA	9.70	9.10		0.98 [0.46-1.95]	
RETN	rs1862513	0.28	GG	54.90	50.30	0.6693	1.00	0.3745
			CG	38.90	42.20		0.85 [0.55-1.30]	
			CC	6.20	7.50		0.76 [0.30-1.70]	
RETN	rs3745367	0.23	GG	64.90	56.40	0.2546	1.00	0.1083
			AG	31.60	38.70		0.71 [0.45-1.10]	
			AA	3.50	4.90		0.63 [0.18-1.70]	
RETN	rs3745369	0.50	GG	25.40	26.30	0.86	1.00	0.8851
			CG	50.90	48.10		1.09 [0.67-1.82]	
			CC	23.70	25.60		0.96 [0.53-1.71]	
PPARγ	rs2972164	0.47	CC	24.10	28.10	0.5491	1.00	0.2757
			CT	51.80	51.80		1.17 [0.71-1.95]	
			TT	24.10	20.10		1.40 [0.77-2.54]	
PPARγ	rs6809631	0.29	AA	53.50	50.00	0.5309	1.00	0.3255
			AT	40.40	40.70		0.93 [0.60-1.42]	
			TT	6.10	9.30		0.62 [0.24-1.36]	
PPARγ	rs17793951	0.31	AA	44.10	47.80	0.3464	1.00	0.2421
			AG	42.30	43.30		1.06 [0.68-1.65]	
			GG	13.50	9.00		1.63 [0.82-3.14]	
PPARγ	rs12497191	0.14	AA	78.10	73.20	0.5658	1.00	0.2914
			AG	20.20	24.30		0.78 [0.46-1.27]	
			GG	1.80	2.40		0.68 [0.10-2.58]	
PPARγ	rs1801282	0.15	CC	72.80	72.60	0.9028	1.00	0.9392
			CG	24.60	25.40		0.96 [0.59-1.54]	
			GG	2.60	2.00		1.32 [0.29-4.53]	
PPARγ	rs12629751	0.09	CC	83.90	82.80	0.9115	1.00	0.7262
			CT	15.20	15.80		0.92 [0.51-1.59]	
			TT	0.90	1.40			
PPARγ	rs2028759	0.48	AA	29.50	26.40	0.6772	1.00	0.8333
			AG	45.50	50.10		0.81 [0.50-1.34]	
			GG	25.00	23.50		0.95 [0.54-1.68]	
PPARγ	rs1151996	0.36	TT	38.60	41.70	0.8223	1.00	0.6575
			GT	48.20	45.20		1.15 [0.74-1.80]	
			GG	13.20	13.10		1.09 [0.55-2.06]	
PPARγ	rs7645903	0.18	AA	67.90	66.50	0.7513	1.00	0.6389
			AT	30.40	30.40		0.98 [0.62-1.53]	
			TT	1.80	3.10		0.56 [0.09-2.08]	

Gene	SNP	MAF[a]	Allele	Obese	Non-Obese	P-value[b]	OR [95% CI]	P-trend[c]
PPARγ	rs1175540	0.34	CC	39.80	44.40	0.3925	1.00	0.7579
			CA	51.30	44.40		1.29 [0.84-2.00]	
			AA	8.80	11.30		0.88 [0.39-1.79]	
PPARγ	rs6782475	0.17	TT	69.00	68.10	0.6231	1.00	0.6289
			GT	29.20	28.30		1.02 [0.64-1.59]	
			GG	1.80	3.60		0.49 [0.08-1.77]	
PPARγ	rs3856806	0.14	CC	72.60	73.80	0.4017	1.00	0.5333
			CT	23.90	24.60		0.99 [0.60-1.59]	
			CC	3.50	1.60		2.30 [0.59-7.80]	
PPARγC1	rs6821591	0.48	CC	21.90	25.80	0.6696	1.00	0.5795
			CT	56.10	52.30		1.26 [0.76-2.14]	
			TT	21.90	21.90		1.18 [0.64-2.19]	
PPARγC1	rs3736265	0.05	GG	89.50	90.20	0.8394	1.00	0.8647
			AG	10.50	9.50		1.09 [0.53-2.07]	
			AA	0.00	0.20			
PPARγC1	rs3755863	0.40	GG	35.10	34.70	0.8476	1.00	0.7283
			AG	51.80	50.00		1.02 [0.66-1.62]	
			AA	13.20	15.30		0.85 [0.43-1.62]	
PPARγC1	rs8192678	0.35	GG	39.80	43.60	0.7172	1.00	0.6385
			AG	48.70	44.50		1.20 [0.77-1.87]	
			AA	11.50	11.90		1.05 [0.51-2.05]	
PPARγC1	rs2970849	0.33	TT	48.20	42.50	0.4445	1.00	0.2045
			CT	43.90	46.50		0.83 [0.54-1.28]	
			CC	7.90	10.90		0.64 [0.28-1.32]	
PPARγC1	rs2932976	0.27	GG	59.60	51.80	0.2763	1.00	0.1101
			AG	35.10	40.30		0.76 [0.49-1.16]	
			AA	5.30	8.00		0.57 [0.21-1.33]	
PPARγC1	rs4697046	0.33	TT	39.50	45.60	0.3565	1.00	0.1567
			CT	46.50	44.20		1.21 [0.78-1.89]	
			CC	14.00	10.20		1.58 [0.81-3.01]	
PPARγC1	rs4235308	0.41	TT	30.10	34.80	0.3145	1.00	0.1555
			CT	49.60	50.30		1.14 [0.71-1.84]	
			CC	20.40	14.90		1.59 [0.86-2.88]	
PPARγC1	rs7677000	0.16	CC	71.90	69.90	0.9124	1.00	0.6985
			CT	26.30	28.30		0.90 [0.56-1.43]	
			TT	1.80	1.80		0.96 [0.14-3.93]	
PPARγC1	rs4469064	0.08	AA	81.60	84.10	0.7239	1.00	0.4678
			AG	17.50	15.50		1.19 [0.69-2.01]	
			GG	0.90	0.40			
PPARγC1	rs3774902	0.05	CC	91.20	89.60	0.7184	1.00	0.5342
			CT	8.80	10.00		0.83 [0.38-1.63]	
			TT	0.00	0.40			

[a] minor allele frequency; [b] p-value of the main effect models incorporating SNPs as categorical variables with two or three categories; [c] p-value of the main effect models assuming additive genetic effects.

B Supplementary Material - Metabolomics and Fat Free Mass

Table B1: Full biochemical names, abbreviation, mean ± standard deviation of all metabolite concentrations measured in µmol/l with the Biocrates Absolute*IDQ* kits p150 (KORA F4, $n = 890$) and p180 (KORA S4, $n = 965$) *(Jourdan et al., 2012).*

Abbrevation	Full biochemical name	KORA S4 Mean ± SD	KORA F4 Mean ± SD
C0	Carnitine	40.52 ± 8.49	35.05 ± 7.36
C2	Acetylcarnitine	8.62 ± 2.86	8.08 ± 2.78
C3	Propionylcarnitine	0.47 ± 0.15	0.38 ± 0.12
C3-OH	Hydroxypropionylcarnitine	0.12 ± 0.06	*
C3:1	Propenonylcarnitine	*	*
C4	Butyrylcarnitine	0.22 ± 0.10	0.22 ± 0.09
C4-OH (C3-DC)	Hydroxybutyrylcarnitine	0.06 ± 0.02	0.09 ± 0.05
C4:1	Butenylcarnitine	0.02 ± 0.01	*
C5	Valerylcarnitine	0.16 ± 0.06	0.11 ± 0.04
C5-DC (C6-OH)	Glutarylcarnitine	*	0.03 ± 0.01
C5-M-DC	Methylglutarylcarnitine	*	0.03 ± 0.01
C5-OH (C3-DC-M)	Hydroxyvalerylcarnitine (Methylmalonylcarnitine)	0.03 ± 0.01	0.04 ± 0.02
C5:1	Tiglylcarnitine	0.05 ± 0.01	0.03 ± 0.01
C5:1-DC	Glutaconylcarnitine	*	0.02 ± 0.01
C6 (C4:1-DC)	Hexanoylcarnitine	0.09 ± 0.03	0.07 ± 0.03
C6:1	Hexenoylcarnitine	0.02 ± 0.01	0.02 ± 0.01
C7-DC	Pimelylcarnitine	0.05 ± 0.02	0.05 ± 0.02
C8	Octanoylcarnitine	0.26 ± 0.10	0.22 ± 0.09
C8:1	Octenoylcarnitine	∼	0.09 ± 0.04
C9	Nonaylcarnitine	0.04 ± 0.02	0.05 ± 0.02
C10	Decanoylcarnitine	0.38 ± 0.17	0.36 ± 0.15
C10:1	Decenoylcarnitine	0.18 ± 0.06	0.17 ± 0.06
C10:2	Decadienylcarnitine	0.04 ± 0.01	0.04 ± 0.01
C12	Dodecanoylcarnitine	0.16 ± 0.06	0.13 ± 0.05
C12-DC	Dodecanedioylcarnitine	0.07 ± 0.01	0.06 ± 0.01
C12:1	Dodecenoylcarnitine	0.17 ± 0.06	0.15 ± 0.05
C14	Tetradecanoylcarnitine	0.06 ± 0.02	0.05 ± 0.01
C14:1	Tetradecenoylcarnitine	0.15 ± 0.05	0.15 ± 0.05
C14:1-OH	Hydroxytetradecenoylcarnitine	0.02 ± 0.01	0.01 ± 0.00
C14:2	Tetradecadienylcarnitine	0.04 ± 0.02	0.03 ± 0.01
C14:2-OH	Hydroxytetradecadienylcarnitine	*	0.01 ± 0.00
C16	Hexadecanoylcarnitine	0.14 ± 0.03	0.12 ± 0.03
C16-OH	Hydroxyhexadecanoylcarnitine	*	*
C16:1	Hexadecenoylcarnitine	0.04 ± 0.01	0.04 ± 0.01
C16:1-OH	Hydroxyhexadecenoylcarnitine	*	0.01 ± 0.00
C16:2	Hexadecadienylcarnitine	*	*
C16:2-OH	Hydroxyhexadecadienylcarnitine	*	0.01 ± 0.00
C18	Octadecanoylcarnitine	0.06 ± 0.01	0.05 ± 0.01
C18:1	Octadecenoylcarnitine	0.14 ± 0.04	0.13 ± 0.04
C18:1-OH	Hydroxyoctadecenoylcarnitine	*	*
C18:2	Octadecadienylcarnitine	0.05 ± 0.02	0.05 ± 0.01
Ala	Alanine	417.99 ± 101.4	∼

Abbrevation	Full biochemical name	KORA S4	KORA F4
		Mean ± SD	Mean ± SD
Arg	Arginine	126.87 ± 26.78	115.67 ± 17.45
Asn	Asparagine	46.18 ± 8.31	∼
Asp	Aspartate	29.76 ± 9.77	∼
Cit	Citrulline	34.64 ± 9.16	∼
Gln	Glutamine	581.2 ± 113.95	627.31 ± 91.44
Glu	Glutamate	80.13 ± 32.04	∼
Gly	Glycine	264.35 ± 73.19	314.88 ± 83.47
His	Histidine	82.87 ± 14.75	99.86 ± 16.47
Ile	Isoleucine	72.14 ± 20.22	∼
Leu	Leucine	160.51 ± 44.33	∼
Lys	Lysine	166.44 ± 36.59	∼
Met	Methionine	23.86 ± 5.21	32.01 ± 5.69
Orn	Ornithine	58.97 ± 14.83	81.5 ± 18.59
Phe	Phenylalanine	76.73 ± 17.19	61.17 ± 10.20
Pro	Proline	193.96 ± 58.92	171.51 ± 51.25
Ser	Serine	127.36 ± 28.85	130.82 ± 24.44
Thr	Threonine	120.75 ± 31.79	107.56 ± 24.41
Trp	Tryptophan	60.17 ± 12.43	83.28 ± 9.85
Tyr	Tyrosine	72.09 ± 20.06	84.6 ± 17.27
Val	Valine	227.26 ± 53.13	273.25 ± 59.21
xLeu	Leucine/Isoleucine	∼	210.42 ± 43.19
Ac Orn	Acetylornithine	0.74 ± 0.41	∼
ADMA	Asymmetric dimethylarginine#	0.56 ± 0.13	∼
SDMA	Symmetric Dimethylarginine	0.76 ± 0.24	∼
total DMA	Sum of ADMA and SDMA	1.21 ± 0.23	∼
alpha AAA	alpha-Aminoadipic acid	0.68 ± 0.27	∼
Carnosine	Carnosine	*	∼
Creatinine	Creatinine	75.04 ± 18.99	∼
Histamine	Histamine#	0.4 ± 0.17	∼
Kynurenine	Kynurenine	2.88 ± 0.69	∼
Met SO	Methioninesulfoxide	0.78 ± 0.24	∼
Nitro-Tyr	Nitrotyrosine	*	∼
OH-Pro	Hydroxyproline	*	∼
PEA	Phenylethylamine	*	∼
Putrescine	Putrescine#	0.15 ± 0.05	∼
Sarcosine	Sarcosine	*	∼
Serotonin	Serotonin#	0.7 ± 0.34	∼
Spermidine	Spermidine	0.27 ± 0.07	∼
Spermine	Spermine	*	∼
Taurine	Taurine	93.66 ± 23.95	∼
PC aa C24:0	Phosphatidylcholine diacyl C24:0#	0.09 ± 0.04	0.15 ± 0.08
PC aa C26:0	Phosphatidylcholine diacyl C26:0	0.74 ± 0.24	1.06 ± 0.49
PC aa C28:1	Phosphatidylcholine diacyl C28:1	3.62 ± 0.84	3.43 ± 0.79
PC aa C30:0	Phosphatidylcholine diacyl C30:0	5.95 ± 1.67	4.83 ± 1.54
PC aa C30:2	Phosphatidylcholine diacyl C30:2	*	*
PC aa C32:0	Phosphatidylcholine diacyl C32:0	14.98 ± 2.78	15.39 ± 3.43
PC aa C32:1	Phosphatidylcholine diacyl C32:1	21.17 ± 10.62	21.95 ± 11.38
PC aa C32:2	Phosphatidylcholine diacyl C32:2	4.42 ± 1.63	4.05 ± 1.72
PC aa C32:3	Phosphatidylcholine diacyl C32:3	0.55 ± 0.14	0.49 ± 0.12

Abbrevation	Full biochemical name	KORA S4	KORA F4
		Mean ± SD	Mean ± SD
PC aa C34:1	Phosphatidylcholine diacyl C34:1	223.91 ± 46.33	243.79 ± 61.88
PC aa C34:2	Phosphatidylcholine diacyl C34:2	367.86 ± 48.54	400.11 ± 93.65
PC aa C34:3	Phosphatidylcholine diacyl C34:3	18.5 ± 5.14	18.42 ± 5.45
PC aa C34:4	Phosphatidylcholine diacyl C34:4	2.21 ± 0.77	2.29 ± 0.82
PC aa C36:0	Phosphatidylcholine diacyl C36:0	3.00 ± 0.77	2.76 ± 0.86
PC aa C36:1	Phosphatidylcholine diacyl C36:1	54.06 ± 13.95	54.48 ± 13.27
PC aa C36:2	Phosphatidylcholine diacyl C36:2	256.73 ± 42.39	235.95 ± 42.37
PC aa C36:3	Phosphatidylcholine diacyl C36:3	153.12 ± 29.82	151.14 ± 32.7
PC aa C36:4	Phosphatidylcholine diacyl C36:4	208.91 ± 44.39	219.15 ± 54.41
PC aa C36:5	Phosphatidylcholine diacyl C36:5	30.8 ± 14.81	29.88 ± 14.32
PC aa C36:6	Phosphatidylcholine diacyl C36:6	1.13 ± 0.43	1.15 ± 0.46
PC aa C38:0	Phosphatidylcholine diacyl C38:0	3.37 ± 0.87	3.30 ± 0.89
PC aa C38:1	Phosphatidylcholine diacyl C38:1	1.38 ± 0.41	*
PC aa C38:3	Phosphatidylcholine diacyl C38:3	57.77 ± 14.01	53.25 ± 12.82
PC aa C38:4	Phosphatidylcholine diacyl C38:4	117.93 ± 29.14	117.39 ± 28.78
PC aa C38:5	Phosphatidylcholine diacyl C38:5	63.10 ± 14.94	63.04 ± 15.64
PC aa C38:6	Phosphatidylcholine diacyl C38:6	90.3 ± 26.3	91.23 ± 27.32
PC aa C40:1	Phosphatidylcholine diacyl C40:1	0.42 ± 0.09	0.47 ± 0.10
PC aa C40:2	Phosphatidylcholine diacyl C40:2	0.37 ± 0.10	0.36 ± 0.10
PC aa C40:3	Phosphatidylcholine diacyl C40:3	0.69 ± 0.15	0.66 ± 0.15
PC aa C40:4	Phosphatidylcholine diacyl C40:4	4.16 ± 1.2	4.13 ± 1.16
PC aa C40:5	Phosphatidylcholine diacyl C40:5	12.79 ± 3.53	11.52 ± 3.14
PC aa C40:6	Phosphatidylcholine diacyl C40:6	32.3 ± 10.00	28.37 ± 9.35
PC aa C42:0	Phosphatidylcholine diacyl C42:0	0.56 ± 0.16	0.61 ± 0.17
PC aa C42:1	Phosphatidylcholine diacyl C42:1	0.27 ± 0.07	0.30 ± 0.08
PC aa C42:2	Phosphatidylcholine diacyl C42:2	0.20 ± 0.05	0.22 ± 0.06
PC aa C42:4	Phosphatidylcholine diacyl C42:4	0.21 ± 0.04	0.22 ± 0.05
PC aa C42:5	Phosphatidylcholine diacyl C42:5	0.44 ± 0.13	0.43 ± 0.13
PC aa C42:6	Phosphatidylcholine diacyl C42:6	0.60 ± 0.13	0.63 ± 0.14
PC ae C30:0	Phosphatidylcholine acyl-akyl C30:0	0.46 ± 0.13	0.48 ± 0.14
PC ae C30:1	Phosphatidylcholine acyl-akyl C30:1	*	*
PC ae C30:2	Phosphatidylcholine acyl-akyl C30:2	0.13 ± 0.04	0.16 ± 0.04
PC ae C32:1	Phosphatidylcholine acyl-akyl C32:1	2.83 ± 0.55	2.95 ± 0.62
PC ae C32:2	Phosphatidylcholine acyl-akyl C32:2	0.72 ± 0.16	0.77 ± 0.17
PC ae C34:0	Phosphatidylcholine acyl-akyl C34:0	1.69 ± 0.43	1.77 ± 0.46
PC ae C34:1	Phosphatidylcholine acyl-akyl C34:1	10.58 ± 2.21	10.83 ± 2.39
PC ae C34:2	Phosphatidylcholine acyl-akyl C34:2	12.19 ± 2.95	13.16 ± 3.39
PC ae C34:3	Phosphatidylcholine acyl-akyl C34:3	7.66 ± 2.14	8.74 ± 2.45
PC ae C36:0	Phosphatidylcholine acyl-akyl C36:0	0.93 ± 0.25	1.08 ± 0.34
PC ae C36:1	Phosphatidylcholine acyl-akyl C36:1	8.91 ± 2.08	8.51 ± 1.96
PC ae C36:2	Phosphatidylcholine acyl-akyl C36:2	15.33 ± 3.88	15.72 ± 4.00
PC ae C36:3	Phosphatidylcholine acyl-akyl C36:3	8.04 ± 1.85	8.83 ± 2.10
PC ae C36:4	Phosphatidylcholine acyl-akyl C36:4	20.11 ± 4.74	21.07 ± 5.53
PC ae C36:5	Phosphatidylcholine acyl-akyl C36:5	13.02 ± 3.2	14.02 ± 3.60
PC ae C38:0	Phosphatidylcholine acyl-akyl C38:0	2.24 ± 0.67	2.55 ± 0.78
PC ae C38:1	Phosphatidylcholine acyl-akyl C38:1	0.63 ± 0.26	0.83 ± 0.29
PC ae C38:2	Phosphatidylcholine acyl-akyl C38:2	2.14 ± 0.48	2.20 ± 0.51
PC ae C38:3	Phosphatidylcholine acyl-akyl C38:3	4.29 ± 0.99	4.35 ± 0.94
PC ae C38:4	Phosphatidylcholine acyl-akyl C38:4	15.49 ± 3.16	15.88 ± 3.38

Abbrevation	Full biochemical name	KORA S4	KORA F4
		Mean ± SD	Mean ± SD
PC ae C38:5	Phosphatidylcholine acyl-akyl C38:5	19.36 ± 3.83	20.17 ± 4.55
PC ae C38:6	Phosphatidylcholine acyl-akyl C38:6	8.77 ± 2.11	8.82 ± 2.21
PC ae C40:0	Phosphatidylcholine acyl-akyl C40:0 #	∼	10.31 ± 1.66
PC ae C40:1	Phosphatidylcholine acyl-akyl C40:1	1.60 ± 0.37	1.72 ± 0.40
PC ae C40:2	Phosphatidylcholine acyl-akyl C40:2	2.14 ± 0.49	2.12 ± 0.48
PC ae C40:3	Phosphatidylcholine acyl-akyl C40:3	1.20 ± 0.24	1.16 ± 0.23
PC ae C40:4	Phosphatidylcholine acyl-akyl C40:4	2.71 ± 0.51	2.62 ± 0.48
PC ae C40:5	Phosphatidylcholine acyl-akyl C40:5	3.71 ± 0.70	3.62 ± 0.65
PC ae C40:6	Phosphatidylcholine acyl-akyl C40:6	5.48 ± 1.35	5.16 ± 1.31
PC ae C42:0	Phosphatidylcholine acyl-akyl C42:0	0.52 ± 0.10	0.51 ± 0.12
PC ae C42:1	Phosphatidylcholine acyl-akyl C42:1	0.38 ± 0.09	0.38 ± 0.09
PC ae C42:2	Phosphatidylcholine acyl-akyl C42:2	0.64 ± 0.14	0.69 ± 0.15
PC ae C42:3	Phosphatidylcholine acyl-akyl C42:3	0.85 ± 0.19	0.90 ± 0.20
PC ae C42:4	Phosphatidylcholine acyl-akyl C42:4	0.96 ± 0.22	1.04 ± 0.24
PC ae C42:5	Phosphatidylcholine acyl-akyl C42:5	2.21 ± 0.46	2.40 ± 0.49
PC ae C44:3	Phosphatidylcholine acyl-akyl C44:3	0.13 ± 0.04	0.11 ± 0.03
PC ae C44:4	Phosphatidylcholine acyl-akyl C44:4	0.38 ± 0.10	0.44 ± 0.11
PC ae C44:5	Phosphatidylcholine acyl-akyl C44:5	1.75 ± 0.47	2.16 ± 0.54
PC ae C44:6	Phosphatidylcholine acyl-akyl C44:6	1.26 ± 0.34	1.40 ± 0.37
lysoPC a C14:0	lysoPhosphatidylcholine acyl C14:0#	6.29 ± 0.79	3.23 ± 0.86
lysoPC a C16:0	lysoPhosphatidylcholine acyl C16:0	122.98 ± 25.91	96.65 ± 20.18
lysoPC a C16:1	lysoPhosphatidylcholine acyl C16:1	3.72 ± 1.17	2.97 ± 1.04
lysoPC a C17:0	lysoPhosphatidylcholine acyl C17:0	2.10 ± 0.68	1.81 ± 0.52
lysoPC a C18:0	lysoPhosphatidylcholine acyl C18:0	32.73 ± 8.09	26.91 ± 6.16
lysoPC a C18:1	lysoPhosphatidylcholine acyl C18:1	21.61 ± 6.10	20.26 ± 5.87
lysoPC a C18:2	lysoPhosphatidylcholine acyl C18:2	28.46 ± 9.04	29.29 ± 9.85
lysoPC a C6:0	lysoPhosphatidylcholine acyl C6:0	∼	*
lysoPC a C20:3	lysoPhosphatidylcholine acyl C20:3	2.28 ± 0.66	2.46 ± 0.73
lysoPC a C20:4	lysoPhosphatidylcholine acyl C20:4	6.14 ± 1.83	6.94 ± 2.19
lysoPC a C24:0	lysoPhosphatidylcholine acyl C24:0	0.20 ± 0.06	0.37 ± 0.11
lysoPC a C26:0	lysoPhosphatidylcholine acyl C26:0#	0.30 ± 0.14	*
lysoPC a C26:1	lysoPhosphatidylcholine acyl C26:1#	1.67 ± 0.17	2.02 ± 0.25
lysoPC a C28:0	lysoPhosphatidylcholine acyl C28:0#	0.33 ± 0.11	0.50 ± 0.21
lysoPC a C28:1	lysoPhosphatidylcholine acyl C28:1	0.47 ± 0.15	0.63 ± 0.22
SM C16:0	Sphingomyelin C16:0	151.19 ± 23.84	108.15 ± 21.38
SM C16:1	Sphingomyelin C16:1	23.93 ± 4.67	16.07 ± 3.61
SM C18:0	Sphingomyelin C18:0	33.23 ± 6.89	23.23 ± 5.00
SM C18:1	Sphingomyelin C18:1	16.75 ± 4.16	11.25 ± 2.98
SM C20:2	Sphingomyelin C20:2	0.67 ± 0.23	0.38 ± 0.12
SM C22:3	Sphingomyelin C22:3	*	*
SM C24:0	Sphingomyelin C24:0	30.53 ± 5.71	22.14 ± 5.13
SM C24:1	Sphingomyelin C24:1	76.96 ± 14.39	53.14 ± 12.02
SM C26:0	Sphingomyelin C26:0#	*	0.18 ± 0.05
SM C26:1	Sphingomyelin C26:1	0.64 ± 0.19	0.42 ± 0.13
SM (OH) C14:1	Hydroxysphingomyelin C14:1	9.54 ± 2.56	6.38 ± 1.86
SM (OH) C16:1	Hydroxysphingomyelin C16:1	5.19 ± 1.37	3.42 ± 0.89
SM (OH) C22:1	Hydroxysphingomyelin C22:1	20.42 ± 4.61	13.83 ± 3.50
SM (OH) C22:2	Hydroxysphingomyelin C22:2	16.56 ± 4.17	11.74 ± 3.14
SM (OH) C24:1	Hydroxysphingomyelin C24:1	2.00 ± 0.49	1.37 ± 0.36

Abbrevation	Full biochemical name	KORA S4 Mean ± SD	KORA F4 Mean ± SD
H1	Hexose	5300.07 ± 891.29	5005.34 ± 670.72

Metabolites excluded from the analyses are marked with * and their mean and standard deviation are not given. Metabolites marked with ∼ were not part of the other kit. # results with these metabolites require careful interpretation since the number of samples below detection and/or the coefficient of variation across all plates is relatively high.

Table B2: Metabolic traits significantly associated with FFMI[a] in a linear regression model adjusted for age, and sex (α = 5%, p-gain > 170) in the KORA S4 sample *(Jourdan et al., 2012)*.

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
Val	227.26	53.13	0.15	$2.97\text{x}10^{-18}$	$4.75\text{x}10^{-16}$	0.16	
Glu	80.13	32.04	0.15	$7.60\text{x}10^{-18}$	$1.22\text{x}10^{-15}$	0.11	
Ile	72.14	20.22	0.12	$1.23\text{x}10^{-13}$	$1.96\text{x}10^{-11}$	0.22	
Tyr	72.09	20.06	0.13	$2.98\text{x}10^{-12}$	$4.77\text{x}10^{-10}$	0.06	
Leu	160.51	44.33	0.11	$1.61\text{x}10^{-10}$	$2.57\text{x}10^{-08}$	0.18	
Phe	76.73	17.19	0.11	$1.58\text{x}10^{-09}$	$2.53\text{x}10^{-07}$	0.05	
Ala	417.99	101.4	0.10	$5.59\text{x}10^{-08}$	$8.95\text{x}10^{-06}$	0.03	
Trp	60.17	12.43	0.07	$4.85\text{x}10^{-05}$	$7.77\text{x}10^{-03}$	0.07	
Pro	193.96	58.92	0.08	$1.23\text{x}10^{-05}$	$1.97\text{x}10^{-03}$	0.14	
Met	23.86	5.21	0.07	$1.17\text{x}10^{-04}$	$1.86\text{x}10^{-02}$	0.08	
Lys	166.44	36.59	0.07	$1.18\text{x}10^{-04}$	$1.88\text{x}10^{-02}$	0.01	
Σ BCAAs	459.91	113.06	0.13	$1.30\text{x}10^{-15}$	$2.07\text{x}10^{-13}$	0.19	
Σ aromatic AAs	208.98	43.75	0.12	$2.11\text{x}10^{-11}$	$3.37\text{x}10^{-09}$	0.07	
Gln/Val	2.64	0.6	-0.19	$4.48\text{x}10^{-28}$	$7.17\text{x}10^{-26}$	0.18	$6.63\text{x}10^{+09}$
Asn/Val	0.21	0.05	-0.18	$1.12\text{x}10^{-26}$	$1.80\text{x}10^{-24}$	0.17	$2.65\text{x}10^{+08}$
His/Val	0.38	0.07	-0.17	$1.22\text{x}10^{-23}$	$1.95\text{x}10^{-21}$	0.21	$2.43\text{x}10^{+05}$
Glu/Gly	0.33	0.17	0.16	$4.77\text{x}10^{-22}$	$7.64\text{x}10^{-20}$	0.19	$1.59\text{x}10^{+04}$
Asn/Ile	0.68	0.19	-0.16	$5.17\text{x}10^{-22}$	$8.27\text{x}10^{-20}$	0.23	$2.37\text{x}10^{+08}$
Asn/Glu	0.67	0.29	-0.17	$1.17\text{x}10^{-21}$	$1.87\text{x}10^{-19}$	0.11	$6.49\text{x}10^{+03}$
Gln/Tyr	8.47	2.16	-0.17	$1.83\text{x}10^{-21}$	$2.93\text{x}10^{-19}$	0.10	$1.63\text{x}10^{+09}$
Asn/Tyr	0.68	0.18	-0.17	$6.16\text{x}10^{-21}$	$9.85\text{x}10^{-19}$	0.10	$4.85\text{x}10^{+08}$
Gln/Ile	8.53	2.37	-0.15	$1.20\text{x}10^{-20}$	$1.92\text{x}10^{-18}$	0.23	$1.02\text{x}10^{+07}$
Asn/Leu	0.30	0.08	-0.15	$1.75\text{x}10^{-18}$	$2.81\text{x}10^{-16}$	0.19	$9.15\text{x}10^{+07}$
Gly/Tyr	3.89	1.38	-0.15	$7.44\text{x}10^{-18}$	$1.19\text{x}10^{-15}$	0.17	$4.01\text{x}10^{+05}$
Gly/Phe	3.55	1.08	-0.14	$1.03\text{x}10^{-17}$	$1.65\text{x}10^{-15}$	0.19	$1.53\text{x}10^{+08}$
Gln/Leu	3.81	1.02	-0.14	$3.20\text{x}10^{-17}$	$5.12\text{x}10^{-15}$	0.19	$5.02\text{x}10^{+06}$
Asn/Phe	0.62	0.14	-0.15	$4.14\text{x}10^{-17}$	$6.62\text{x}10^{-15}$	0.08	$3.82\text{x}10^{+07}$
Gly/Ile	3.96	1.64	-0.13	$1.00\text{x}10^{-16}$	$1.61\text{x}10^{-14}$	0.30	$1.22\text{x}10^{+03}$
His/Tyr	1.20	0.27	-0.14	$5.94\text{x}10^{-16}$	$9.51\text{x}10^{-14}$	0.09	$5.02\text{x}10^{+03}$
Ala/Asn	9.20	2.38	0.15	$8.82\text{x}10^{-16}$	$1.41\text{x}10^{-13}$	0.07	$6.34\text{x}10^{+07}$
Gly/Leu	1.76	0.69	-0.12	$9.16\text{x}10^{-15}$	$1.46\text{x}10^{-12}$	0.29	$1.75\text{x}10^{+04}$
Gln/Phe	7.83	1.85	-0.14	$3.55\text{x}10^{-14}$	$5.69\text{x}10^{-12}$	0.06	$4.44\text{x}10^{+04}$
Asn/Met	1.98	0.37	-0.13	$5.83\text{x}10^{-13}$	$9.32\text{x}10^{-11}$	0.11	$2.00\text{x}10^{+08}$
Ala/Gly	1.68	0.57	0.12	$7.14\text{x}10^{-12}$	$1.14\text{x}10^{-09}$	0.11	$7.83\text{x}10^{+03}$
Gln/Lys	3.57	0.71	-0.12	$7.34\text{x}10^{-12}$	$1.17\text{x}10^{-09}$	0.05	$1.60\text{x}10^{+07}$
Asn/Lys	0.29	0.06	-0.12	$7.36\text{x}10^{-11}$	$1.18\text{x}10^{-08}$	0.04	$1.60\text{x}10^{+06}$
Ala/Gln	0.74	0.20	0.12	$9.21\text{x}10^{-11}$	$1.47\text{x}10^{-08}$	0.04	$6.07\text{x}10^{+02}$
Gly/Trp	4.53	1.43	-0.11	$1.91\text{x}10^{-10}$	$3.06\text{x}10^{-08}$	0.20	$2.54\text{x}10^{+05}$
Gln/Met	24.99	5.09	-0.11	$2.70\text{x}10^{-10}$	$4.31\text{x}10^{-08}$	0.09	$4.32\text{x}10^{+05}$
Gln/Pro	3.19	0.87	-0.11	$3.22\text{x}10^{-10}$	$5.16\text{x}10^{-08}$	0.13	$3.82\text{x}10^{+04}$
Asn/Trp	0.79	0.17	-0.11	$3.76\text{x}10^{-10}$	$6.02\text{x}10^{-08}$	0.06	$1.29\text{x}10^{+05}$
Gly/Lys	1.64	0.50	-0.11	$5.33\text{x}10^{-10}$	$8.52\text{x}10^{-08}$	0.10	$2.21\text{x}10^{+05}$
Gly/Pro	1.47	0.59	-0.10	$7.17\text{x}10^{-10}$	$1.15\text{x}10^{-07}$	0.24	$1.72\text{x}10^{+04}$
Gly/Met	11.46	3.64	-0.10	$7.94\text{x}10^{-10}$	$1.27\text{x}10^{-07}$	0.22	$1.47\text{x}10^{+05}$

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
Asn/Pro	0.25	0.07	-0.11	$8.12\text{x}10^{-10}$	$1.30\text{x}10^{-07}$	0.13	$1.52\text{x}10^{+04}$
Gln/Trp	9.91	2.26	-0.11	$1.32\text{x}10^{-09}$	$2.12\text{x}10^{-07}$	0.07	$3.67\text{x}10^{+04}$
Asp/Gly	0.12	0.04	0.10	$7.07\text{x}10^{-09}$	$1.13\text{x}10^{-06}$	0.06	$6.18\text{x}10^{+04}$
Asn/Asp	1.72	0.67	-0.09	$1.66\text{x}10^{-06}$	$2.66\text{x}10^{-04}$	0.03	$9.48\text{x}10^{+02}$
Gln/Orn	10.22	2.28	-0.08	$2.22\text{x}10^{-05}$	$3.55\text{x}10^{-03}$	0.02	$6.32\text{x}10^{+02}$
Gln/His	7.07	1.08	-0.08	$3.01\text{x}10^{-05}$	$4.82\text{x}10^{-03}$	0.03	$4.66\text{x}10^{+02}$
Arg/Gln	0.22	0.04	0.07	$5.45\text{x}10^{-05}$	$8.72\text{x}10^{-03}$	0.02	$2.58\text{x}10^{+02}$
Asn/Orn	0.82	0.20	-0.07	$8.86\text{x}10^{-05}$	$1.42\text{x}10^{-02}$	0.03	$4.40\text{x}10^{+02}$
Arg/Asn	2.80	0.64	0.07	$1.37\text{x}10^{-04}$	$2.19\text{x}10^{-02}$	0.02	$2.85\text{x}10^{+02}$
Σ BCAAs/ Σ glucogenic AAs	0.58	0.14	0.10	$9.34\text{x}10^{-11}$	$1.49\text{x}10^{-08}$	0.26	
C5	0.16	0.06	0.09	$2.18\text{x}10^{-07}$	$3.49\text{x}10^{-05}$	0.17	
C3	0.47	0.15	0.09	$3.03\text{x}10^{-07}$	$4.85\text{x}10^{-05}$	0.13	
C0	40.52	8.49	0.07	$7.45\text{x}10^{-05}$	$1.19\text{x}10^{-02}$	0.13	
C18	0.06	0.01	-0.06	$2.47\text{x}10^{-04}$	$3.96\text{x}10^{-02}$	0.10	
C18/C5	0.37	0.14	-0.12	$9.00\text{x}10^{-12}$	$1.44\text{x}10^{-09}$	0.08	$2.42\text{x}10^{+04}$
C18/C3	0.13	0.05	-0.12	$2.28\text{x}10^{-11}$	$3.65\text{x}10^{-09}$	0.05	$1.33\text{x}10^{+04}$
C0/C18	769.01	221.78	0.11	$3.40\text{x}10^{-09}$	$5.44\text{x}10^{-07}$	0.05	$2.19\text{x}10^{+04}$
C18/C5:1	1.22	0.43	-0.09	$1.31\text{x}10^{-06}$	$2.10\text{x}10^{-04}$	0.05	$1.89\text{x}10^{+02}$
Single PCs							
PC aa C42:0	0.56	0.16	-0.12	$2.43\text{x}10^{-11}$	$3.89\text{x}10^{-09}$	0.06	
PC aa C42:1	0.27	0.07	-0.11	$4.40\text{x}10^{-10}$	$7.04\text{x}10^{-08}$	0.05	
PC aa C42:2	0.20	0.05	-0.11	$1.82\text{x}10^{-09}$	$2.91\text{x}10^{-07}$	0.03	
PC aa C38:3	57.77	14.01	0.1	$4.39\text{x}10^{-08}$	$7.02\text{x}10^{-06}$	0.06	
PC aa C40:1	0.42	0.09	-0.08	$1.55\text{x}10^{-05}$	$2.47\text{x}10^{-03}$	0.02	
PC aa C40:2	0.37	0.10	-0.08	$1.57\text{x}10^{-05}$	$2.52\text{x}10^{-03}$	0.02	
PC ae C42:3	0.85	0.19	-0.16	$3.19\text{x}10^{-20}$	$5.10\text{x}10^{-18}$	0.10	
PC ae C36:2	15.33	3.88	-0.14	$1.51\text{x}10^{-17}$	$2.42\text{x}10^{-15}$	0.19	
PC ae C42:4	0.96	0.22	-0.12	$5.26\text{x}10^{-12}$	$8.42\text{x}10^{-10}$	0.06	
PC ae C34:3	7.66	2.14	-0.12	$6.28\text{x}10^{-12}$	$1.00\text{x}10^{-09}$	0.12	
PC ae C40:6	5.48	1.35	-0.12	$2.60\text{x}10^{-11}$	$4.16\text{x}10^{-09}$	0.09	
PC ae C44:6	1.26	0.34	-0.12	$3.18\text{x}10^{-11}$	$5.09\text{x}10^{-09}$	0.05	
PC ae C38:2	2.14	0.48	-0.11	$8.21\text{x}10^{-11}$	$1.31\text{x}10^{-08}$	0.10	
PC ae C40:5	3.71	0.70	-0.11	$5.67\text{x}10^{-10}$	$9.08\text{x}10^{-08}$	0.06	
PC ae C42:5	2.21	0.46	-0.11	$1.09\text{x}10^{-09}$	$1.75\text{x}10^{-07}$	0.05	
PC ae C42:2	0.64	0.14	-0.11	$1.86\text{x}10^{-09}$	$2.97\text{x}10^{-07}$	0.06	
PC ae C32:1	2.83	0.55	-0.1	$3.65\text{x}10^{-09}$	$5.84\text{x}10^{-07}$	0.09	
PC ae C44:4	0.38	0.10	-0.11	$4.23\text{x}10^{-09}$	$6.76\text{x}10^{-07}$	0.04	
PC ae C36:1	8.91	2.08	-0.1	$1.19\text{x}10^{-08}$	$1.91\text{x}10^{-06}$	0.15	
PC ae C44:5	1.75	0.47	-0.1	$1.22\text{x}10^{-08}$	$1.96\text{x}10^{-06}$	0.03	
PC ae C40:3	1.20	0.24	-0.1	$1.46\text{x}10^{-08}$	$2.33\text{x}10^{-06}$	0.17	
PC ae C32:2	0.72	0.16	-0.09	$1.81\text{x}10^{-08}$	$2.90\text{x}10^{-06}$	0.19	
PC ae C34:2	12.19	2.95	-0.1	$2.29\text{x}10^{-08}$	$3.67\text{x}10^{-06}$	0.14	
PC ae C34:1	10.58	2.21	-0.09	$8.47\text{x}10^{-08}$	$1.35\text{x}10^{-05}$	0.14	
PC ae C34:0	1.69	0.43	-0.09	$1.28\text{x}10^{-07}$	$2.04\text{x}10^{-05}$	0.08	
PC ae C44:3	0.13	0.04	-0.1	$2.03\text{x}10^{-07}$	$3.24\text{x}10^{-05}$	0.03	
PC ae C40:1	1.60	0.37	-0.09	$3.80\text{x}10^{-07}$	$6.08\text{x}10^{-05}$	0.03	
PC ae C40:4	2.71	0.51	-0.08	$6.01\text{x}10^{-06}$	$9.62\text{x}10^{-04}$	0.05	
PC ae C40:2	2.14	0.49	-0.08	$7.35\text{x}10^{-06}$	$1.18\text{x}10^{-03}$	0.09	
PC ae C30:0	0.46	0.13	-0.08	$1.50\text{x}10^{-05}$	$2.40\text{x}10^{-03}$	0.09	

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
PC ae C38:1	0.63	0.26	-0.08	$2.00x10^{-05}$	$3.19x10^{-03}$	0.02	
PC ae C36:3	8.04	1.85	-0.07	$2.08x10^{-05}$	$3.33x10^{-03}$	0.10	
PC ae C38:0	2.24	0.67	-0.07	$1.16x10^{-04}$	$1.86x10^{-02}$	0.07	
Σ PC ae	181.45	30.52	-0.09	$8.61x10^{-07}$	$1.38x10^{-04}$	0.10	
lysoPC a C18:2	28.46	9.04	-0.15	$5.12x10^{-18}$	$8.19x10^{-16}$	0.16	
lysoPC a C17:0	2.10	0.68	-0.13	$2.68x10^{-13}$	$4.29x10^{-11}$	0.07	
lysoPC a C18:1	21.61	6.10	-0.13	$1.44x10^{-12}$	$2.30x10^{-10}$	0.11	
Σ lysoPC a	229.29	47.21	-0.08	$2.72x10^{-06}$	$4.36x10^{-04}$	0.07	
PC aa/PC aa Ratios							
PC aa C38:3/PC aa C42:6	97.71	21.87	0.16	$6.52x10^{-20}$	$1.04x10^{-17}$	0.09	$6.73x10^{+11}$
PC aa C38:3/PC aa C42:2	297.65	96.51	0.16	$1.07x10^{-18}$	$1.72x10^{-16}$	0.10	$1.69x10^{+09}$
PC aa C36:2/PC aa C38:3	4.59	0.87	-0.16	$1.65x10^{-18}$	$2.65x10^{-16}$	0.09	$2.65x10^{+10}$
PC aa C38:3/PC aa C42:0	111.66	41.58	0.16	$6.60x10^{-18}$	$1.06x10^{-15}$	0.07	$3.68x10^{+06}$
PC aa C38:3/PC aa C42:1	228.35	80.97	0.15	$3.81x10^{-17}$	$6.09x10^{-15}$	0.07	$1.15x10^{+07}$
PC aa C36:1/PC aa C38:3	0.95	0.19	-0.15	$6.36x10^{-16}$	$1.02x10^{-13}$	0.08	$6.90x10^{+07}$
PC aa C38:3/PC aa C40:3	85.86	19.98	0.14	$8.33x10^{-16}$	$1.33x10^{-13}$	0.08	$5.27x10^{+07}$
PC aa C38:3/PC aa C42:4	282.32	70.15	0.14	$3.18x10^{-15}$	$5.08x10^{-13}$	0.09	$1.38x10^{+07}$
PC aa C32:0/PC aa C38:3	0.27	0.06	-0.14	$3.42x10^{-15}$	$5.47x10^{-13}$	0.09	$1.28x10^{+07}$
PC aa C38:3/PC aa C40:2	164.64	48.82	0.14	$8.28x10^{-15}$	$1.32x10^{-12}$	0.07	$5.30x10^{+06}$
PC aa C34:2/PC aa C38:3	6.64	1.37	-0.14	$8.98x10^{-15}$	$1.44x10^{-12}$	0.08	$4.88x10^{+06}$
PC aa C34:3/PC aa C38:3	0.33	0.09	-0.14	$1.09x10^{-14}$	$1.75x10^{-12}$	0.07	$4.01x10^{+06}$
PC aa C36:3/PC aa C38:3	2.71	0.40	-0.14	$1.52x10^{-14}$	$2.43x10^{-12}$	0.07	$2.89x10^{+06}$
PC aa C34:1/PC aa C38:3	3.99	0.83	-0.13	$7.06x10^{-14}$	$1.13x10^{-11}$	0.09	$6.21x10^{+05}$
PC aa C38:4/PC aa C42:1	462.94	156.72	0.14	$7.51x10^{-14}$	$1.20x10^{-11}$	0.06	$5.86x10^{+03}$
PC aa C38:4/PC aa C42:0	227.74	87.12	0.14	$9.35x10^{-14}$	$1.50x10^{-11}$	0.06	$2.60x10^{+02}$
PC aa C38:4/PC aa C42:2	607.9	202.09	0.13	$4.40x10^{-13}$	$7.04x10^{-11}$	0.06	$4.13x10^{+03}$
PC aa C38:3/PC aa C38:5	0.94	0.21	0.13	$1.16x10^{-12}$	$1.86x10^{-10}$	0.07	$3.77x10^{+04}$
PC aa C38:3/PC aa C40:1	143.14	43.12	0.13	$1.80x10^{-12}$	$2.88x10^{-10}$	0.06	$2.44x10^{+04}$
PC aa C32:3/PC aa C38:3	0.01	0.00	-0.12	$5.26x10^{-12}$	$8.42x10^{-10}$	0.12	$8.34x10^{+03}$
PC aa C38:4/PC aa C42:6	199.88	47.26	0.12	$2.45x10^{-11}$	$3.92x10^{-09}$	0.04	$1.96x10^{+07}$
PC aa C38:3/PC aa C42:5	138.06	37.74	0.12	$4.17x10^{-11}$	$6.68x10^{-09}$	0.05	$1.05x10^{+03}$
PC aa C38:4/PC aa C38:5	1.89	0.33	0.12	$4.73x10^{-11}$	$7.57x10^{-09}$	0.04	$1.01x10^{+07}$
PC aa C38:0/PC aa C38:3	0.06	0.02	-0.12	$4.91x10^{-11}$	$7.85x10^{-09}$	0.04	$8.94x10^{+02}$
PC aa C38:3/PC aa C40:5	4.62	0.83	0.12	$8.49x10^{-11}$	$1.36x10^{-08}$	0.09	$5.17x10^{+02}$
PC aa C36:0/PC aa C38:3	0.05	0.02	-0.12	$9.96x10^{-11}$	$1.59x10^{-08}$	0.05	$4.41x10^{+02}$
PC aa C38:4/PC aa C42:4	573.40	132.08	0.12	$1.08x10^{-10}$	$1.72x10^{-08}$	0.06	$4.46x10^{+06}$
PC aa C28:1/PC aa C38:3	0.07	0.02	-0.12	$1.72x10^{-10}$	$2.74x10^{-08}$	0.06	$2.56x10^{+02}$
PC aa C38:4/PC aa C40:2	335.71	99.57	0.11	$3.34x10^{-10}$	$5.35x10^{-08}$	0.04	$4.70x10^{+04}$
PC aa C38:4/PC aa C40:1	291.96	89.08	0.1	$2.26x10^{-08}$	$3.62x10^{-06}$	0.03	$6.82x10^{+02}$
PC aa C40:4/PC aa C42:6	6.99	1.64	0.1	$2.43x10^{-08}$	$3.89x10^{-06}$	0.04	$2.22x10^{+04}$
PC aa C38:4/PC aa C40:3	175.95	44.68	0.1	$4.75x10^{-08}$	$7.59x10^{-06}$	0.03	$1.01x10^{+04}$
PC aa C32:0/PC aa C38:4	0.13	0.03	-0.1	$5.40x10^{-08}$	$8.64x10^{-06}$	0.04	$8.88x10^{+03}$
PC aa C36:2/PC aa C38:4	2.27	0.50	-0.1	$7.44x10^{-08}$	$1.19x10^{-05}$	0.03	$6.45x10^{+03}$
PC aa C38:0/PC aa C38:4	0.03	0.01	-0.1	$7.96x10^{-08}$	$1.27x10^{-05}$	0.03	$6.02x10^{+03}$
PC aa C36:0/PC aa C38:4	0.03	0.01	-0.1	$1.02x10^{-07}$	$1.63x10^{-05}$	0.03	$4.71x10^{+03}$
PC aa C34:3/PC aa C34:4	8.81	2.14	-0.1	$1.08x10^{-07}$	$1.73x10^{-05}$	0.03	$3.80x10^{+05}$
PC aa C36:4/PC aa C42:6	355.68	78.78	0.1	$1.76x10^{-07}$	$2.81x10^{-05}$	0.03	$3.07x10^{+03}$
PC aa C38:4/PC aa C38:6	1.38	0.41	0.09	$2.82x10^{-07}$	$4.52x10^{-05}$	0.02	$1.70x10^{+03}$
PC aa C40:4/PC aa C42:4	20.11	4.91	0.09	$5.52x10^{-07}$	$8.83x10^{-05}$	0.02	$4.26x10^{+03}$

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
PC aa C34:2/PC aa C38:4	3.27	0.75	-0.09	$6.59\text{x}10^{-07}$	$1.05\text{x}10^{-04}$	0.03	$7.28\text{x}10^{+02}$
PC aa C36:4/PC aa C42:4	1020.10	217.04	0.09	$8.45\text{x}10^{-07}$	$1.35\text{x}10^{-04}$	0.05	$2.78\text{x}10^{+03}$
PC aa C32:3/PC aa C38:4	0.00	0.00	-0.08	$1.17\text{x}10^{-06}$	$1.87\text{x}10^{-04}$	0.12	$4.09\text{x}10^{+02}$
PC aa C32:2/PC aa C34:4	2.04	0.48	-0.09	$1.36\text{x}10^{-06}$	$2.17\text{x}10^{-04}$	0.04	$4.18\text{x}10^{+04}$
PC aa C38:6/PC aa C40:6	2.84	0.40	-0.09	$1.40\text{x}10^{-06}$	$2.25\text{x}10^{-04}$	0.05	$9.23\text{x}10^{+03}$
PC aa C38:4/PC aa C42:5	281.77	77.17	0.09	$1.73\text{x}10^{-06}$	$2.76\text{x}10^{-04}$	0.02	$2.78\text{x}10^{+02}$
PC aa C32:0/PC aa C36:4	0.07	0.01	-0.09	$1.75\text{x}10^{-06}$	$2.79\text{x}10^{-04}$	0.06	$1.02\text{x}10^{+04}$
PC aa C34:3/PC aa C36:3	0.12	0.02	-0.08	$3.56\text{x}10^{-06}$	$5.70\text{x}10^{-04}$	0.07	$1.15\text{x}10^{+04}$
PC aa C30:0/PC aa C34:4	2.83	0.72	-0.08	$4.20\text{x}10^{-06}$	$6.72\text{x}10^{-04}$	0.05	$1.35\text{x}10^{+04}$
PC aa C36:4/PC aa C38:5	3.37	0.53	0.08	$6.38\text{x}10^{-06}$	$1.02\text{x}10^{-03}$	0.03	$5.28\text{x}10^{+03}$
PC aa C36:0/PC aa C36:4	0.01	0.00	-0.08	$1.22\text{x}10^{-05}$	$1.95\text{x}10^{-03}$	0.02	$2.35\text{x}10^{+02}$
PC aa C34:3/PC aa C40:4	4.63	1.35	-0.08	$1.97\text{x}10^{-05}$	$3.15\text{x}10^{-03}$	0.09	$1.11\text{x}10^{+03}$
PC aa C32:1/PC aa C34:3	1.12	0.38	0.08	$2.24\text{x}10^{-05}$	$3.59\text{x}10^{-03}$	0.03	$1.83\text{x}10^{+03}$
PC aa C32:0/PC aa C40:4	3.79	0.93	-0.08	$2.52\text{x}10^{-05}$	$4.03\text{x}10^{-03}$	0.02	$7.09\text{x}10^{+02}$
PC aa C40:3/PC aa C40:4	0.17	0.05	-0.08	$2.66\text{x}10^{-05}$	$4.26\text{x}10^{-03}$	0.02	$4.62\text{x}10^{+02}$
PC aa C32:3/PC aa C34:4	0.27	0.09	-0.08	$2.77\text{x}10^{-05}$	$4.43\text{x}10^{-03}$	0.05	$5.10\text{x}10^{+02}$
PC aa C30:0/PC aa C32:1	0.31	0.09	-0.08	$3.55\text{x}10^{-05}$	$5.68\text{x}10^{-03}$	0.02	$2.52\text{x}10^{+03}$
PC aa C34:4/PC aa C36:6	2.05	0.53	0.08	$3.97\text{x}10^{-05}$	$6.35\text{x}10^{-03}$	0.02	$1.43\text{x}10^{+03}$
PC aa C38:5/PC aa C40:4	15.69	3.54	-0.07	$4.71\text{x}10^{-05}$	$7.54\text{x}10^{-03}$	0.04	$4.65\text{x}10^{+02}$
PC aa C36:4/PC aa C38:6	2.45	0.66	0.07	$4.86\text{x}10^{-05}$	$7.77\text{x}10^{-03}$	0.02	$2.67\text{x}10^{+02}$
PC aa C36:4/PC aa C40:3	312.80	74.28	0.07	$5.46\text{x}10^{-05}$	$8.74\text{x}10^{-03}$	0.02	$2.25\text{x}10^{+02}$
PC aa C36:2/PC aa C36:3	1.70	0.22	-0.07	$6.29\text{x}10^{-05}$	$1.01\text{x}10^{-02}$	0.02	$1.08\text{x}10^{+03}$
PC aa C34:2/PC aa C36:4	1.81	0.32	-0.07	$6.39\text{x}10^{-05}$	$1.02\text{x}10^{-02}$	0.03	$5.27\text{x}10^{+02}$
PC aa C34:3/PC aa C36:4	0.09	0.02	-0.07	$7.40\text{x}10^{-05}$	$1.18\text{x}10^{-02}$	0.06	$4.55\text{x}10^{+02}$
PC aa C36:2/PC aa C40:4	65.02	15.19	-0.07	$8.91\text{x}10^{-05}$	$1.43\text{x}10^{-02}$	0.02	$2.46\text{x}10^{+02}$
PC aa C34:2/PC aa C36:3	2.45	0.30	-0.07	$1.05\text{x}10^{-04}$	$1.68\text{x}10^{-02}$	0.04	$4.74\text{x}10^{+02}$
PC aa C40:4/PC aa C42:5	9.87	2.77	0.07	$1.22\text{x}10^{-04}$	$1.95\text{x}10^{-02}$	0.02	$1.80\text{x}10^{+02}$
PC aa C34:4/PC aa C38:5	0.04	0.01	0.07	$2.83\text{x}10^{-04}$	$4.53\text{x}10^{-02}$	0.05	$2.00\text{x}10^{+02}$
PC ae/PC ae Ratios							
PC ae C34:3/PC ae C36:5	0.60	0.14	-0.14	$1.21\text{x}10^{-14}$	$1.94\text{x}10^{-12}$	0.12	$5.19\text{x}10^{+02}$
PC ae C34:2/PC ae C36:4	0.62	0.14	-0.13	$1.56\text{x}10^{-14}$	$2.50\text{x}10^{-12}$	0.17	$1.47\text{x}10^{+06}$
PC ae C38:6/PC ae C40:6	1.63	0.28	0.13	$7.66\text{x}10^{-14}$	$1.22\text{x}10^{-11}$	0.08	$3.40\text{x}10^{+02}$
PC ae C36:4/PC ae C40:5	5.50	1.20	0.13	$2.22\text{x}10^{-13}$	$3.55\text{x}10^{-11}$	0.08	$2.56\text{x}10^{+03}$
PC ae C38:5/PC ae C40:5	5.28	0.81	0.13	$9.13\text{x}10^{-13}$	$1.46\text{x}10^{-10}$	0.08	$6.21\text{x}10^{+02}$
PC ae C36:3/PC ae C36:4	0.41	0.08	-0.12	$6.91\text{x}10^{-12}$	$1.11\text{x}10^{-09}$	0.13	$3.01\text{x}10^{+06}$
PC ae C36:4/PC ae C40:1	12.99	3.34	0.11	$1.06\text{x}10^{-09}$	$1.70\text{x}10^{-07}$	0.04	$3.57\text{x}10^{+02}$
PC ae C36:4/PC ae C40:4	7.51	1.62	0.11	$1.13\text{x}10^{-09}$	$1.81\text{x}10^{-07}$	0.07	$5.32\text{x}10^{+03}$
PC ae C36:4/PC ae C38:4	1.31	0.21	0.11	$1.99\text{x}10^{-09}$	$3.19\text{x}10^{-07}$	0.10	$3.28\text{x}10^{+06}$
PC ae C36:4/PC ae C38:5	1.04	0.10	0.09	$1.99\text{x}10^{-06}$	$3.19\text{x}10^{-04}$	0.04	$4.50\text{x}10^{+04}$
PC ae C36:4/PC ae C42:1	53.76	13.14	0.08	$7.87\text{x}10^{-06}$	$1.26\text{x}10^{-03}$	0.03	$2.90\text{x}10^{+02}$
PC ae C36:4/PC ae C38:6	2.34	0.43	0.07	$3.84\text{x}10^{-05}$	$6.14\text{x}10^{-03}$	0.05	$2.33\text{x}10^{+03}$
lysoPC/lysoPC Ratios							
lysoPC a C14:0/lysoPC a C18:2	0.24	0.08	0.17	$6.49\text{x}10^{-23}$	$1.04\text{x}10^{-20}$	0.18	$7.88\text{x}10^{+04}$
lysoPC a C14:0/lysoPC a C18:1	0.31	0.08	0.15	$2.91\text{x}10^{-18}$	$4.65\text{x}10^{-16}$	0.13	$4.94\text{x}10^{+05}$
lysoPC a C14:0/lysoPC a C17:0	3.30	1.14	0.16	$4.72\text{x}10^{-18}$	$7.55\text{x}10^{-16}$	0.09	$5.69\text{x}10^{+04}$
lysoPC a C16:0/lysoPC a C18:1	5.87	1.01	0.14	$1.63\text{x}10^{-15}$	$2.60\text{x}10^{-13}$	0.08	$8.83\text{x}10^{+02}$
lysoPC a C14:0/lysoPC a C16:0	0.05	0.01	0.08	$4.87\text{x}10^{-06}$	$7.80\text{x}10^{-04}$	0.07	$1.95\text{x}10^{+03}$
lysoPC a C14:0/lysoPC a C18:0	0.20	0.05	0.08	$6.15\text{x}10^{-06}$	$9.85\text{x}10^{-04}$	0.03	$2.56\text{x}10^{+02}$
PC aa/PC ae Ratios							

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
PC aa C38:3/PC ae C42:3	70.43	21.88	0.20	$1.95\text{x}10^{-28}$	$3.12\text{x}10^{-26}$	0.12	$1.63\text{x}10^{+08}$
PC aa C38:3/PC ae C36:2	3.98	1.36	0.19	$5.11\text{x}10^{-27}$	$8.17\text{x}10^{-25}$	0.13	$2.96\text{x}10^{+09}$
PC aa C38:3/PC ae C38:2	27.89	7.48	0.19	$1.47\text{x}10^{-25}$	$2.35\text{x}10^{-23}$	0.11	$5.58\text{x}10^{+14}$
PC aa C38:3/PC ae C42:2	93.08	24.28	0.19	$2.33\text{x}10^{-25}$	$3.73\text{x}10^{-23}$	0.11	$7.97\text{x}10^{+15}$
PC aa C38:3/PC ae C36:1	6.70	1.85	0.18	$1.55\text{x}10^{-24}$	$2.48\text{x}10^{-22}$	0.12	$7.70\text{x}10^{+15}$
PC aa C38:3/PC ae C34:1	5.59	1.42	0.17	$3.86\text{x}10^{-22}$	$6.18\text{x}10^{-20}$	0.10	$1.14\text{x}10^{+14}$
PC aa C36:3/PC ae C36:2	10.47	2.95	0.17	$1.00\text{x}10^{-21}$	$1.60\text{x}10^{-19}$	0.14	$1.51\text{x}10^{+04}$
PC aa C38:3/PC ae C40:3	49.43	12.96	0.17	$2.25\text{x}10^{-21}$	$3.60\text{x}10^{-19}$	0.10	$6.48\text{x}10^{+12}$
PC ae C36:2/PC ae C38:3	3.60	0.57	-0.17	$7.48\text{x}10^{-21}$	$1.20\text{x}10^{-18}$	0.08	$2.02\text{x}10^{+03}$
PC aa C38:3/PC ae C40:5	15.98	4.41	0.17	$1.10\text{x}10^{-20}$	$1.77\text{x}10^{-18}$	0.09	$5.14\text{x}10^{+10}$
PC aa C38:3/PC ae C40:6	11.11	3.71	0.17	$5.16\text{x}10^{-20}$	$8.26\text{x}10^{-18}$	0.08	$5.04\text{x}10^{+08}$
PC aa C38:3/PC ae C40:1	37.45	10.56	0.16	$5.48\text{x}10^{-20}$	$8.77\text{x}10^{-18}$	0.10	$8.01\text{x}10^{+11}$
PC aa C38:3/PC ae C42:4	63.03	21.22	0.16	$7.50\text{x}10^{-20}$	$1.20\text{x}10^{-17}$	0.08	$7.02\text{x}10^{+07}$
PC aa C38:3/PC ae C32:1	20.97	5.75	0.16	$1.21\text{x}10^{-19}$	$1.93\text{x}10^{-17}$	0.08	$3.02\text{x}10^{+10}$
PC aa C38:3/PC ae C34:0	35.71	10.67	0.16	$1.53\text{x}10^{-19}$	$2.44\text{x}10^{-17}$	0.08	$2.87\text{x}10^{+11}$
PC aa C38:3/PC ae C34:3	8.12	3.05	0.16	$1.56\text{x}10^{-19}$	$2.49\text{x}10^{-17}$	0.09	$4.03\text{x}10^{+07}$
PC aa C38:3/PC ae C38:3	13.77	3.21	0.16	$3.61\text{x}10^{-19}$	$5.77\text{x}10^{-17}$	0.12	$1.22\text{x}10^{+11}$
PC aa C38:4/PC ae C40:1	75.56	17.61	0.16	$5.26\text{x}10^{-19}$	$8.42\text{x}10^{-17}$	0.08	$7.22\text{x}10^{+11}$
PC aa C38:3/PC ae C44:4	158.91	53.81	0.16	$8.21\text{x}10^{-19}$	$1.31\text{x}10^{-16}$	0.08	$5.15\text{x}10^{+09}$
PC aa C38:3/PC ae C32:2	83.58	24.52	0.16	$1.87\text{x}10^{-18}$	$3.00\text{x}10^{-16}$	0.10	$9.68\text{x}10^{+09}$
PC aa C38:3/PC ae C42:1	153.87	36.76	0.16	$3.50\text{x}10^{-18}$	$5.60\text{x}10^{-16}$	0.10	$1.25\text{x}10^{+10}$
PC aa C38:3/PC ae C44:3	477.53	161.71	0.16	$8.53\text{x}10^{-18}$	$1.36\text{x}10^{-15}$	0.08	$5.15\text{x}10^{+09}$
PC aa C38:4/PC ae C40:5	32.36	8.09	0.15	$1.65\text{x}10^{-17}$	$2.65\text{x}10^{-15}$	0.07	$3.43\text{x}10^{+07}$
PC aa C38:3/PC ae C44:6	49.21	18.31	0.15	$2.27\text{x}10^{-17}$	$3.63\text{x}10^{-15}$	0.08	$1.40\text{x}10^{+06}$
PC aa C38:3/PC ae C36:3	7.44	2.10	0.15	$2.27\text{x}10^{-17}$	$3.64\text{x}10^{-15}$	0.08	$1.93\text{x}10^{+09}$
PC ae C34:3/PC ae C36:4	0.39	0.11	-0.15	$3.97\text{x}10^{-17}$	$6.35\text{x}10^{-15}$	0.13	$1.58\text{x}10^{+05}$
PC aa C36:4/PC ae C40:1	133.83	26.17	0.15	$6.61\text{x}10^{-17}$	$1.06\text{x}10^{-14}$	0.07	$5.75\text{x}10^{+09}$
PC aa C38:3/PC ae C34:2	4.99	1.69	0.15	$7.01\text{x}10^{-17}$	$1.12\text{x}10^{-14}$	0.08	$3.27\text{x}10^{+08}$
PC aa C38:3/PC ae C42:5	27.15	8.60	0.15	$8.34\text{x}10^{-17}$	$1.33\text{x}10^{-14}$	0.07	$1.31\text{x}10^{+07}$
PC aa C38:3/PC ae C40:4	21.79	5.83	0.15	$1.48\text{x}10^{-16}$	$2.37\text{x}10^{-14}$	0.07	$2.97\text{x}10^{+08}$
PC aa C38:4/PC ae C40:6	22.55	7.14	0.15	$2.40\text{x}10^{-16}$	$3.84\text{x}10^{-14}$	0.08	$1.08\text{x}10^{+05}$
PC aa C38:3/PC ae C44:5	35.38	12.76	0.15	$5.16\text{x}10^{-16}$	$8.25\text{x}10^{-14}$	0.08	$2.37\text{x}10^{+07}$
PC aa C36:3/PC ae C38:2	73.66	15.81	0.14	$1.41\text{x}10^{-15}$	$2.25\text{x}10^{-13}$	0.08	$5.82\text{x}10^{+04}$
PC aa C38:4/PC ae C42:2	190.68	52.74	0.14	$2.65\text{x}10^{-15}$	$4.24\text{x}10^{-13}$	0.06	$7.01\text{x}10^{+05}$
PC aa C38:3/PC ae C38:0	27.33	8.44	0.14	$3.53\text{x}10^{-15}$	$5.65\text{x}10^{-13}$	0.07	$1.24\text{x}10^{+07}$
PC aa C38:4/PC ae C34:3	16.57	6.42	0.14	$6.57\text{x}10^{-15}$	$1.05\text{x}10^{-12}$	0.08	$9.56\text{x}10^{+02}$
PC aa C38:4/PC ae C44:6	99.78	36.38	0.14	$1.29\text{x}10^{-14}$	$2.06\text{x}10^{-12}$	0.06	$2.47\text{x}10^{+03}$
PC aa C38:3/PC ae C40:2	28.29	9.38	0.14	$2.55\text{x}10^{-14}$	$4.09\text{x}10^{-12}$	0.06	$1.72\text{x}10^{+06}$
PC aa C38:4/PC ae C38:2	57.49	18.01	0.14	$2.89\text{x}10^{-14}$	$4.62\text{x}10^{-12}$	0.07	$2.84\text{x}10^{+03}$
PC aa C38:4/PC ae C42:1	312.06	66.19	0.14	$4.18\text{x}10^{-14}$	$6.68\text{x}10^{-12}$	0.06	$1.15\text{x}10^{+10}$
PC aa C38:4/PC ae C36:1	13.80	4.35	0.13	$1.34\text{x}10^{-13}$	$2.15\text{x}10^{-11}$	0.09	$8.89\text{x}10^{+04}$
PC aa C38:4/PC ae C42:5	55.06	16.83	0.13	$1.53\text{x}10^{-13}$	$2.44\text{x}10^{-11}$	0.05	$7.17\text{x}10^{+03}$
PC aa C38:3/PC ae C42:0	113.47	30.57	0.13	$3.88\text{x}10^{-13}$	$6.21\text{x}10^{-11}$	0.07	$1.13\text{x}10^{+05}$
PC aa C38:3/PC ae C38:4	3.82	1.01	0.13	$4.01\text{x}10^{-13}$	$6.41\text{x}10^{-11}$	0.05	$1.10\text{x}10^{+05}$
PC aa C38:3/PC ae C30:0	135.46	48.03	0.13	$3.22\text{x}10^{-13}$	$5.16\text{x}10^{-11}$	0.06	$1.36\text{x}10^{+05}$
PC aa C36:3/PC ae C36:1	17.74	4.05	0.13	$5.23\text{x}10^{-13}$	$8.37\text{x}10^{-11}$	0.10	$2.28\text{x}10^{+04}$
PC aa C38:4/PC ae C40:4	44.19	10.85	0.13	$5.51\text{x}10^{-13}$	$8.81\text{x}10^{-11}$	0.05	$1.09\text{x}10^{+07}$
PC aa C38:4/PC ae C44:5	71.81	25.07	0.13	$8.75\text{x}10^{-13}$	$1.40\text{x}10^{-10}$	0.05	$1.40\text{x}10^{+04}$
PC aa C38:3/PC ae C38:1	109.71	77.67	0.13	$8.97\text{x}10^{-13}$	$1.44\text{x}10^{-10}$	0.05	$4.89\text{x}10^{+04}$

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
PC aa C36:4/PC ae C40:5	57.60	13.47	0.13	$9.00\text{x}10^{-13}$	$1.44\text{x}10^{-10}$	0.06	$6.30\text{x}10^{+02}$
PC aa C38:4/PC ae C32:2	170.96	52.95	0.13	$1.34\text{x}10^{-12}$	$2.14\text{x}10^{-10}$	0.10	$1.35\text{x}10^{+04}$
PC aa C38:4/PC ae C32:1	42.98	12.90	0.13	$1.67\text{x}10^{-12}$	$2.68\text{x}10^{-10}$	0.06	$2.18\text{x}10^{+03}$
PC aa C38:4/PC ae C44:3	975.91	336.09	0.13	$1.89\text{x}10^{-12}$	$3.03\text{x}10^{-10}$	0.05	$1.07\text{x}10^{+05}$
PC aa C36:4/PC ae C42:2	338.33	84.46	0.13	$2.21\text{x}10^{-12}$	$3.54\text{x}10^{-10}$	0.05	$8.40\text{x}10^{+02}$
PC aa C38:4/PC ae C38:4	7.71	1.67	0.12	$6.82\text{x}10^{-12}$	$1.09\text{x}10^{-09}$	0.05	$7.02\text{x}10^{+07}$
PC aa C40:4/PC ae C42:2	6.70	1.99	0.12	$7.82\text{x}10^{-12}$	$1.25\text{x}10^{-09}$	0.06	$2.37\text{x}10^{+02}$
PC aa C36:3/PC ae C42:2	247.25	55.47	0.12	$8.01\text{x}10^{-12}$	$1.28\text{x}10^{-09}$	0.05	$2.32\text{x}10^{+02}$
PC aa C38:4/PC ae C40:3	101.79	30.82	0.12	$1.02\text{x}10^{-11}$	$1.63\text{x}10^{-09}$	0.08	$1.43\text{x}10^{+03}$
PC aa C38:4/PC ae C34:1	11.54	3.54	0.12	$1.25\text{x}10^{-11}$	$1.99\text{x}10^{-09}$	0.07	$6.79\text{x}10^{+03}$
PC aa C38:4/PC ae C44:4	327.70	125.99	0.12	$1.32\text{x}10^{-11}$	$2.10\text{x}10^{-09}$	0.04	$3.21\text{x}10^{+02}$
PC aa C38:4/PC ae C34:0	73.64	25.41	0.12	$1.47\text{x}10^{-11}$	$2.35\text{x}10^{-09}$	0.06	$8.67\text{x}10^{+03}$
PC aa C36:3/PC ae C34:1	14.79	2.93	0.12	$1.59\text{x}10^{-11}$	$2.55\text{x}10^{-09}$	0.09	$5.31\text{x}10^{+03}$
PC aa C40:4/PC ae C36:1	0.49	0.17	0.12	$1.64\text{x}10^{-11}$	$2.63\text{x}10^{-09}$	0.12	$7.28\text{x}10^{+02}$
PC aa C36:4/PC ae C36:1	24.42	6.87	0.12	$2.28\text{x}10^{-11}$	$3.65\text{x}10^{-09}$	0.11	$5.24\text{x}10^{+02}$
PC aa C38:4/PC ae C34:2	10.24	3.81	0.12	$6.44\text{x}10^{-11}$	$1.03\text{x}10^{-08}$	0.07	$3.56\text{x}10^{+02}$
PC aa C36:4/PC ae C32:2	302.36	82.77	0.11	$1.01\text{x}10^{-10}$	$1.61\text{x}10^{-08}$	0.13	$1.80\text{x}10^{+02}$
PC aa C38:3/PC ae C36:0	64.84	18.88	0.12	$1.33\text{x}10^{-10}$	$2.12\text{x}10^{-08}$	0.06	$3.30\text{x}10^{+02}$
PC aa C34:4/PC ae C40:1	1.40	0.41	0.11	$2.10\text{x}10^{-10}$	$3.36\text{x}10^{-08}$	0.08	$1.81\text{x}10^{+03}$
PC aa C38:4/PC ae C38:0	55.75	17.01	0.11	$2.51\text{x}10^{-10}$	$4.01\text{x}10^{-08}$	0.06	$4.65\text{x}10^{+05}$
PC aa C36:4/PC ae C44:3	1727.9	547.87	0.12	$2.58\text{x}10^{-10}$	$4.13\text{x}10^{-08}$	0.04	$7.85\text{x}10^{+02}$
PC aa C40:4/PC ae C34:1	0.40	0.13	0.11	$3.95\text{x}10^{-10}$	$6.32\text{x}10^{-08}$	0.10	$2.14\text{x}10^{+02}$
PC aa C40:4/PC ae C40:1	2.68	0.81	0.11	$4.30\text{x}10^{-10}$	$6.88\text{x}10^{-08}$	0.04	$8.84\text{x}10^{+02}$
PC aa C36:4/PC ae C34:0	129.92	39.18	0.11	$4.34\text{x}10^{-10}$	$6.94\text{x}10^{-08}$	0.08	$2.94\text{x}10^{+02}$
PC aa C34:4/PC ae C34:0	1.34	0.44	0.11	$4.61\text{x}10^{-10}$	$7.37\text{x}10^{-08}$	0.05	$2.77\text{x}10^{+02}$
PC aa C36:3/PC ae C34:0	94.54	24.27	0.11	$5.19\text{x}10^{-10}$	$8.31\text{x}10^{-08}$	0.06	$2.46\text{x}10^{+02}$
PC aa C40:4/PC ae C34:0	2.58	0.92	0.11	$5.78\text{x}10^{-10}$	$9.26\text{x}10^{-08}$	0.08	$2.21\text{x}10^{+02}$
PC aa C36:3/PC ae C40:1	99.08	23.05	0.11	$6.12\text{x}10^{-10}$	$9.79\text{x}10^{-08}$	0.05	$6.21\text{x}10^{+02}$
PC aa C38:4/PC ae C36:3	15.34	5.11	0.11	$2.21\text{x}10^{-09}$	$3.54\text{x}10^{-07}$	0.05	$9.40\text{x}10^{+03}$
PC aa C38:4/PC ae C40:2	57.90	19.88	0.11	$2.45\text{x}10^{-09}$	$3.92\text{x}10^{-07}$	0.05	$3.00\text{x}10^{+03}$
PC aa C40:4/PC ae C42:1	10.94	2.43	0.11	$2.95\text{x}10^{-09}$	$4.72\text{x}10^{-07}$	0.04	$7.75\text{x}10^{+05}$
PC aa C36:4/PC ae C42:1	555.46	109.61	0.11	$4.33\text{x}10^{-09}$	$6.94\text{x}10^{-07}$	0.04	$5.27\text{x}10^{+05}$
PC aa C36:4/PC ae C40:4	78.61	17.85	0.11	$6.18\text{x}10^{-09}$	$9.89\text{x}10^{-07}$	0.05	$9.73\text{x}10^{+02}$
PC aa C40:4/PC ae C40:4	1.56	0.47	0.10	$7.98\text{x}10^{-09}$	$1.28\text{x}10^{-06}$	0.05	$7.53\text{x}10^{+02}$
PC aa C38:4/PC ae C38:1	226.20	162.23	0.10	$1.06\text{x}10^{-08}$	$1.70\text{x}10^{-06}$	0.03	$1.88\text{x}10^{+03}$
PC aa C36:4/PC ae C38:0	98.56	26.41	0.10	$1.76\text{x}10^{-08}$	$2.82\text{x}10^{-06}$	0.07	$6.61\text{x}10^{+03}$
PC aa C36:3/PC ae C36:3	19.62	4.36	0.10	$2.17\text{x}10^{-08}$	$3.47\text{x}10^{-06}$	0.05	$9.60\text{x}10^{+02}$
PC aa C38:4/PC ae C42:0	231.10	60.62	0.10	$3.25\text{x}10^{-08}$	$5.20\text{x}10^{-06}$	0.04	$1.47\text{x}10^{+04}$
PC aa C34:4/PC ae C38:0	1.02	0.32	0.10	$6.42\text{x}10^{-08}$	$1.03\text{x}10^{-05}$	0.03	$1.81\text{x}10^{+03}$
PC aa C38:4/PC ae C30:0	281.12	116.99	0.10	$7.20\text{x}10^{-08}$	$1.15\text{x}10^{-05}$	0.05	$2.08\text{x}10^{+02}$
PC aa C36:4/PC ae C38:4	13.73	2.81	0.09	$2.19\text{x}10^{-07}$	$3.50\text{x}10^{-05}$	0.05	$2.99\text{x}10^{+04}$
PC aa C38:4/PC ae C38:3	28.55	8.61	0.09	$3.21\text{x}10^{-07}$	$5.13\text{x}10^{-05}$	0.08	$1.49\text{x}10^{+03}$
PC aa C40:4/PC ae C38:4	0.27	0.08	0.09	$1.18\text{x}10^{-06}$	$1.89\text{x}10^{-04}$	0.05	$5.55\text{x}10^{+03}$
PC aa C38:4/PC ae C38:6	13.87	3.63	0.09	$1.81\text{x}10^{-06}$	$2.89\text{x}10^{-04}$	0.02	$2.65\text{x}10^{+02}$
PC aa C38:4/PC ae C38:5	6.15	1.27	0.09	$1.88\text{x}10^{-06}$	$3.01\text{x}10^{-04}$	0.03	$2.54\text{x}10^{+02}$
PC aa C38:0/PC ae C36:4	0.17	0.05	-0.08	$4.24\text{x}10^{-06}$	$6.78\text{x}10^{-04}$	0.04	$3.54\text{x}10^{+02}$
PC aa C40:4/PC ae C38:3	1.00	0.34	0.08	$8.62\text{x}10^{-06}$	$1.38\text{x}10^{-03}$	0.12	$1.48\text{x}10^{+03}$
PC aa C36:3/PC ae C42:1	409.17	84.37	0.08	$9.88\text{x}10^{-06}$	$1.58\text{x}10^{-03}$	0.03	$2.31\text{x}10^{+02}$
PC aa C34:4/PC ae C42:1	5.83	1.84	0.08	$1.10\text{x}10^{-05}$	$1.75\text{x}10^{-03}$	0.07	$2.08\text{x}10^{+02}$

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
PC aa C36:3/PC ae C38:3	36.65	7.41	0.07	$3.22x10^{-05}$	$5.15x10^{-03}$	0.11	$3.96x10^{+02}$
PC aa C36:4/PC ae C36:0	234.4	62.39	0.07	$1.82x10^{-04}$	$2.91x10^{-02}$	0.01	$1.78x10^{+02}$
PC/lysoPC Ratios							
PC aa C38:3/lysoPC a C18:2	2.27	0.99	0.17	$2.10x10^{-22}$	$3.37x10^{-20}$	0.19	$2.43x10^{+04}$
PC aa C38:3/lysoPC a C18:1	2.87	1.03	0.16	$8.65x10^{-22}$	$1.38x10^{-19}$	0.17	$1.66x10^{+09}$
PC aa C38:3/lysoPC a C17:0	30.75	14.02	0.16	$1.73x10^{-19}$	$2.77x10^{-17}$	0.08	$1.55x10^{+06}$
PC aa C38:4/lysoPC a C18:1	5.85	2.10	0.14	$3.80x10^{-16}$	$6.09x10^{-14}$	0.12	$3.77x10^{+03}$
PC aa C38:3/lysoPC a C18:0	1.85	0.56	0.13	$1.56x10^{-13}$	$2.49x10^{-11}$	0.10	$2.82x10^{+05}$
PC aa C42:2/lysoPC a C26:1	0.12	0.03	-0.12	$7.58x10^{-12}$	$1.21x10^{-09}$	0.05	$2.40x10^{+02}$
PC aa C38:3/lysoPC a C16:0	0.49	0.14	0.12	$1.67x10^{-11}$	$2.67x10^{-09}$	0.12	$2.63x10^{+03}$
PC aa C38:4/lysoPC a C20:4	20.19	5.51	0.10	$4.73x10^{-10}$	$7.57x10^{-08}$	0.19	$1.01x10^{+06}$
PC aa C38:4/lysoPC a C18:0	3.76	1.14	0.11	$5.19x10^{-09}$	$8.30x10^{-07}$	0.06	$9.24x10^{+04}$
PC aa C40:1/lysoPC a C26:1	0.25	0.06	-0.10	$5.03x10^{-08}$	$8.05x10^{-06}$	0.04	$3.07x10^{+02}$
PC aa C36:4/lysoPC a C20:4	35.84	9.27	0.09	$3.29x10^{-07}$	$5.26x10^{-05}$	0.18	$3.68x10^{+04}$
PC aa C38:4/lysoPC a C16:0	0.99	0.28	0.09	$7.55x10^{-07}$	$1.21x10^{-04}$	0.07	$6.35x10^{+02}$
PC aa C42:6/lysoPC a C14:0	0.10	0.02	-0.09	$1.04x10^{-06}$	$1.66x10^{-04}$	0.03	$5.22x10^{+02}$
PC aa C40:4/lysoPC a C18:0	0.13	0.04	0.08	$4.76x10^{-06}$	$7.62x10^{-04}$	0.02	$3.31x10^{+02}$
PC aa C40:4/lysoPC a C20:4	0.72	0.24	0.07	$3.62x10^{-05}$	$5.79x10^{-03}$	0.09	$3.35x10^{+02}$
PC aa C36:4/lysoPC a C16:0	1.75	0.44	0.07	$5.22x10^{-05}$	$8.35x10^{-03}$	0.06	$1.82x10^{+02}$
PC ae C38:2/lysoPC a C14:0	0.34	0.08	-0.14	$1.64x10^{-14}$	$2.62x10^{-12}$	0.11	$5.01x10^{+03}$
PC ae C36:1/lysoPC a C14:0	1.43	0.33	-0.12	$7.20x10^{-13}$	$1.15x10^{-10}$	0.16	$1.66x10^{+04}$
PC ae C34:0/lysoPC a C14:0	0.27	0.06	-0.13	$8.82x10^{-13}$	$1.41x10^{-10}$	0.12	$1.45x10^{+05}$
PC ae C42:2/lysoPC a C14:0	0.10	0.02	-0.13	$1.45x10^{-12}$	$2.32x10^{-10}$	0.07	$1.28x10^{+03}$
PC ae C34:1/lysoPC a C14:0	1.69	0.35	-0.12	$1.08x10^{-11}$	$1.73x10^{-09}$	0.15	$7.85x10^{+03}$
PC ae C40:1/lysoPC a C14:0	0.26	0.06	-0.12	$1.54x10^{-10}$	$2.47x10^{-08}$	0.05	$2.46x10^{+03}$
PC ae C30:0/lysoPC a C14:0	0.07	0.02	-0.11	$6.13x10^{-10}$	$9.80x10^{-08}$	0.12	$2.44x10^{+04}$
PC ae C42:0/lysoPC a C26:1	0.31	0.06	-0.09	$1.86x10^{-06}$	$2.98x10^{-04}$	0.02	$3.42x10^{+02}$
PC ae C36:4/lysoPC a C20:4	3.46	0.97	0.07	$2.73x10^{-05}$	$4.37x10^{-03}$	0.12	$4.44x10^{+02}$
SM C16:0	151.19	23.84	-0.07	$2.97x10^{-05}$	$4.76x10^{-03}$	0.07	
SM (OH) C14:1	9.54	2.56	-0.07	$9.83x10^{-05}$	$1.57x10^{-02}$	0.18	
SM (OH) C16:1	5.19	1.37	-0.06	$1.08x10^{-04}$	$1.73x10^{-02}$	0.18	
SM C16:0/SM C16:1	6.40	0.76	-0.12	$9.51x10^{-14}$	$1.52x10^{-11}$	0.29	$3.13x10^{+08}$
SM (OH) C16:1/SM C18:0	0.16	0.03	-0.12	$2.05x10^{-12}$	$3.28x10^{-10}$	0.10	$5.27x10^{+07}$
SM (OH) C16:1/SM C18:1	0.31	0.06	-0.13	$2.19x10^{-12}$	$3.51x10^{-10}$	0.05	$4.94x10^{+07}$
SM C16:0/SM C18:0	4.64	0.71	-0.11	$3.20x10^{-10}$	$5.11x10^{-08}$	0.09	$9.30x10^{+04}$
SM C16:0/SM C18:1	9.36	1.83	-0.10	$3.57x10^{-10}$	$5.71x10^{-08}$	0.24	$8.33x10^{+04}$
SM (OH) C22:2/SM C18:1	1.00	0.19	-0.11	$2.59x10^{-09}$	$4.14x10^{-07}$	0.05	$2.93x10^{+05}$
SM (OH) C14:1/SM C18:1	0.58	0.14	-0.10	$3.40x10^{-08}$	$5.45x10^{-06}$	0.03	$2.89x10^{+03}$
SM (OH) C14:1/SM C18:0	0.29	0.06	-0.10	$6.07x10^{-08}$	$9.71x10^{-06}$	0.06	$1.62x10^{+03}$
SM (OH) C22:2/SM C16:1	0.69	0.12	-0.09	$3.32x10^{-07}$	$5.31x10^{-05}$	0.10	$2.29x10^{+03}$
SM (OH) C22:2/SM C18:0	0.50	0.10	-0.09	$3.59x10^{-07}$	$5.74x10^{-05}$	0.15	$2.12x10^{+03}$
SM (OH) C14:1/SM C16:1	0.40	0.08	-0.09	$4.60x10^{-07}$	$7.36x10^{-05}$	0.03	$2.14x10^{+02}$
SM C18:1/SM C26:1	27.63	8.81	0.08	$9.87x10^{-06}$	$1.58x10^{-03}$	0.14	$3.76x10^{+02}$
SM (OH) C24:1/SM C18:1	0.12	0.03	-0.08	$1.21x10^{-05}$	$1.94x10^{-03}$	0.08	$4.27x10^{+02}$
SM (OH) C24:1/SM C18:0	0.06	0.01	-0.08	$1.59x10^{-05}$	$2.54x10^{-03}$	0.02	$3.26x10^{+02}$
SM C18:0/SM C26:1	54.77	15.49	0.08	$2.17x10^{-05}$	$3.47x10^{-03}$	0.06	$1.71x10^{+02}$
SM C18:1/SM C24:1	0.22	0.05	0.06	$7.06x10^{-05}$	$1.13x10^{-02}$	0.23	$4.92x10^{+02}$
H1	5300.1	891.29	0.17	$2.67x10^{-21}$	$4.27x10^{-19}$	0.14	
Kynurenine	2.88	0.69	0.13	$1.11x10^{-13}$	$1.78x10^{-11}$	0.11	

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
alpha AAA	0.68	0.27	0.09	$8.51\text{x}10^{-07}$	$1.36\text{x}10^{-04}$	0.05	
Serotonin	0.70	0.34	-0.08	$2.21\text{x}10^{-05}$	$3.54\text{x}10^{-03}$	0.03	
Kynurenine/total DMA	2.43	0.65	0.15	$5.16\text{x}10^{-18}$	$8.25\text{x}10^{-16}$	0.09	$2.16\text{x}10^{+04}$
Serotonin/alpha AAA	2.85	29.44	-0.11	$1.24\text{x}10^{-09}$	$1.98\text{x}10^{-07}$	0.06	$6.89\text{x}10^{+02}$
alpha AAA/total DMA	0.58	0.26	0.11	$1.59\text{x}10^{-09}$	$2.54\text{x}10^{-07}$	0.06	$5.37\text{x}10^{+02}$
Met SO/SDMA	1.19	1.78	0.08	$3.47\text{x}10^{-06}$	$5.55\text{x}10^{-04}$	0.02	$1.35\text{x}10^{+03}$
Met SO/total DMA	0.66	0.23	0.08	$8.03\text{x}10^{-06}$	$1.28\text{x}10^{-03}$	0.02	$5.00\text{x}10^{+02}$

[a] Fat Free Mass Index; [b] for multiple testing adjusted p-value; [c] adjusted R^2 of the linear model; [d] p-gain, fold decrease in the p-value of association for the pair of metabolites, compared to the lowest of two p-values for the single metabolites; AAs amino acids; Σ aromatic amino acids is the sum of tyrosine, phenylalanine, and tryptophan; Σ BCAAs is the sum of valine, isoleucine, and leucine; Σ glucogenic amino acids is the sum of alanine, glycine, and serine.

Table B3: Metabolic traits significantly associated with FFMI[a] in a linear regression model adjusted for age, sex and batch (α = 5%, p-gain > 150) in the KORA F4 weight stable sample *(Jourdan et al., 2012)*.

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
xLeu	210.42	43.19	0.13	$4.75\text{x}10^{-16}$	$6.80\text{x}10^{-14}$	0.39	
Gly	314.88	83.47	-0.13	$6.53\text{x}10^{-12}$	$9.33\text{x}10^{-10}$	0.14	
Val	273.25	59.21	0.11	$2.05\text{x}10^{-11}$	$2.94\text{x}10^{-09}$	0.35	
Tyr	84.60	17.27	0.10	$1.19\text{x}10^{-07}$	$1.70\text{x}10^{-05}$	0.10	
Ser	130.82	24.44	-0.09	$1.65\text{x}10^{-05}$	$2.36\text{x}10^{-03}$	0.04	
Orn	81.50	18.59	0.07	$1.17\text{x}10^{-04}$	$1.67\text{x}10^{-02}$	0.14	
Σ BCAAs	483.67	97.47	0.13	$1.51\text{x}10^{-14}$	$2.15\text{x}10^{-12}$	0.38	
Σ aromatic AAs	229.04	32.96	0.08	$5.37\text{x}10^{-05}$	$7.68\text{x}10^{-03}$	0.11	
Gly/xLeu	1.57	0.57	-0.17	$6.01\text{x}10^{-27}$	$8.60\text{x}10^{-25}$	0.42	$7.90\text{x}10^{+10}$
Gly/Val	1.22	0.46	-0.16	$3.71\text{x}10^{-22}$	$5.31\text{x}10^{-20}$	0.39	$1.76\text{x}10^{+10}$
Gly/Tyr	3.87	1.30	-0.17	$5.22\text{x}10^{-21}$	$7.47\text{x}10^{-19}$	0.25	$1.25\text{x}10^{+09}$
Ser/xLeu	0.65	0.18	-0.16	$9.84\text{x}10^{-21}$	$1.41\text{x}10^{-18}$	0.35	$4.83\text{x}10^{+04}$
Ser/Val	0.50	0.13	-0.15	$2.37\text{x}10^{-20}$	$3.38\text{x}10^{-18}$	0.36	$8.68\text{x}10^{+08}$
Gln/xLeu	3.07	0.62	-0.16	$9.30\text{x}10^{-20}$	$1.33\text{x}10^{-17}$	0.27	$5.11\text{x}10^{+03}$
Gly/Orn	4.05	1.40	-0.15	$8.50\text{x}10^{-19}$	$1.21\text{x}10^{-16}$	0.31	$7.68\text{x}10^{+06}$
Gln/Val	2.37	0.45	-0.16	$1.88\text{x}10^{-18}$	$2.69\text{x}10^{-16}$	0.21	$1.09\text{x}10^{+07}$
His/xLeu	0.49	0.10	-0.13	$2.16\text{x}10^{-18}$	$3.09\text{x}10^{-16}$	0.52	$2.20\text{x}10^{+02}$
Ser/Tyr	1.60	0.40	-0.15	$3.97\text{x}10^{-16}$	$5.68\text{x}10^{-14}$	0.19	$2.99\text{x}10^{+08}$
Gly/Phe	5.28	1.64	-0.15	$2.67\text{x}10^{-15}$	$3.82\text{x}10^{-13}$	0.21	$2.44\text{x}10^{+03}$
Trp/Val	0.31	0.06	-0.12	$3.34\text{x}10^{-14}$	$4.77\text{x}10^{-12}$	0.43	$6.15\text{x}10^{+02}$
Gln/Tyr	7.64	1.50	-0.14	$1.20\text{x}10^{-12}$	$1.72\text{x}10^{-10}$	0.12	$9.88\text{x}10^{+04}$
Met/Tyr	0.38	0.06	-0.13	$6.70\text{x}10^{-12}$	$9.58\text{x}10^{-10}$	0.21	$1.77\text{x}10^{+04}$
Phe/Ser	0.48	0.10	0.13	$1.90\text{x}10^{-11}$	$2.72\text{x}10^{-09}$	0.14	$8.65\text{x}10^{+05}$
Orn/Ser	0.64	0.17	0.12	$2.12\text{x}10^{-11}$	$3.03\text{x}10^{-09}$	0.22	$7.78\text{x}10^{+05}$
Trp/Tyr	1.01	0.16	-0.12	$5.93\text{x}10^{-10}$	$8.48\text{x}10^{-08}$	0.13	$2.00\text{x}10^{+02}$
Gln/Orn	8.00	1.72	-0.11	$1.21\text{x}10^{-08}$	$1.73\text{x}10^{-06}$	0.06	$9.65\text{x}10^{+03}$
Gln/Phe	10.44	1.79	-0.10	$2.50\text{x}10^{-07}$	$3.57\text{x}10^{-05}$	0.13	$4.18\text{x}10^{+03}$
Σ BCAAs/ Σ glucogenic AAs	1.14	0.34	0.17	$2.68\text{x}10^{-27}$	$3.83\text{x}10^{-25}$	0.43	
C8:1	0.09	0.04	0.11	$1.39\text{x}10^{-08}$	$1.98\text{x}10^{-06}$	0.07	
C9	0.05	0.02	-0.08	$2.37\text{x}10^{-05}$	$3.40\text{x}10^{-03}$	0.06	
C3	0.38	0.12	0.08	$3.41\text{x}10^{-05}$	$4.88\text{x}10^{-03}$	0.14	
C5	0.11	0.04	0.08	$5.85\text{x}10^{-05}$	$8.36\text{x}10^{-03}$	0.17	
C0	35.05	7.36	0.07	$1.17\text{x}10^{-04}$	$1.68\text{x}10^{-02}$	0.13	
C8:1/C9	1.91	1.20	0.15	$2.23\text{x}10^{-14}$	$3.18\text{x}10^{-12}$	0.07	$6.23\text{x}10^{+05}$
C12/C8:1	1.77	0.83	-0.15	$7.98\text{x}10^{-14}$	$1.14\text{x}10^{-11}$	0.06	$1.74\text{x}10^{+05}$
C14:2/C8:1	0.41	0.19	-0.14	$3.38\text{x}10^{-13}$	$4.84\text{x}10^{-11}$	0.08	$4.10\text{x}10^{+04}$
C7-DC/C8:1	0.61	0.28	-0.14	$6.24\text{x}10^{-13}$	$8.92\text{x}10^{-11}$	0.09	$2.22\text{x}10^{+04}$
C10/C8:1	4.79	2.45	-0.14	$1.78\text{x}10^{-12}$	$2.55\text{x}10^{-10}$	0.07	$7.78\text{x}10^{+03}$
C14:1-OH/C8:1	0.20	0.08	-0.14	$3.77\text{x}10^{-12}$	$5.40\text{x}10^{-10}$	0.05	$3.68\text{x}10^{+03}$
C12:1/C8:1	1.97	0.85	-0.14	$6.67\text{x}10^{-12}$	$9.53\text{x}10^{-10}$	0.06	$2.08\text{x}10^{+03}$
C14:1/C8:1	2.08	0.92	-0.13	$1.63\text{x}10^{-11}$	$2.33\text{x}10^{-09}$	0.12	$8.53\text{x}10^{+02}$
C14:2-OH/C8:1	0.13	0.06	-0.13	$2.93\text{x}10^{-11}$	$4.19\text{x}10^{-09}$	0.14	$4.74\text{x}10^{+02}$
C5/C9	2.56	1.17	0.13	$3.11\text{x}10^{-11}$	$4.44\text{x}10^{-09}$	0.15	$7.64\text{x}10^{+05}$
C14/C8:1	0.63	0.28	-0.13	$6.95\text{x}10^{-11}$	$9.93\text{x}10^{-09}$	0.06	$2.00\text{x}10^{+02}$

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
C3/C9	8.46	4.00	0.13	$7.71\text{x}10^{-11}$	$1.10\text{x}10^{-08}$	0.11	$3.08\text{x}10^{+05}$
C0/C9	792.55	331.39	0.12	$3.58\text{x}10^{-09}$	$5.12\text{x}10^{-07}$	0.07	$6.64\text{x}10^{+03}$
C10/C6 (C4:1-DC)	5.07	1.20	-0.12	$4.11\text{x}10^{-09}$	$5.88\text{x}10^{-07}$	0.05	$1.42\text{x}10^{+06}$
C12/C5	1.23	0.55	-0.11	$1.52\text{x}10^{-08}$	$2.17\text{x}10^{-06}$	0.13	$3.85\text{x}10^{+03}$
C14:2-OH/C5	0.09	0.03	-0.10	$3.05\text{x}10^{-08}$	$4.36\text{x}10^{-06}$	0.23	$1.92\text{x}10^{+03}$
C5/C7-DC	2.85	1.29	0.11	$3.20\text{x}10^{-08}$	$4.58\text{x}10^{-06}$	0.10	$1.83\text{x}10^{+03}$
C12/C3	0.37	0.17	-0.11	$6.35\text{x}10^{-08}$	$9.07\text{x}10^{-06}$	0.07	$5.38\text{x}10^{+02}$
C14:1-OH/C5	0.14	0.05	-0.10	$9.97\text{x}10^{-08}$	$1.43\text{x}10^{-05}$	0.13	$5.87\text{x}10^{+02}$
C12/C16	1.12	0.34	-0.10	$1.32\text{x}10^{-07}$	$1.89\text{x}10^{-05}$	0.07	$7.85\text{x}10^{+03}$
C14/C16	0.39	0.06	-0.09	$1.86\text{x}10^{-07}$	$2.66\text{x}10^{-05}$	0.27	$3.57\text{x}10^{+05}$
C12/C6 (C4:1-DC)	1.92	0.52	-0.10	$2.23\text{x}10^{-07}$	$3.18\text{x}10^{-05}$	0.03	$4.66\text{x}10^{+03}$
C10/C5	3.33	1.68	-0.10	$3.20\text{x}10^{-07}$	$4.58\text{x}10^{-05}$	0.13	$1.83\text{x}10^{+02}$
C0/C12	300.33	117.20	0.10	$3.40\text{x}10^{-07}$	$4.87\text{x}10^{-05}$	0.07	$3.45\text{x}10^{+02}$
C12/C18:1	1.02	0.32	-0.10	$3.78\text{x}10^{-07}$	$5.41\text{x}10^{-05}$	0.08	$2.74\text{x}10^{+03}$
C12/C2	0.02	0.01	-0.10	$7.38\text{x}10^{-07}$	$1.06\text{x}10^{-04}$	0.04	$1.40\text{x}10^{+03}$
C10/C8	1.61	0.20	-0.09	$7.00\text{x}10^{-06}$	$1.00\text{x}10^{-03}$	0.05	$8.32\text{x}10^{+02}$
C14:1-OH/C16	0.13	0.03	-0.09	$7.38\text{x}10^{-06}$	$1.06\text{x}10^{-03}$	0.02	$3.26\text{x}10^{+03}$
C16/C7-DC	2.89	0.95	0.08	$1.37\text{x}10^{-05}$	$1.96\text{x}10^{-03}$	0.10	$4.52\text{x}10^{+02}$
C18:1/C7-DC	3.17	1.09	0.08	$1.62\text{x}10^{-05}$	$2.32\text{x}10^{-03}$	0.13	$3.82\text{x}10^{+02}$
C2/C7-DC	192.69	63.81	0.08	$1.90\text{x}10^{-05}$	$2.71\text{x}10^{-03}$	0.12	$3.27\text{x}10^{+02}$
C10/C10:1	2.14	0.48	-0.08	$2.78\text{x}10^{-05}$	$3.98\text{x}10^{-03}$	0.03	$2.09\text{x}10^{+02}$
C14:1-OH/C18:1	0.12	0.03	-0.08	$3.14\text{x}10^{-05}$	$4.49\text{x}10^{-03}$	0.03	$7.66\text{x}10^{+02}$
C14:1/C18:1	1.20	0.31	-0.07	$8.34\text{x}10^{-05}$	$1.19\text{x}10^{-02}$	0.35	$7.25\text{x}10^{+02}$
C14:2/C18:2	0.68	0.22	-0.07	$1.05\text{x}10^{-04}$	$1.51\text{x}10^{-02}$	0.13	$2.16\text{x}10^{+02}$
C14:2/C18:1	0.24	0.08	-0.08	$1.09\text{x}10^{-04}$	$1.56\text{x}10^{-02}$	0.10	$2.09\text{x}10^{+02}$
C12:1/C18:1	1.14	0.29	-0.08	$1.16\text{x}10^{-04}$	$1.66\text{x}10^{-02}$	0.08	$3.81\text{x}10^{+02}$
C14/C18:1	0.36	0.07	-0.07	$1.26\text{x}10^{-04}$	$1.80\text{x}10^{-02}$	0.20	$5.30\text{x}10^{+02}$
C12:1/C16	1.25	0.34	-0.08	$1.34\text{x}10^{-04}$	$1.91\text{x}10^{-02}$	0.06	$3.31\text{x}10^{+02}$
C6 (C4:1-DC)/C8	0.33	0.06	0.08	$1.36\text{x}10^{-04}$	$1.95\text{x}10^{-02}$	0.01	$1.03\text{x}10^{+03}$
C16/C16:1-OH	10.99	2.14	0.07	$1.69\text{x}10^{-04}$	$2.41\text{x}10^{-02}$	0.25	$6.79\text{x}10^{+02}$
C14:1/C16	1.31	0.34	-0.06	$1.95\text{x}10^{-04}$	$2.78\text{x}10^{-02}$	0.30	$3.11\text{x}10^{+02}$
C16/C18	2.34	0.43	0.07	$2.76\text{x}10^{-04}$	$3.94\text{x}10^{-02}$	0.06	$4.16\text{x}10^{+02}$
Single PC							
PC aa C42:0	0.61	0.17	-0.15	$9.14\text{x}10^{-15}$	$1.31\text{x}10^{-12}$	0.11	
PC aa C42:1	0.30	0.08	-0.14	$8.48\text{x}10^{-13}$	$1.21\text{x}10^{-10}$	0.08	
PC aa C38:3	53.25	12.82	0.14	$3.20\text{x}10^{-12}$	$4.58\text{x}10^{-10}$	0.11	
PC aa C42:2	0.22	0.06	-0.11	$3.22\text{x}10^{-08}$	$4.60\text{x}10^{-06}$	0.05	
PC aa C38:4	117.39	28.78	0.10	$1.86\text{x}10^{-06}$	$2.66\text{x}10^{-04}$	0.05	
PC aa C40:1	0.47	0.10	-0.09	$4.32\text{x}10^{-06}$	$6.18\text{x}10^{-04}$	0.09	
PC aa C40:4	4.13	1.16	0.08	$5.63\text{x}10^{-05}$	$8.05\text{x}10^{-03}$	0.02	
PC aa C42:6	0.63	0.14	-0.08	$1.01\text{x}10^{-04}$	$1.45\text{x}10^{-02}$	0.03	
PC aa C40:2	0.36	0.10	-0.08	$1.37\text{x}10^{-04}$	$1.96\text{x}10^{-02}$	0.04	
PC ae C42:3	0.90	0.20	-0.16	$1.00\text{x}10^{-15}$	$1.44\text{x}10^{-13}$	0.10	
PC ae C42:4	1.04	0.24	-0.15	$2.27\text{x}10^{-14}$	$3.25\text{x}10^{-12}$	0.12	
PC ae C44:4	0.44	0.11	-0.14	$7.20\text{x}10^{-13}$	$1.03\text{x}10^{-10}$	0.10	
PC ae C44:6	1.40	0.37	-0.14	$7.50\text{x}10^{-13}$	$1.07\text{x}10^{-10}$	0.08	
PC ae C42:5	2.40	0.49	-0.14	$2.84\text{x}10^{-12}$	$4.07\text{x}10^{-10}$	0.10	
PC ae C36:2	15.72	4.00	-0.13	$3.67\text{x}10^{-12}$	$5.24\text{x}10^{-10}$	0.20	
PC ae C40:5	3.62	0.65	-0.13	$2.70\text{x}10^{-11}$	$3.86\text{x}10^{-09}$	0.08	

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
PC ae C44:5	2.16	0.54	-0.13	$1.47\text{x}10^{-10}$	$2.10\text{x}10^{-08}$	0.06	
PC ae C40:6	5.16	1.31	-0.12	$2.10\text{x}10^{-10}$	$3.00\text{x}10^{-08}$	0.13	
PC ae C30:0	0.48	0.14	-0.12	$3.05\text{x}10^{-10}$	$4.37\text{x}10^{-08}$	0.20	
PC ae C38:2	2.20	0.51	-0.12	$1.76\text{x}10^{-09}$	$2.52\text{x}10^{-07}$	0.11	
PC ae C40:3	1.16	0.23	-0.11	$3.29\text{x}10^{-09}$	$4.70\text{x}10^{-07}$	0.19	
PC ae C44:3	0.11	0.03	-0.12	$4.64\text{x}10^{-09}$	$6.63\text{x}10^{-07}$	0.05	
PC ae C34:0	1.77	0.46	-0.11	$9.30\text{x}10^{-09}$	$1.33\text{x}10^{-06}$	0.14	
PC ae C42:2	0.69	0.15	-0.11	$5.43\text{x}10^{-08}$	$7.77\text{x}10^{-06}$	0.11	
PC ae C36:1	8.51	1.96	-0.10	$8.57\text{x}10^{-08}$	$1.22\text{x}10^{-05}$	0.14	
PC ae C34:1	10.83	2.39	-0.10	$1.47\text{x}10^{-07}$	$2.11\text{x}10^{-05}$	0.18	
PC ae C34:3	8.74	2.45	-0.10	$4.66\text{x}10^{-07}$	$6.66\text{x}10^{-05}$	0.07	
PC ae C40:4	2.62	0.48	-0.10	$9.74\text{x}10^{-07}$	$1.39\text{x}10^{-04}$	0.07	
PC ae C32:2	0.77	0.17	-0.09	$1.20\text{x}10^{-06}$	$1.71\text{x}10^{-04}$	0.15	
PC ae C40:2	2.12	0.48	-0.09	$1.70\text{x}10^{-06}$	$2.43\text{x}10^{-04}$	0.16	
PC ae C40:1	1.72	0.40	-0.10	$2.00\text{x}10^{-06}$	$2.86\text{x}10^{-04}$	0.03	
PC ae C32:1	2.95	0.62	-0.09	$4.72\text{x}10^{-06}$	$6.74\text{x}10^{-04}$	0.13	
PC ae C34:2	13.16	3.39	-0.08	$1.06\text{x}10^{-05}$	$1.52\text{x}10^{-03}$	0.13	
PC ae C38:0	2.55	0.78	-0.08	$5.20\text{x}10^{-05}$	$7.43\text{x}10^{-03}$	0.05	
PC ae C40:0	10.31	1.66	-0.07	$1.83\text{x}10^{-04}$	$2.62\text{x}10^{-02}$	0.13	
Σ PC ae	199.62	34.61	-0.08	$3.29\text{x}10^{-05}$	$4.71\text{x}10^{-03}$	0.11	
lysoPC a C17:0	1.81	0.52	-0.15	$1.28\text{x}10^{-14}$	$1.84\text{x}10^{-12}$	0.10	
lysoPC a C18:1	20.26	5.87	-0.13	$1.64\text{x}10^{-12}$	$2.35\text{x}10^{-10}$	0.16	
lysoPC a C18:2	29.29	9.85	-0.13	$2.36\text{x}10^{-12}$	$3.37\text{x}10^{-10}$	0.19	
lysoPC a C28:1	0.63	0.22	-0.08	$2.48\text{x}10^{-05}$	$3.55\text{x}10^{-03}$	0.06	
Σ lysoPC	194.05	40.53	-0.09	$1.19\text{x}10^{-06}$	$1.70\text{x}10^{-04}$	0.14	
PC aa/PC aa Ratios							
PC aa C38:3/PC aa C42:6	85.92	19.67	0.21	$3.67\text{x}10^{-29}$	$5.25\text{x}10^{-27}$	0.19	$8.71\text{x}10^{+16}$
PC aa C38:3/PC aa C42:1	187.87	67.29	0.20	$4.04\text{x}10^{-24}$	$5.77\text{x}10^{-22}$	0.13	$2.10\text{x}10^{+11}$
PC aa C38:3/PC aa C42:0	95.48	37.12	0.20	$4.59\text{x}10^{-24}$	$6.56\text{x}10^{-22}$	0.14	$1.99\text{x}10^{+09}$
PC aa C38:4/PC aa C42:1	410.11	138.19	0.19	$2.58\text{x}10^{-21}$	$3.69\text{x}10^{-19}$	0.11	$3.28\text{x}10^{+08}$
PC aa C38:3/PC aa C42:2	263.42	87.32	0.19	$4.50\text{x}10^{-21}$	$6.43\text{x}10^{-19}$	0.10	$7.11\text{x}10^{+08}$
PC aa C38:3/PC aa C42:4	243.89	55.88	0.18	$1.40\text{x}10^{-20}$	$2.01\text{x}10^{-18}$	0.11	$2.28\text{x}10^{+08}$
PC aa C38:4/PC aa C42:0	209.21	80.15	0.18	$1.84\text{x}10^{-20}$	$2.63\text{x}10^{-18}$	0.12	$4.98\text{x}10^{+05}$
PC aa C36:3/PC aa C38:3	2.89	0.49	-0.15	$1.20\text{x}10^{-19}$	$1.71\text{x}10^{-17}$	0.35	$2.68\text{x}10^{+07}$
PC aa C28:1/PC aa C38:3	0.07	0.02	-0.18	$1.87\text{x}10^{-19}$	$2.68\text{x}10^{-17}$	0.11	$1.71\text{x}10^{+07}$
PC aa C30:0/PC aa C38:3	0.09	0.03	-0.17	$2.70\text{x}10^{-19}$	$3.86\text{x}10^{-17}$	0.18	$1.19\text{x}10^{+07}$
PC aa C38:3/PC aa C40:1	116.93	35.7	0.17	$2.69\text{x}10^{-18}$	$3.85\text{x}10^{-16}$	0.15	$1.19\text{x}10^{+06}$
PC aa C32:0/PC aa C38:3	0.30	0.07	-0.17	$2.81\text{x}10^{-18}$	$4.02\text{x}10^{-16}$	0.16	$1.14\text{x}10^{+06}$
PC aa C38:3/PC aa C40:2	155.08	45.98	0.17	$3.44\text{x}10^{-18}$	$4.93\text{x}10^{-16}$	0.10	$9.29\text{x}10^{+05}$
PC aa C38:3/PC aa C42:5	129.66	33.97	0.17	$3.88\text{x}10^{-18}$	$5.55\text{x}10^{-16}$	0.10	$8.24\text{x}10^{+05}$
PC aa C38:4/PC aa C42:6	189.31	43.84	0.17	$4.26\text{x}10^{-18}$	$6.09\text{x}10^{-16}$	0.11	$4.36\text{x}10^{+11}$
PC aa C36:1/PC aa C38:3	1.04	0.19	-0.17	$2.50\text{x}10^{-17}$	$3.58\text{x}10^{-15}$	0.09	$1.28\text{x}10^{+05}$
PC aa C40:4/PC aa C42:6	6.62	1.51	0.17	$6.51\text{x}10^{-17}$	$9.31\text{x}10^{-15}$	0.10	$8.65\text{x}10^{+11}$
PC aa C32:3/PC aa C38:3	0.01	0.00	-0.16	$8.02\text{x}10^{-17}$	$1.15\text{x}10^{-14}$	0.14	$3.99\text{x}10^{+04}$
PC aa C38:4/PC aa C42:2	578.15	187.71	0.16	$3.79\text{x}10^{-16}$	$5.42\text{x}10^{-14}$	0.07	$8.49\text{x}10^{+07}$
PC aa C34:3/PC aa C38:3	0.35	0.10	-0.15	$6.22\text{x}10^{-16}$	$8.89\text{x}10^{-14}$	0.17	$5.15\text{x}10^{+03}$
PC aa C38:3/PC aa C38:5	0.87	0.20	0.16	$6.62\text{x}10^{-16}$	$9.47\text{x}10^{-14}$	0.14	$4.83\text{x}10^{+03}$
PC aa C40:4/PC aa C42:1	14.58	5.79	0.16	$7.57\text{x}10^{-16}$	$1.08\text{x}10^{-13}$	0.09	$1.12\text{x}10^{+03}$
PC aa C38:4/PC aa C38:5	1.89	0.32	0.15	$2.79\text{x}10^{-15}$	$3.99\text{x}10^{-13}$	0.13	$6.65\text{x}10^{+08}$

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
PC aa C36:2/PC aa C38:3	4.59	0.98	-0.14	$4.80\text{x}10^{-15}$	$6.87\text{x}10^{-13}$	0.21	$6.66\text{x}10^{+02}$
PC aa C38:4/PC aa C42:4	534.83	111.92	0.16	$6.55\text{x}10^{-15}$	$9.36\text{x}10^{-13}$	0.07	$2.84\text{x}10^{+08}$
PC aa C40:5/PC aa C42:6	18.36	3.65	0.15	$4.28\text{x}10^{-14}$	$6.12\text{x}10^{-12}$	0.10	$2.36\text{x}10^{+09}$
PC aa C38:4/PC aa C40:3	181.57	42.79	0.15	$5.40\text{x}10^{-14}$	$7.73\text{x}10^{-12}$	0.07	$3.44\text{x}10^{+07}$
PC aa C38:4/PC aa C40:1	256.42	74.82	0.14	$1.30\text{x}10^{-13}$	$1.86\text{x}10^{-11}$	0.11	$1.43\text{x}10^{+07}$
PC aa C38:4/PC aa C40:2	339.98	94.47	0.15	$1.65\text{x}10^{-13}$	$2.36\text{x}10^{-11}$	0.07	$1.13\text{x}10^{+07}$
PC aa C38:6/PC aa C40:6	3.28	0.49	-0.13	$4.37\text{x}10^{-13}$	$6.25\text{x}10^{-11}$	0.25	$1.80\text{x}10^{+11}$
PC aa C40:4/PC aa C42:2	20.46	7.50	0.14	$1.66\text{x}10^{-12}$	$2.37\text{x}10^{-10}$	0.05	$1.94\text{x}10^{+04}$
PC aa C38:4/PC aa C42:5	285.15	73.15	0.14	$6.36\text{x}10^{-12}$	$9.09\text{x}10^{-10}$	0.06	$2.92\text{x}10^{+05}$
PC aa C40:4/PC aa C42:4	18.76	4.34	0.14	$6.99\text{x}10^{-12}$	$1.00\text{x}10^{-09}$	0.07	$8.05\text{x}10^{+06}$
PC aa C40:3/PC aa C40:4	0.17	0.05	-0.14	$8.95\text{x}10^{-12}$	$1.28\text{x}10^{-09}$	0.06	$6.29\text{x}10^{+06}$
PC aa C30:0/PC aa C40:4	1.21	0.39	-0.13	$3.65\text{x}10^{-11}$	$5.23\text{x}10^{-09}$	0.13	$1.54\text{x}10^{+06}$
PC aa C40:6/PC aa C42:2	135.72	41.45	0.13	$4.42\text{x}10^{-11}$	$6.32\text{x}10^{-09}$	0.08	$7.28\text{x}10^{+02}$
PC aa C36:4/PC aa C42:2	1074.77	332.11	0.13	$6.30\text{x}10^{-11}$	$9.01\text{x}10^{-09}$	0.10	$5.11\text{x}10^{+02}$
PC aa C32:0/PC aa C38:4	0.14	0.03	-0.13	$8.37\text{x}10^{-11}$	$1.20\text{x}10^{-08}$	0.10	$2.22\text{x}10^{+04}$
PC aa C28:1/PC aa C38:4	0.03	0.01	-0.13	$8.53\text{x}10^{-11}$	$1.22\text{x}10^{-08}$	0.08	$2.18\text{x}10^{+04}$
PC aa C40:4/PC aa C42:5	9.99	2.63	0.13	$9.76\text{x}10^{-11}$	$1.40\text{x}10^{-08}$	0.06	$5.76\text{x}10^{+05}$
PC aa C40:2/PC aa C40:4	0.09	0.03	-0.13	$1.17\text{x}10^{-10}$	$1.68\text{x}10^{-08}$	0.05	$4.79\text{x}10^{+05}$
PC aa C38:0/PC aa C38:4	0.03	0.01	-0.13	$1.28\text{x}10^{-10}$	$1.83\text{x}10^{-08}$	0.07	$1.45\text{x}10^{+04}$
PC aa C30:0/PC aa C38:4	0.04	0.01	-0.12	$2.60\text{x}10^{-10}$	$3.71\text{x}10^{-08}$	0.11	$7.15\text{x}10^{+03}$
PC aa C40:1/PC aa C40:4	0.12	0.04	-0.12	$9.92\text{x}10^{-10}$	$1.42\text{x}10^{-07}$	0.07	$4.36\text{x}10^{+03}$
PC aa C32:3/PC aa C38:4	0.00	0.00	-0.12	$1.68\text{x}10^{-09}$	$2.41\text{x}10^{-07}$	0.11	$1.10\text{x}10^{+03}$
PC aa C38:5/PC aa C40:4	15.68	3.34	-0.12	$1.85\text{x}10^{-09}$	$2.65\text{x}10^{-07}$	0.06	$3.03\text{x}10^{+04}$
PC aa C32:0/PC aa C40:4	3.89	0.96	-0.12	$2.09\text{x}10^{-09}$	$2.99\text{x}10^{-07}$	0.08	$2.69\text{x}10^{+04}$
PC aa C36:4/PC aa C42:6	353.04	80.73	0.12	$2.42\text{x}10^{-09}$	$3.46\text{x}10^{-07}$	0.09	$4.18\text{x}10^{+04}$
PC aa C28:1/PC aa C40:4	0.88	0.26	-0.11	$5.64\text{x}10^{-09}$	$8.07\text{x}10^{-07}$	0.10	$9.97\text{x}10^{+03}$
PC aa C40:5/PC aa C42:5	27.62	6.19	0.12	$6.12\text{x}10^{-09}$	$8.75\text{x}10^{-07}$	0.05	$2.05\text{x}10^{+06}$
PC aa C36:0/PC aa C38:4	0.02	0.01	-0.11	$6.83\text{x}10^{-09}$	$9.77\text{x}10^{-07}$	0.08	$2.72\text{x}10^{+02}$
PC aa C38:4/PC aa C38:6	1.36	0.39	0.12	$7.67\text{x}10^{-09}$	$1.10\text{x}10^{-06}$	0.06	$2.42\text{x}10^{+02}$
PC aa C40:3/PC aa C40:5	0.06	0.02	-0.11	$2.11\text{x}10^{-08}$	$3.01\text{x}10^{-06}$	0.04	$5.79\text{x}10^{+04}$
PC aa C36:3/PC aa C42:6	244.39	51.71	0.11	$5.69\text{x}10^{-08}$	$8.13\text{x}10^{-06}$	0.06	$1.78\text{x}10^{+03}$
PC aa C40:2/PC aa C40:5	0.03	0.01	-0.11	$6.11\text{x}10^{-08}$	$8.74\text{x}10^{-06}$	0.03	$2.24\text{x}10^{+03}$
PC aa C32:3/PC aa C40:4	0.13	0.04	-0.10	$6.75\text{x}10^{-08}$	$9.66\text{x}10^{-06}$	0.13	$8.33\text{x}10^{+02}$
PC aa C40:6/PC aa C42:6	44.99	11.65	0.10	$7.36\text{x}10^{-08}$	$1.05\text{x}10^{-05}$	0.15	$1.37\text{x}10^{+03}$
PC aa C36:4/PC aa C40:2	633.22	172.28	0.11	$9.52\text{x}10^{-08}$	$1.36\text{x}10^{-05}$	0.09	$1.44\text{x}10^{+03}$
PC aa C34:3/PC aa C40:4	4.62	1.36	-0.10	$1.07\text{x}10^{-07}$	$1.52\text{x}10^{-05}$	0.11	$5.28\text{x}10^{+02}$
PC aa C38:0/PC aa C40:6	0.12	0.03	-0.10	$1.29\text{x}10^{-07}$	$1.85\text{x}10^{-05}$	0.11	$1.11\text{x}10^{+04}$
PC aa C30:0/PC aa C40:5	0.43	0.14	-0.10	$1.35\text{x}10^{-07}$	$1.93\text{x}10^{-05}$	0.11	$1.59\text{x}10^{+04}$
PC aa C30:0/PC aa C36:3	0.03	0.01	-0.10	$2.06\text{x}10^{-07}$	$2.94\text{x}10^{-05}$	0.05	$1.04\text{x}10^{+04}$
PC aa C30:0/PC aa C36:4	0.02	0.01	-0.10	$2.85\text{x}10^{-07}$	$4.07\text{x}10^{-05}$	0.06	$7.54\text{x}10^{+03}$
PC aa C32:0/PC aa C36:4	0.07	0.01	-0.10	$3.07\text{x}10^{-07}$	$4.39\text{x}10^{-05}$	0.10	$8.52\text{x}10^{+04}$
PC aa C36:4/PC aa C42:4	998.53	211.75	0.10	$3.74\text{x}10^{-07}$	$5.35\text{x}10^{-05}$	0.16	$4.53\text{x}10^{+04}$
PC aa C36:4/PC aa C40:3	338.74	79.41	0.10	$5.07\text{x}10^{-07}$	$7.25\text{x}10^{-05}$	0.10	$2.41\text{x}10^{+03}$
PC aa C38:5/PC aa C40:5	5.56	0.89	-0.10	$8.94\text{x}10^{-07}$	$1.28\text{x}10^{-04}$	0.07	$1.57\text{x}10^{+04}$
PC aa C36:6/PC aa C40:6	0.04	0.01	-0.10	$1.12\text{x}10^{-06}$	$1.61\text{x}10^{-04}$	0.06	$1.02\text{x}10^{+04}$
PC aa C40:5/PC aa C42:4	52.43	12.16	0.10	$1.29\text{x}10^{-06}$	$1.85\text{x}10^{-04}$	0.03	$1.09\text{x}10^{+04}$
PC aa C30:0/PC aa C32:1	0.25	0.07	-0.09	$1.73\text{x}10^{-06}$	$2.48\text{x}10^{-04}$	0.06	$1.24\text{x}10^{+03}$
PC aa C36:6/PC aa C40:5	0.10	0.04	-0.09	$3.42\text{x}10^{-06}$	$4.89\text{x}10^{-04}$	0.06	$3.36\text{x}10^{+03}$
PC aa C30:0/PC aa C34:4	2.22	0.57	-0.09	$3.69\text{x}10^{-06}$	$5.28\text{x}10^{-04}$	0.10	$5.82\text{x}10^{+02}$

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
PC aa C36:0/PC aa C40:6	0.10	0.03	-0.09	$3.81\text{x}10^{-06}$	$5.45\text{x}10^{-04}$	0.14	$3.19\text{x}10^{+03}$
PC aa C40:6/PC aa C42:5	67.18	16.98	0.09	$3.83\text{x}10^{-06}$	$5.47\text{x}10^{-04}$	0.08	$3.28\text{x}10^{+03}$
PC aa C28:1/PC aa C36:3	0.02	0.01	-0.09	$4.02\text{x}10^{-06}$	$5.75\text{x}10^{-04}$	0.15	$4.21\text{x}10^{+02}$
PC aa C28:1/PC aa C40:5	0.31	0.09	-0.09	$4.04\text{x}10^{-06}$	$5.78\text{x}10^{-04}$	0.07	$4.19\text{x}10^{+02}$
PC aa C36:3/PC aa C40:3	234.08	48.61	0.09	$4.65\text{x}10^{-06}$	$6.65\text{x}10^{-04}$	0.08	$2.62\text{x}10^{+02}$
PC aa C28:1/PC aa C36:4	0.02	0.00	-0.09	$5.82\text{x}10^{-06}$	$8.33\text{x}10^{-04}$	0.15	$2.91\text{x}10^{+02}$
PC aa C36:4/PC aa C38:0	69.93	21.54	0.09	$8.88\text{x}10^{-06}$	$1.27\text{x}10^{-03}$	0.05	$1.61\text{x}10^{+02}$
PC aa C36:4/PC aa C42:5	533.12	140.27	0.09	$9.54\text{x}10^{-06}$	$1.36\text{x}10^{-03}$	0.08	$1.32\text{x}10^{+03}$
PC aa C36:4/PC aa C38:5	3.52	0.54	0.09	$9.81\text{x}10^{-06}$	$1.40\text{x}10^{-03}$	0.11	$2.66\text{x}10^{+03}$
PC aa C36:4/PC aa C36:6	213.15	79.58	0.09	$1.11\text{x}10^{-05}$	$1.58\text{x}10^{-03}$	0.11	$1.04\text{x}10^{+03}$
PC aa C34:4/PC aa C36:6	2.09	0.54	0.09	$1.30\text{x}10^{-05}$	$1.86\text{x}10^{-03}$	0.03	$8.82\text{x}10^{+02}$
PC aa C32:0/PC aa C40:5	1.39	0.33	-0.09	$1.36\text{x}10^{-05}$	$1.95\text{x}10^{-03}$	0.06	$1.03\text{x}10^{+03}$
PC aa C34:3/PC aa C36:3	0.12	0.02	-0.08	$1.63\text{x}10^{-05}$	$2.33\text{x}10^{-03}$	0.09	$4.82\text{x}10^{+03}$
PC aa C32:3/PC aa C36:4	0.00	0.00	-0.08	$2.65\text{x}10^{-05}$	$3.79\text{x}10^{-03}$	0.20	$6.37\text{x}10^{+02}$
PC aa C32:3/PC aa C36:3	0.00	0.00	-0.08	$2.78\text{x}10^{-05}$	$3.97\text{x}10^{-03}$	0.20	$6.08\text{x}10^{+02}$
PC aa C32:0/PC aa C36:3	0.10	0.02	-0.08	$2.98\text{x}10^{-05}$	$4.26\text{x}10^{-03}$	0.06	$2.31\text{x}10^{+03}$
PC aa C36:0/PC aa C36:4	0.01	0.00	-0.08	$3.04\text{x}10^{-05}$	$4.34\text{x}10^{-03}$	0.03	$3.99\text{x}10^{+02}$
PC aa C32:3/PC aa C40:5	0.04	0.01	-0.08	$3.29\text{x}10^{-05}$	$4.70\text{x}10^{-03}$	0.12	$4.27\text{x}10^{+02}$
PC aa C36:3/PC aa C42:4	693.57	146.97	0.08	$6.76\text{x}10^{-05}$	$9.67\text{x}10^{-03}$	0.10	$2.50\text{x}10^{+02}$
PC aa C36:4/PC aa C38:6	2.53	0.68	0.08	$1.10\text{x}10^{-04}$	$1.57\text{x}10^{-02}$	0.07	$2.38\text{x}10^{+02}$
PC aa C32:2/PC aa C34:4	1.78	0.50	-0.07	$2.05\text{x}10^{-04}$	$2.93\text{x}10^{-02}$	0.21	$9.21\text{x}10^{+02}$
PC ae/PC ae Ratios							
PC ae C36:4/PC ae C44:6	15.71	5.02	0.16	$1.10\text{x}10^{-15}$	$1.58\text{x}10^{-13}$	0.12	$6.80\text{x}10^{+02}$
PC ae C36:4/PC ae C42:5	8.95	2.36	0.16	$2.13\text{x}10^{-15}$	$3.05\text{x}10^{-13}$	0.11	$1.33\text{x}10^{+03}$
PC ae C36:4/PC ae C40:6	4.24	1.20	0.15	$1.61\text{x}10^{-14}$	$2.31\text{x}10^{-12}$	0.14	$1.30\text{x}10^{+04}$
PC ae C34:2/PC ae C36:4	0.64	0.15	-0.14	$4.48\text{x}10^{-14}$	$6.41\text{x}10^{-12}$	0.18	$2.36\text{x}10^{+08}$
PC ae C36:4/PC ae C44:5	10.14	3.12	0.15	$7.90\text{x}10^{-14}$	$1.13\text{x}10^{-11}$	0.08	$1.86\text{x}10^{+03}$
PC ae C38:6/PC ae C40:6	1.73	0.29	0.14	$1.30\text{x}10^{-13}$	$1.86\text{x}10^{-11}$	0.18	$1.62\text{x}10^{+03}$
PC ae C34:3/PC ae C36:4	0.43	0.12	-0.14	$7.63\text{x}10^{-13}$	$1.09\text{x}10^{-10}$	0.14	$6.10\text{x}10^{+05}$
PC ae C36:4/PC ae C40:4	8.11	1.88	0.14	$1.61\text{x}10^{-12}$	$2.31\text{x}10^{-10}$	0.15	$6.04\text{x}10^{+05}$
PC ae C36:4/PC ae C38:5	1.04	0.10	0.13	$1.30\text{x}10^{-11}$	$1.86\text{x}10^{-09}$	0.08	$2.55\text{x}10^{+09}$
PC ae C36:3/PC ae C36:4	0.43	0.08	-0.12	$1.09\text{x}10^{-10}$	$1.56\text{x}10^{-08}$	0.14	$3.67\text{x}10^{+07}$
PC ae C36:4/PC ae C40:1	12.62	3.46	0.13	$1.21\text{x}10^{-10}$	$1.73\text{x}10^{-08}$	0.07	$1.65\text{x}10^{+04}$
PC ae C36:4/PC ae C42:2	31.47	8.87	0.13	$2.24\text{x}10^{-10}$	$3.20\text{x}10^{-08}$	0.07	$2.43\text{x}10^{+02}$
PC ae C34:3/PC ae C36:5	0.64	0.15	-0.12	$3.43\text{x}10^{-10}$	$4.90\text{x}10^{-08}$	0.15	$1.36\text{x}10^{+03}$
PC ae C36:4/PC ae C38:4	1.33	0.22	0.12	$6.24\text{x}10^{-10}$	$8.92\text{x}10^{-08}$	0.13	$5.32\text{x}10^{+07}$
PC ae C34:1/PC ae C36:4	0.54	0.15	-0.12	$8.22\text{x}10^{-10}$	$1.18\text{x}10^{-07}$	0.13	$1.79\text{x}10^{+02}$
PC ae C32:1/PC ae C36:4	0.15	0.04	-0.12	$8.80\text{x}10^{-10}$	$1.26\text{x}10^{-07}$	0.10	$5.36\text{x}10^{+03}$
PC ae C32:2/PC ae C36:4	0.04	0.01	-0.11	$4.64\text{x}10^{-09}$	$6.64\text{x}10^{-07}$	0.16	$2.58\text{x}10^{+02}$
PC ae C36:4/PC ae C38:6	2.43	0.49	0.09	$9.05\text{x}10^{-07}$	$1.29\text{x}10^{-04}$	0.17	$3.66\text{x}10^{+04}$
lysoPC/lysoPC Ratios							
lysoPC a C18:1/lysoPC a C20:3	8.41	1.74	-0.18	$1.47\text{x}10^{-19}$	$2.10\text{x}10^{-17}$	0.09	$1.12\text{x}10^{+07}$
PC aa/PC ae Ratios							
PC aa C38:3/PC ae C42:3	61.98	19.51	0.22	$1.09\text{x}10^{-31}$	$1.55\text{x}10^{-29}$	0.18	$9.25\text{x}10^{+15}$
PC aa C38:3/PC ae C40:3	47.15	12.34	0.22	$9.19\text{x}10^{-31}$	$1.31\text{x}10^{-28}$	0.21	$3.48\text{x}10^{+18}$
PC aa C38:3/PC ae C36:1	6.45	1.72	0.22	$4.41\text{x}10^{-30}$	$6.31\text{x}10^{-28}$	0.16	$7.25\text{x}10^{+17}$
PC aa C38:3/PC ae C38:3	12.44	2.77	0.21	$1.83\text{x}10^{-29}$	$2.62\text{x}10^{-27}$	0.19	$1.75\text{x}10^{+17}$
PC aa C38:3/PC ae C38:2	25.07	6.88	0.22	$1.90\text{x}10^{-29}$	$2.71\text{x}10^{-27}$	0.17	$1.69\text{x}10^{+17}$
PC aa C38:3/PC ae C42:2	79.82	21.99	0.21	$3.58\text{x}10^{-29}$	$5.12\text{x}10^{-27}$	0.23	$8.95\text{x}10^{+16}$

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
PC aa C38:3/PC ae C44:4	128.33	43.91	0.21	$5.73\text{x}10^{-29}$	$8.20\text{x}10^{-27}$	0.20	$1.25\text{x}10^{+16}$
PC aa C38:3/PC ae C40:5	15.04	4.11	0.22	$3.05\text{x}10^{-28}$	$4.36\text{x}10^{-26}$	0.14	$1.05\text{x}10^{+16}$
PC aa C38:3/PC ae C42:4	53.97	18.28	0.21	$3.54\text{x}10^{-28}$	$5.06\text{x}10^{-26}$	0.20	$6.42\text{x}10^{+13}$
PC aa C38:3/PC ae C34:1	5.08	1.40	0.20	$4.06\text{x}10^{-28}$	$5.81\text{x}10^{-26}$	0.24	$7.88\text{x}10^{+15}$
PC aa C38:3/PC ae C36:2	3.60	1.31	0.20	$2.47\text{x}10^{-27}$	$3.53\text{x}10^{-25}$	0.21	$1.29\text{x}10^{+15}$
PC aa C38:3/PC ae C34:0	31.53	9.70	0.20	$5.34\text{x}10^{-27}$	$7.64\text{x}10^{-25}$	0.19	$5.99\text{x}10^{+14}$
PC aa C38:3/PC ae C44:3	494.02	150.03	0.20	$1.18\text{x}10^{-26}$	$1.69\text{x}10^{-24}$	0.17	$2.71\text{x}10^{+14}$
PC aa C38:4/PC ae C40:5	32.85	7.81	0.21	$2.24\text{x}10^{-26}$	$3.20\text{x}10^{-24}$	0.12	$1.21\text{x}10^{+15}$
PC aa C38:3/PC ae C40:1	32.11	9.03	0.21	$3.73\text{x}10^{-26}$	$5.33\text{x}10^{-24}$	0.15	$8.58\text{x}10^{+13}$
PC aa C38:4/PC ae C40:1	69.92	15.87	0.20	$1.76\text{x}10^{-25}$	$2.51\text{x}10^{-23}$	0.13	$1.06\text{x}10^{+19}$
PC aa C38:3/PC aa C40:3	82.26	18.55	0.20	$5.11\text{x}10^{-25}$	$7.30\text{x}10^{-23}$	0.14	$6.27\text{x}10^{+12}$
PC aa C38:3/PC ae C42:5	23.09	7.35	0.19	$2.10\text{x}10^{-24}$	$3.01\text{x}10^{-22}$	0.17	$1.35\text{x}10^{+12}$
PC aa C38:3/PC ae C40:4	20.79	5.57	0.20	$2.72\text{x}10^{-24}$	$3.89\text{x}10^{-22}$	0.16	$1.18\text{x}10^{+12}$
PC aa C38:4/PC ae C42:3	136.35	42.29	0.20	$5.01\text{x}10^{-24}$	$7.16\text{x}10^{-22}$	0.14	$2.01\text{x}10^{+08}$
PC aa C38:3/PC ae C30:0	119.06	43.89	0.18	$6.82\text{x}10^{-24}$	$9.75\text{x}10^{-22}$	0.25	$4.69\text{x}10^{+11}$
PC aa C38:3/PC ae C40:6	10.95	3.83	0.19	$1.56\text{x}10^{-23}$	$2.22\text{x}10^{-21}$	0.15	$2.06\text{x}10^{+11}$
PC aa C38:3/PC ae C44:5	26.19	9.39	0.19	$9.10\text{x}10^{-23}$	$1.30\text{x}10^{-20}$	0.15	$3.52\text{x}10^{+10}$
PC aa C38:3/PC ae C44:6	40.69	15.40	0.19	$9.65\text{x}10^{-23}$	$1.38\text{x}10^{-20}$	0.13	$7.76\text{x}10^{+09}$
PC aa C36:2/PC ae C36:2	15.60	3.46	0.18	$2.99\text{x}10^{-22}$	$4.28\text{x}10^{-20}$	0.20	$1.23\text{x}10^{+10}$
PC aa C38:3/PC ae C40:0	5.24	1.29	0.18	$7.03\text{x}10^{-22}$	$1.01\text{x}10^{-19}$	0.20	$4.55\text{x}10^{+09}$
PC aa C38:4/PC ae C42:5	50.50	15.17	0.18	$1.81\text{x}10^{-21}$	$2.58\text{x}10^{-19}$	0.15	$1.57\text{x}10^{+09}$
PC aa C38:4/PC ae C42:4	118.88	41.13	0.18	$2.49\text{x}10^{-21}$	$3.56\text{x}10^{-19}$	0.15	$9.11\text{x}10^{+06}$
PC aa C38:3/PC ae C40:2	26.13	7.85	0.19	$5.27\text{x}10^{-21}$	$7.53\text{x}10^{-19}$	0.11	$6.08\text{x}10^{+08}$
PC aa C38:3/PC ae C32:2	72.26	22.14	0.18	$6.54\text{x}10^{-21}$	$9.35\text{x}10^{-19}$	0.15	$4.89\text{x}10^{+08}$
PC aa C38:3/PC ae C32:1	18.71	5.60	0.18	$1.43\text{x}10^{-20}$	$2.04\text{x}10^{-18}$	0.17	$2.24\text{x}10^{+08}$
PC aa C38:4/PC ae C40:4	45.49	11.00	0.18	$1.52\text{x}10^{-20}$	$2.17\text{x}10^{-18}$	0.13	$6.43\text{x}10^{+13}$
PC aa C38:4/PC ae C40:6	23.87	7.46	0.18	$1.71\text{x}10^{-20}$	$2.45\text{x}10^{-18}$	0.14	$1.22\text{x}10^{+10}$
PC aa C38:4/PC ae C44:6	88.79	32.11	0.18	$2.17\text{x}10^{-20}$	$3.11\text{x}10^{-18}$	0.12	$3.45\text{x}10^{+07}$
PC aa C36:2/PC ae C38:2	109.88	18.12	0.18	$3.02\text{x}10^{-20}$	$4.32\text{x}10^{-18}$	0.18	$5.83\text{x}10^{+10}$
PC aa C38:3/PC ae C38:0	22.23	6.96	0.18	$3.52\text{x}10^{-20}$	$5.03\text{x}10^{-18}$	0.10	$9.09\text{x}10^{+07}$
PC aa C38:3/PC ae C42:1	144.58	33.32	0.17	$8.59\text{x}10^{-20}$	$1.23\text{x}10^{-17}$	0.15	$3.73\text{x}10^{+07}$
PC aa C38:4/PC ae C42:2	175.65	47.68	0.17	$9.18\text{x}10^{-20}$	$1.31\text{x}10^{-17}$	0.17	$5.92\text{x}10^{+11}$
PC aa C36:3/PC ae C36:2	10.05	2.86	0.17	$2.12\text{x}10^{-19}$	$3.03\text{x}10^{-17}$	0.17	$1.73\text{x}10^{+07}$
PC aa C38:4/PC ae C44:5	57.29	19.78	0.17	$3.76\text{x}10^{-19}$	$5.38\text{x}10^{-17}$	0.12	$3.91\text{x}10^{+08}$
PC aa C38:4/PC ae C44:4	284.94	107.16	0.17	$6.67\text{x}10^{-19}$	$9.54\text{x}10^{-17}$	0.13	$1.08\text{x}10^{+06}$
PC aa C40:4/PC ae C40:5	1.16	0.34	0.18	$1.11\text{x}10^{-18}$	$1.59\text{x}10^{-16}$	0.10	$2.43\text{x}10^{+07}$
PC aa C40:4/PC ae C42:4	4.18	1.63	0.17	$1.18\text{x}10^{-18}$	$1.68\text{x}10^{-16}$	0.13	$1.93\text{x}10^{+04}$
PC aa C38:4/PC ae C36:2	7.97	3.01	0.17	$1.60\text{x}10^{-18}$	$2.29\text{x}10^{-16}$	0.16	$2.29\text{x}10^{+06}$
PC aa C40:4/PC ae C42:3	4.82	1.73	0.17	$2.17\text{x}10^{-18}$	$3.10\text{x}10^{-16}$	0.11	$4.64\text{x}10^{+02}$
PC aa C34:2/PC ae C36:2	26.32	6.53	0.14	$2.57\text{x}10^{-18}$	$3.68\text{x}10^{-16}$	0.38	$1.42\text{x}10^{+06}$
PC aa C40:6/PC ae C40:6	5.58	1.57	0.16	$4.10\text{x}10^{-18}$	$5.87\text{x}10^{-16}$	0.19	$5.11\text{x}10^{+07}$
PC aa C36:3/PC ae C42:3	174.42	45.25	0.17	$5.62\text{x}10^{-18}$	$8.03\text{x}10^{-16}$	0.10	$1.79\text{x}10^{+02}$
PC aa C36:2/PC ae C42:3	272.07	61.81	0.17	$6.60\text{x}10^{-18}$	$9.44\text{x}10^{-16}$	0.10	$1.52\text{x}10^{+02}$
PC aa C40:4/PC ae C44:4	9.98	4.04	0.17	$8.47\text{x}10^{-18}$	$1.21\text{x}10^{-15}$	0.12	$8.49\text{x}10^{+04}$
PC aa C38:4/PC ae C40:3	104.47	29.93	0.17	$8.54\text{x}10^{-18}$	$1.22\text{x}10^{-15}$	0.14	$3.85\text{x}10^{+08}$
PC aa C36:3/PC ae C38:2	70.54	15.38	0.16	$9.88\text{x}10^{-18}$	$1.41\text{x}10^{-15}$	0.16	$1.78\text{x}10^{+08}$
PC aa C36:4/PC ae C40:1	129.94	27.23	0.16	$1.33\text{x}10^{-17}$	$1.90\text{x}10^{-15}$	0.15	$1.50\text{x}10^{+11}$
PC aa C38:3/PC ae C34:2	4.32	1.60	0.16	$1.51\text{x}10^{-17}$	$2.16\text{x}10^{-15}$	0.17	$2.12\text{x}10^{+05}$
PC aa C38:4/PC ae C44:3	1091.87	351.39	0.17	$2.13\text{x}10^{-17}$	$3.04\text{x}10^{-15}$	0.11	$2.18\text{x}10^{+08}$

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
PC aa C38:3/PC ae C36:0	52.49	15.87	0.16	$2.16\text{x}10^{-17}$	$3.09\text{x}10^{-15}$	0.14	$1.48\text{x}10^{+05}$
PC aa C38:3/PC ae C34:3	6.58	2.54	0.17	$2.38\text{x}10^{-17}$	$3.41\text{x}10^{-15}$	0.11	$1.34\text{x}10^{+05}$
PC aa C40:4/PC ae C42:2	6.16	1.80	0.16	$3.46\text{x}10^{-17}$	$4.95\text{x}10^{-15}$	0.14	$1.57\text{x}10^{+09}$
PC aa C38:4/PC ae C38:2	55.70	17.18	0.17	$4.37\text{x}10^{-17}$	$6.25\text{x}10^{-15}$	0.11	$4.03\text{x}10^{+07}$
PC aa C38:3/PC ae C36:3	6.30	1.93	0.16	$5.16\text{x}10^{-17}$	$7.38\text{x}10^{-15}$	0.20	$6.20\text{x}10^{+04}$
PC aa C38:4/PC ae C34:0	69.86	22.89	0.16	$5.83\text{x}10^{-17}$	$8.34\text{x}10^{-15}$	0.13	$1.60\text{x}10^{+08}$
PC aa C40:4/PC ae C36:2	0.28	0.12	0.16	$6.42\text{x}10^{-17}$	$9.17\text{x}10^{-15}$	0.16	$5.71\text{x}10^{+04}$
PC aa C38:4/PC ae C36:1	14.32	4.26	0.16	$1.09\text{x}10^{-16}$	$1.55\text{x}10^{-14}$	0.10	$7.88\text{x}10^{+08}$
PC ae C36:4/PC ae C40:5	5.87	1.39	0.16	$1.38\text{x}10^{-16}$	$1.97\text{x}10^{-14}$	0.18	$1.96\text{x}10^{+05}$
PC aa C40:4/PC ae C38:2	1.95	0.64	0.16	$1.52\text{x}10^{-16}$	$2.18\text{x}10^{-14}$	0.12	$1.16\text{x}10^{+07}$
PC aa C40:4/PC ae C40:4	1.60	0.47	0.16	$2.65\text{x}10^{-16}$	$3.79\text{x}10^{-14}$	0.11	$3.68\text{x}10^{+09}$
PC aa C38:3/PC ae C42:0	107.87	30.84	0.15	$2.71\text{x}10^{-16}$	$3.87\text{x}10^{-14}$	0.19	$1.18\text{x}10^{+04}$
PC aa C38:4/PC ae C38:4	7.52	1.73	0.15	$3.51\text{x}10^{-16}$	$5.01\text{x}10^{-14}$	0.20	$5.30\text{x}10^{+09}$
PC aa C40:4/PC ae C36:1	0.50	0.16	0.16	$3.61\text{x}10^{-16}$	$5.16\text{x}10^{-14}$	0.13	$2.38\text{x}10^{+08}$
PC aa C40:4/PC ae C34:1	0.39	0.12	0.15	$4.01\text{x}10^{-16}$	$5.74\text{x}10^{-14}$	0.17	$3.67\text{x}10^{+08}$
PC aa C40:4/PC ae C34:0	2.45	0.85	0.16	$4.35\text{x}10^{-16}$	$6.22\text{x}10^{-14}$	0.14	$2.14\text{x}10^{+07}$
PC aa C40:4/PC ae C40:1	2.47	0.71	0.16	$5.93\text{x}10^{-16}$	$8.49\text{x}10^{-14}$	0.07	$3.37\text{x}10^{+09}$
PC aa C38:3/PC ae C38:4	3.46	0.99	0.15	$8.80\text{x}10^{-16}$	$1.26\text{x}10^{-13}$	0.19	$3.64\text{x}10^{+03}$
PC aa C40:4/PC ae C42:5	1.78	0.63	0.16	$1.13\text{x}10^{-15}$	$1.61\text{x}10^{-13}$	0.11	$2.52\text{x}10^{+03}$
PC aa C40:4/PC ae C44:3	38.28	12.76	0.16	$1.23\text{x}10^{-15}$	$1.77\text{x}10^{-13}$	0.09	$3.76\text{x}10^{+06}$
PC aa C34:2/PC ae C38:2	186.71	44.17	0.12	$1.78\text{x}10^{-15}$	$2.55\text{x}10^{-13}$	0.46	$9.89\text{x}10^{+05}$
PC aa C38:4/PC ae C34:1	11.27	3.44	0.15	$2.11\text{x}10^{-15}$	$3.02\text{x}10^{-13}$	0.15	$6.97\text{x}10^{+07}$
PC aa C40:4/PC ae C40:3	3.67	1.19	0.15	$2.53\text{x}10^{-15}$	$3.62\text{x}10^{-13}$	0.15	$1.30\text{x}10^{+06}$
PC aa C42:1/PC ae C36:4	0.02	0.00	-0.15	$2.54\text{x}10^{-15}$	$3.63\text{x}10^{-13}$	0.12	$3.34\text{x}10^{+02}$
PC aa C36:3/PC ae C44:4	360.79	104.54	0.16	$2.68\text{x}10^{-15}$	$3.83\text{x}10^{-13}$	0.09	$2.69\text{x}10^{+02}$
PC aa C40:4/PC ae C44:6	3.15	1.33	0.16	$2.86\text{x}10^{-15}$	$4.09\text{x}10^{-13}$	0.09	$2.62\text{x}10^{+02}$
PC aa C36:4/PC ae C40:5	61.46	15.62	0.15	$3.15\text{x}10^{-15}$	$4.51\text{x}10^{-13}$	0.18	$8.57\text{x}10^{+03}$
PC aa C40:4/PC ae C30:0	9.27	3.93	0.15	$3.33\text{x}10^{-15}$	$4.76\text{x}10^{-13}$	0.18	$9.18\text{x}10^{+04}$
PC aa C36:3/PC ae C34:1	14.24	2.82	0.15	$5.47\text{x}10^{-15}$	$7.83\text{x}10^{-13}$	0.14	$2.69\text{x}10^{+07}$
PC aa C38:4/PC ae C38:0	48.82	14.76	0.16	$7.17\text{x}10^{-15}$	$1.03\text{x}10^{-12}$	0.08	$2.59\text{x}10^{+08}$
PC aa C36:3/PC ae C36:1	18.24	4.14	0.14	$8.26\text{x}10^{-15}$	$1.18\text{x}10^{-12}$	0.22	$1.04\text{x}10^{+07}$
PC aa C38:3/PC ae C38:1	70.46	26.94	0.16	$9.26\text{x}10^{-15}$	$1.32\text{x}10^{-12}$	0.07	$3.46\text{x}10^{+02}$
PC aa C40:4/PC ae C44:5	2.02	0.80	0.15	$9.37\text{x}10^{-15}$	$1.34\text{x}10^{-12}$	0.09	$1.57\text{x}10^{+04}$
PC aa C38:4/PC ae C30:0	264.99	107.03	0.15	$9.92\text{x}10^{-15}$	$1.42\text{x}10^{-12}$	0.17	$3.08\text{x}10^{+04}$
PC aa C38:4/PC ae C32:2	159.11	49.29	0.15	$1.06\text{x}10^{-14}$	$1.51\text{x}10^{-12}$	0.12	$1.13\text{x}10^{+08}$
PC aa C38:4/PC ae C40:0	11.5	2.65	0.15	$1.22\text{x}10^{-14}$	$1.75\text{x}10^{-12}$	0.14	$1.52\text{x}10^{+08}$
PC aa C38:4/PC ae C40:2	57.61	17.37	0.15	$1.78\text{x}10^{-14}$	$2.55\text{x}10^{-12}$	0.09	$9.55\text{x}10^{+07}$
PC aa C38:4/PC ae C32:1	41.25	12.65	0.15	$2.22\text{x}10^{-14}$	$3.18\text{x}10^{-12}$	0.13	$8.36\text{x}10^{+07}$
PC aa C40:5/PC ae C42:2	17.08	4.43	0.15	$2.47\text{x}10^{-14}$	$3.54\text{x}10^{-12}$	0.15	$2.20\text{x}10^{+06}$
PC aa C36:3/PC ae C34:0	88.54	21.38	0.15	$3.18\text{x}10^{-14}$	$4.55\text{x}10^{-12}$	0.11	$2.92\text{x}10^{+05}$
PC aa C40:4/PC ae C40:6	0.85	0.34	0.15	$5.04\text{x}10^{-14}$	$7.20\text{x}10^{-12}$	0.11	$4.16\text{x}10^{+03}$
PC aa C38:4/PC ae C42:1	316.84	65.17	0.15	$6.00\text{x}10^{-14}$	$8.58\text{x}10^{-12}$	0.10	$3.10\text{x}10^{+07}$
PC aa C38:4/PC ae C34:3	14.45	5.52	0.15	$1.62\text{x}10^{-13}$	$2.32\text{x}10^{-11}$	0.09	$2.87\text{x}10^{+06}$
PC aa C36:4/PC ae C40:6	44.41	13.52	0.14	$1.74\text{x}10^{-13}$	$2.49\text{x}10^{-11}$	0.11	$1.20\text{x}10^{+03}$
PC aa C34:1/PC ae C34:1	22.79	4.59	0.13	$2.55\text{x}10^{-13}$	$3.65\text{x}10^{-11}$	0.22	$5.77\text{x}10^{+05}$
PC aa C36:3/PC ae C42:2	224.74	48.80	0.15	$3.17\text{x}10^{-13}$	$4.54\text{x}10^{-11}$	0.06	$1.71\text{x}10^{+05}$
PC aa C36:4/PC ae C42:2	325.38	79.48	0.15	$3.33\text{x}10^{-13}$	$4.76\text{x}10^{-11}$	0.08	$1.63\text{x}10^{+05}$
PC aa C36:4/PC ae C34:0	128.93	37.64	0.14	$4.17\text{x}10^{-13}$	$5.96\text{x}10^{-11}$	0.12	$2.23\text{x}10^{+04}$
PC aa C36:3/PC ae C30:0	332.08	98.14	0.14	$4.49\text{x}10^{-13}$	$6.42\text{x}10^{-11}$	0.11	$6.80\text{x}10^{+02}$

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
PC aa C36:3/PC ae C40:3	133.46	30.09	0.14	$5.82\text{x}10^{-13}$	$8.33\text{x}10^{-11}$	0.18	$5.65\text{x}10^{+03}$
PC aa C40:5/PC ae C40:1	6.87	1.77	0.14	$1.12\text{x}10^{-12}$	$1.60\text{x}10^{-10}$	0.07	$1.79\text{x}10^{+06}$
PC aa C40:5/PC ae C40:6	2.35	0.82	0.14	$1.27\text{x}10^{-12}$	$1.81\text{x}10^{-10}$	0.10	$1.66\text{x}10^{+02}$
PC aa C40:5/PC ae C34:0	6.79	2.21	0.14	$1.27\text{x}10^{-12}$	$1.82\text{x}10^{-10}$	0.12	$7.31\text{x}10^{+03}$
PC aa C40:6/PC ae C38:0	11.37	2.82	0.14	$2.06\text{x}10^{-12}$	$2.95\text{x}10^{-10}$	0.11	$2.52\text{x}10^{+07}$
PC aa C40:4/PC ae C32:1	1.45	0.50	0.14	$2.32\text{x}10^{-12}$	$3.31\text{x}10^{-10}$	0.11	$2.03\text{x}10^{+06}$
PC aa C36:1/PC ae C36:1	6.54	1.57	0.13	$2.36\text{x}10^{-12}$	$3.37\text{x}10^{-10}$	0.14	$3.63\text{x}10^{+04}$
PC aa C38:4/PC ae C34:2	9.51	3.57	0.14	$3.02\text{x}10^{-12}$	$4.32\text{x}10^{-10}$	0.13	$6.15\text{x}10^{+05}$
PC aa C40:5/PC ae C44:3	106.36	33.39	0.14	$3.31\text{x}10^{-12}$	$4.73\text{x}10^{-10}$	0.09	$1.40\text{x}10^{+03}$
PC aa C34:2/PC ae C34:0	233.74	58.43	0.12	$8.33\text{x}10^{-12}$	$1.19\text{x}10^{-09}$	0.31	$1.12\text{x}10^{+03}$
PC aa C40:4/PC ae C42:1	11.08	2.34	0.14	$1.22\text{x}10^{-11}$	$1.74\text{x}10^{-09}$	0.07	$4.62\text{x}10^{+06}$
PC aa C36:3/PC ae C44:3	1398.09	384.63	0.13	$1.52\text{x}10^{-11}$	$2.18\text{x}10^{-09}$	0.07	$3.04\text{x}10^{+02}$
PC aa C40:5/PC ae C36:1	1.40	0.42	0.13	$1.69\text{x}10^{-11}$	$2.41\text{x}10^{-09}$	0.11	$5.08\text{x}10^{+03}$
PC aa C40:4/PC ae C32:2	5.62	2.01	0.13	$1.82\text{x}10^{-11}$	$2.60\text{x}10^{-09}$	0.12	$6.59\text{x}10^{+04}$
PC aa C36:1/PC ae C34:0	31.89	8.56	0.12	$1.93\text{x}10^{-11}$	$2.77\text{x}10^{-09}$	0.20	$4.81\text{x}10^{+02}$
PC aa C36:3/PC ae C40:1	90.72	21.49	0.13	$2.20\text{x}10^{-11}$	$3.15\text{x}10^{-09}$	0.08	$9.09\text{x}10^{+04}$
PC aa C36:4/PC ae C34:1	20.78	5.50	0.13	$2.27\text{x}10^{-11}$	$3.25\text{x}10^{-09}$	0.12	$6.49\text{x}10^{+03}$
PC aa C38:4/PC ae C36:0	115.73	35.3	0.13	$2.28\text{x}10^{-11}$	$3.27\text{x}10^{-09}$	0.09	$8.13\text{x}10^{+04}$
PC aa C36:4/PC ae C36:1	26.67	7.79	0.12	$3.61\text{x}10^{-11}$	$5.17\text{x}10^{-09}$	0.19	$2.37\text{x}10^{+03}$
PC aa C36:2/PC ae C34:0	138.87	31.74	0.13	$3.89\text{x}10^{-11}$	$5.56\text{x}10^{-09}$	0.08	$2.39\text{x}10^{+02}$
PC aa C34:1/PC ae C34:0	141.93	35.69	0.13	$4.12\text{x}10^{-11}$	$5.89\text{x}10^{-09}$	0.14	$2.26\text{x}10^{+02}$
PC aa C36:2/PC ae C42:2	351.86	69.37	0.13	$4.31\text{x}10^{-11}$	$6.17\text{x}10^{-09}$	0.05	$1.26\text{x}10^{+03}$
PC aa C40:4/PC ae C34:3	0.51	0.22	0.13	$4.62\text{x}10^{-11}$	$6.60\text{x}10^{-09}$	0.08	$1.01\text{x}10^{+04}$
PC aa C38:4/PC ae C38:3	27.78	7.79	0.13	$5.18\text{x}10^{-11}$	$7.40\text{x}10^{-09}$	0.09	$3.59\text{x}10^{+04}$
PC aa C40:4/PC ae C38:0	1.73	0.62	0.13	$5.37\text{x}10^{-11}$	$7.68\text{x}10^{-09}$	0.07	$9.67\text{x}10^{+05}$
PC aa C34:2/PC ae C34:1	37.62	7.99	0.11	$6.10\text{x}10^{-11}$	$8.72\text{x}10^{-09}$	0.36	$2.41\text{x}10^{+03}$
PC aa C36:2/PC ae C36:1	28.60	6.02	0.12	$6.15\text{x}10^{-11}$	$8.80\text{x}10^{-09}$	0.18	$1.39\text{x}10^{+03}$
PC aa C36:4/PC ae C40:4	84.85	20.53	0.13	$7.00\text{x}10^{-11}$	$1.00\text{x}10^{-08}$	0.13	$1.39\text{x}10^{+04}$
PC aa C36:1/PC ae C34:1	5.14	1.19	0.11	$7.80\text{x}10^{-11}$	$1.12\text{x}10^{-08}$	0.29	$1.89\text{x}10^{+03}$
PC aa C40:4/PC ae C34:2	0.34	0.14	0.13	$8.37\text{x}10^{-11}$	$1.20\text{x}10^{-08}$	0.11	$1.27\text{x}10^{+05}$
PC aa C40:5/PC ae C34:1	1.10	0.33	0.12	$1.12\text{x}10^{-10}$	$1.60\text{x}10^{-08}$	0.14	$1.32\text{x}10^{+03}$
PC aa C38:4/PC ae C42:0	237.08	66.26	0.12	$1.46\text{x}10^{-10}$	$2.09\text{x}10^{-08}$	0.13	$1.27\text{x}10^{+04}$
PC aa C40:4/PC ae C36:0	4.06	1.30	0.13	$2.07\text{x}10^{-10}$	$2.96\text{x}10^{-08}$	0.07	$2.71\text{x}10^{+05}$
PC aa C40:4/PC ae C38:4	0.27	0.08	0.12	$2.36\text{x}10^{-10}$	$3.38\text{x}10^{-08}$	0.12	$2.38\text{x}10^{+05}$
PC aa C34:1/PC ae C36:1	29.37	7.64	0.11	$2.90\text{x}10^{-10}$	$4.15\text{x}10^{-08}$	0.29	$2.95\text{x}10^{+02}$
PC aa C40:4/PC ae C38:3	0.97	0.30	0.12	$3.42\text{x}10^{-10}$	$4.90\text{x}10^{-08}$	0.13	$1.64\text{x}10^{+05}$
PC aa C38:4/PC ae C38:5	5.93	1.30	0.12	$3.58\text{x}10^{-10}$	$5.12\text{x}10^{-08}$	0.15	$5.18\text{x}10^{+03}$
PC aa C36:4/PC ae C32:1	76.06	20.02	0.12	$3.60\text{x}10^{-10}$	$5.15\text{x}10^{-08}$	0.08	$1.31\text{x}10^{+04}$
PC aa C40:4/PC ae C40:2	2.05	0.75	0.12	$3.72\text{x}10^{-10}$	$5.32\text{x}10^{-08}$	0.10	$4.57\text{x}10^{+03}$
PC aa C38:4/PC ae C36:3	13.93	4.52	0.12	$3.87\text{x}10^{-10}$	$5.54\text{x}10^{-08}$	0.13	$4.80\text{x}10^{+03}$
PC aa C40:5/PC ae C38:0	4.76	1.44	0.12	$4.42\text{x}10^{-10}$	$6.32\text{x}10^{-08}$	0.07	$1.17\text{x}10^{+05}$
PC aa C40:4/PC ae C40:0	0.41	0.11	0.12	$5.26\text{x}10^{-10}$	$7.52\text{x}10^{-08}$	0.09	$1.07\text{x}10^{+05}$
PC aa C36:4/PC ae C38:0	90.74	26.10	0.12	$5.89\text{x}10^{-10}$	$8.43\text{x}10^{-08}$	0.14	$8.82\text{x}10^{+04}$
PC aa C36:2/PC ae C34:1	22.38	4.35	0.12	$6.07\text{x}10^{-10}$	$8.69\text{x}10^{-08}$	0.09	$2.42\text{x}10^{+02}$
PC aa C38:4/PC ae C38:1	156.15	63.36	0.12	$7.08\text{x}10^{-10}$	$1.01\text{x}10^{-07}$	0.04	$2.62\text{x}10^{+03}$
PC aa C36:2/PC ae C34:3	28.47	7.42	0.12	$1.18\text{x}10^{-09}$	$1.68\text{x}10^{-07}$	0.07	$3.96\text{x}10^{+02}$
PC aa C38:5/PC ae C40:1	37.09	6.37	0.12	$1.35\text{x}10^{-09}$	$1.93\text{x}10^{-07}$	0.05	$1.48\text{x}10^{+03}$
PC aa C36:4/PC ae C32:2	295.14	84.94	0.11	$1.42\text{x}10^{-09}$	$2.03\text{x}10^{-07}$	0.15	$8.43\text{x}10^{+02}$
PC aa C38:4/PC ae C38:6	13.79	3.62	0.12	$1.50\text{x}10^{-09}$	$2.15\text{x}10^{-07}$	0.04	$1.24\text{x}10^{+03}$

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
PC aa C40:6/PC ae C40:1	16.77	4.89	0.12	$2.14\text{x}10^{-09}$	$3.05\text{x}10^{-07}$	0.13	$9.37\text{x}10^{+02}$
PC aa C36:4/PC ae C34:3	26.70	9.31	0.12	$2.38\text{x}10^{-09}$	$3.41\text{x}10^{-07}$	0.09	$1.95\text{x}10^{+02}$
PC aa C36:2/PC ae C40:1	142.13	31.74	0.12	$2.42\text{x}10^{-09}$	$3.47\text{x}10^{-07}$	0.08	$8.25\text{x}10^{+02}$
PC aa C40:4/PC ae C36:3	0.49	0.17	0.12	$2.87\text{x}10^{-09}$	$4.10\text{x}10^{-07}$	0.11	$1.96\text{x}10^{+04}$
PC aa C36:3/PC ae C32:1	52.49	11.97	0.12	$3.48\text{x}10^{-09}$	$4.98\text{x}10^{-07}$	0.05	$1.35\text{x}10^{+03}$
PC aa C40:5/PC ae C40:4	4.49	1.33	0.11	$5.77\text{x}10^{-09}$	$8.25\text{x}10^{-07}$	0.08	$1.69\text{x}10^{+02}$
PC aa C40:4/PC ae C38:1	5.47	2.25	0.12	$7.38\text{x}10^{-09}$	$1.06\text{x}10^{-06}$	0.04	$7.63\text{x}10^{+03}$
PC aa C36:4/PC ae C40:2	107.63	32.61	0.11	$8.06\text{x}10^{-09}$	$1.15\text{x}10^{-06}$	0.21	$2.11\text{x}10^{+02}$
PC aa C36:2/PC ae C34:2	18.66	4.22	0.11	$9.04\text{x}10^{-09}$	$1.29\text{x}10^{-06}$	0.08	$1.17\text{x}10^{+03}$
PC aa C36:3/PC ae C34:2	12.04	3.46	0.11	$2.31\text{x}10^{-08}$	$3.30\text{x}10^{-06}$	0.07	$4.59\text{x}10^{+02}$
PC aa C40:5/PC ae C32:1	4.04	1.36	0.11	$2.92\text{x}10^{-08}$	$4.17\text{x}10^{-06}$	0.10	$1.62\text{x}10^{+02}$
PC aa C40:4/PC ae C42:0	8.36	2.61	0.11	$3.18\text{x}10^{-08}$	$4.55\text{x}10^{-06}$	0.09	$1.77\text{x}10^{+03}$
PC aa C36:3/PC ae C38:0	63.00	17.9	0.11	$5.51\text{x}10^{-08}$	$7.88\text{x}10^{-06}$	0.09	$9.42\text{x}10^{+02}$
PC aa C38:0/PC ae C36:4	0.16	0.04	-0.11	$5.72\text{x}10^{-08}$	$8.18\text{x}10^{-06}$	0.08	$2.50\text{x}10^{+04}$
PC aa C36:4/PC ae C34:2	17.54	5.88	0.11	$5.80\text{x}10^{-08}$	$8.30\text{x}10^{-06}$	0.07	$1.83\text{x}10^{+02}$
PC aa C36:4/PC ae C36:0	213.53	57.08	0.11	$8.78\text{x}10^{-08}$	$1.26\text{x}10^{-05}$	0.04	$7.26\text{x}10^{+03}$
PC aa C38:5/PC ae C38:0	25.56	5.29	0.10	$9.73\text{x}10^{-08}$	$1.39\text{x}10^{-05}$	0.09	$5.34\text{x}10^{+02}$
PC aa C40:5/PC ae C40:0	1.12	0.27	0.10	$1.43\text{x}10^{-07}$	$2.04\text{x}10^{-05}$	0.10	$1.28\text{x}10^{+03}$
PC aa C40:5/PC ae C36:0	11.29	3.44	0.10	$1.87\text{x}10^{-07}$	$2.67\text{x}10^{-05}$	0.06	$3.41\text{x}10^{+03}$
PC aa C36:4/PC ae C40:0	21.34	4.43	0.10	$2.16\text{x}10^{-07}$	$3.09\text{x}10^{-05}$	0.05	$8.49\text{x}10^{+02}$
PC aa C36:3/PC ae C38:3	35.36	7.00	0.09	$2.36\text{x}10^{-07}$	$3.38\text{x}10^{-05}$	0.24	$6.27\text{x}10^{+04}$
PC aa C36:4/PC ae C38:4	13.98	2.94	0.10	$3.93\text{x}10^{-07}$	$5.62\text{x}10^{-05}$	0.05	$6.65\text{x}10^{+04}$
PC aa C40:2/PC ae C36:4	0.02	0.01	-0.10	$8.13\text{x}10^{-07}$	$1.16\text{x}10^{-04}$	0.06	$1.68\text{x}10^{+02}$
PC aa C40:5/PC ae C38:1	15.20	5.95	0.10	$1.75\text{x}10^{-06}$	$2.51\text{x}10^{-04}$	0.03	$3.59\text{x}10^{+02}$
PC aa C40:5/PC ae C42:1	31.02	6.78	0.09	$3.24\text{x}10^{-06}$	$4.64\text{x}10^{-04}$	0.05	$4.33\text{x}10^{+03}$
PC aa C36:3/PC ae C36:0	147.54	35.81	0.10	$5.64\text{x}10^{-07}$	$8.06\text{x}10^{-05}$	0.03	$1.13\text{x}10^{+03}$
PC aa C36:3/PC ae C36:3	17.63	4.00	0.09	$4.29\text{x}10^{-06}$	$6.13\text{x}10^{-04}$	0.04	$9.33\text{x}10^{+02}$
PC aa C40:5/PC ae C42:0	23.16	6.57	0.09	$6.25\text{x}10^{-06}$	$8.93\text{x}10^{-04}$	0.10	$4.76\text{x}10^{+02}$
PC aa C36:0/PC ae C36:4	0.13	0.04	-0.09	$9.53\text{x}10^{-06}$	$1.36\text{x}10^{-03}$	0.05	$1.27\text{x}10^{+03}$
PC aa C40:5/PC ae C38:3	2.72	0.82	0.08	$1.45\text{x}10^{-05}$	$2.07\text{x}10^{-03}$	0.09	$9.69\text{x}10^{+02}$
PC aa C36:4/PC ae C36:3	25.72	7.39	0.09	$1.53\text{x}10^{-05}$	$2.18\text{x}10^{-03}$	0.04	$2.62\text{x}10^{+02}$
PC aa C36:4/PC ae C42:1	591.88	126.66	0.08	$2.30\text{x}10^{-05}$	$3.29\text{x}10^{-03}$	0.08	$1.14\text{x}10^{+03}$
PC aa C42:4/PC ae C36:4	0.01	0.00	-0.08	$2.77\text{x}10^{-05}$	$3.96\text{x}10^{-03}$	0.10	$6.11\text{x}10^{+02}$
PC aa C36:4/PC ae C38:3	51.94	15.10	0.08	$4.65\text{x}10^{-05}$	$6.66\text{x}10^{-03}$	0.17	$3.19\text{x}10^{+02}$
PC aa C36:4/PC ae C38:6	25.75	6.77	0.07	$1.69\text{x}10^{-04}$	$2.42\text{x}10^{-02}$	0.12	$1.55\text{x}10^{+02}$
PC/lysoPC Ratios							
PC aa C38:3/lysoPC a C17:0	32.4	14.58	0.20	$3.41\text{x}10^{-24}$	$4.87\text{x}10^{-22}$	0.12	$3.77\text{x}10^{+09}$
PC aa C38:3/lysoPC a C18:1	2.86	1.12	0.19	$1.58\text{x}10^{-23}$	$2.26\text{x}10^{-21}$	0.21	$1.04\text{x}10^{+11}$
PC aa C38:3/lysoPC a C18:2	2.07	0.97	0.17	$3.61\text{x}10^{-19}$	$5.16\text{x}10^{-17}$	0.21	$6.54\text{x}10^{+06}$
PC aa C38:4/lysoPC a C17:0	71.31	31.03	0.17	$3.19\text{x}10^{-18}$	$4.56\text{x}10^{-16}$	0.09	$4.03\text{x}10^{+03}$
PC aa C38:4/lysoPC a C18:1	6.28	2.45	0.16	$7.03\text{x}10^{-18}$	$1.00\text{x}10^{-15}$	0.16	$2.34\text{x}10^{+05}$
PC aa C40:4/lysoPC a C18:1	0.22	0.08	0.16	$2.74\text{x}10^{-17}$	$3.91\text{x}10^{-15}$	0.14	$6.01\text{x}10^{+04}$
PC aa C38:3/lysoPC a C16:0	0.57	0.17	0.15	$8.84\text{x}10^{-16}$	$1.26\text{x}10^{-13}$	0.16	$3.62\text{x}10^{+03}$
PC aa C38:4/lysoPC a C18:2	4.54	2.14	0.15	$3.95\text{x}10^{-15}$	$5.66\text{x}10^{-13}$	0.18	$5.97\text{x}10^{+02}$
PC aa C38:4/lysoPC a C20:4	18.05	5.67	0.12	$1.29\text{x}10^{-11}$	$1.84\text{x}10^{-09}$	0.27	$1.44\text{x}10^{+05}$
PC aa C38:4/lysoPC a C16:0	1.26	0.38	0.12	$6.64\text{x}10^{-10}$	$9.49\text{x}10^{-08}$	0.11	$2.80\text{x}10^{+03}$
PC aa C38:4/lysoPC a C28:1	206.89	85.78	0.12	$1.23\text{x}10^{-09}$	$1.76\text{x}10^{-07}$	0.06	$1.51\text{x}10^{+03}$
PC aa C38:4/lysoPC a C18:0	4.55	1.46	0.12	$5.00\text{x}10^{-09}$	$7.15\text{x}10^{-07}$	0.07	$3.71\text{x}10^{+02}$
PC aa C40:4/lysoPC a C16:0	0.04	0.01	0.11	$6.95\text{x}10^{-09}$	$9.95\text{x}10^{-07}$	0.08	$8.09\text{x}10^{+03}$

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj. P-Value[b]	Adj.[c] R^2	P-Gain[d]
PC aa C40:4/lysoPC a C28:1	7.30	3.31	0.11	$2.15\text{x}10^{-08}$	$3.08\text{x}10^{-06}$	0.07	$1.15\text{x}10^{+03}$
PC aa C40:4/lysoPC a C18:0	0.16	0.05	0.11	$9.06\text{x}10^{-08}$	$1.30\text{x}10^{-05}$	0.04	$6.21\text{x}10^{+02}$
PC aa C40:4/lysoPC a C20:4	0.64	0.23	0.10	$1.38\text{x}10^{-07}$	$1.97\text{x}10^{-05}$	0.15	$4.08\text{x}10^{+02}$
PC aa C36:4/lysoPC a C20:4	33.77	11.69	0.08	$5.25\text{x}10^{-06}$	$7.50\text{x}10^{-04}$	0.22	$3.95\text{x}10^{+03}$
PC aa C40:5/lysoPC a C16:0	0.12	0.04	0.09	$1.15\text{x}10^{-05}$	$1.65\text{x}10^{-03}$	0.09	$2.13\text{x}10^{+02}$
PC aa C40:5/lysoPC a C18:0	0.44	0.14	0.08	$7.43\text{x}10^{-05}$	$1.06\text{x}10^{-02}$	0.04	$1.89\text{x}10^{+02}$
PC ae C36:4/lysoPC a C20:4	3.24	1.10	0.08	$5.17\text{x}10^{-05}$	$7.39\text{x}10^{-03}$	0.15	$4.01\text{x}10^{+02}$
SM (OH) C14:1	6.38	1.86	-0.12	$1.60\text{x}10^{-11}$	$2.28\text{x}10^{-09}$	0.29	
SM C16:0	108.15	21.38	-0.10	$1.14\text{x}10^{-08}$	$1.63\text{x}10^{-06}$	0.26	
SM (OH) C22:2	11.74	3.14	-0.10	$2.36\text{x}10^{-08}$	$3.38\text{x}10^{-06}$	0.31	
SM (OH) C16:1	3.42	0.89	-0.09	$1.41\text{x}10^{-07}$	$2.01\text{x}10^{-05}$	0.24	
SM C26:0	0.18	0.05	-0.07	$2.97\text{x}10^{-04}$	$4.24\text{x}10^{-02}$	0.06	
SM (OH) C16:1/SM C18:1	0.31	0.06	-0.18	$8.49\text{x}10^{-22}$	$1.21\text{x}10^{-19}$	0.16	$1.66\text{x}10^{+14}$
SM (OH) C14:1/SM C18:1	0.58	0.13	-0.19	$1.15\text{x}10^{-21}$	$1.65\text{x}10^{-19}$	0.10	$1.39\text{x}10^{+10}$
SM (OH) C22:2/SM C18:1	1.06	0.19	-0.19	$1.44\text{x}10^{-21}$	$2.06\text{x}10^{-19}$	0.12	$1.64\text{x}10^{+13}$
SM (OH) C16:1/SM C18:0	0.15	0.02	-0.17	$3.75\text{x}10^{-19}$	$5.36\text{x}10^{-17}$	0.14	$3.76\text{x}10^{+11}$
SM C16:0/SM C16:1	6.81	0.75	-0.16	$5.19\text{x}10^{-19}$	$7.42\text{x}10^{-17}$	0.23	$2.20\text{x}10^{+10}$
SM C16:0/SM C18:1	9.91	1.8	-0.16	$1.26\text{x}10^{-18}$	$1.80\text{x}10^{-16}$	0.20	$9.07\text{x}10^{+09}$
SM (OH) C14:1/SM C18:0	0.28	0.06	-0.17	$6.21\text{x}10^{-18}$	$8.88\text{x}10^{-16}$	0.14	$2.57\text{x}10^{+06}$
SM (OH) C14:1/SM C16:1	0.4	0.08	-0.17	$3.13\text{x}10^{-17}$	$4.47\text{x}10^{-15}$	0.08	$5.10\text{x}10^{+05}$
SM (OH) C22:2/SM C16:1	0.73	0.11	-0.15	$1.25\text{x}10^{-15}$	$1.78\text{x}10^{-13}$	0.15	$1.90\text{x}10^{+07}$
SM C16:0/SM C18:0	4.73	0.72	-0.15	$2.92\text{x}10^{-15}$	$4.18\text{x}10^{-13}$	0.11	$3.90\text{x}10^{+06}$
SM (OH) C22:2/SM C18:0	0.51	0.10	-0.15	$4.15\text{x}10^{-15}$	$5.94\text{x}10^{-13}$	0.17	$5.70\text{x}10^{+06}$
SM (OH) C16:1/SM C16:1	0.21	0.04	-0.12	$8.20\text{x}10^{-10}$	$1.17\text{x}10^{-07}$	0.09	$1.72\text{x}10^{+02}$
SM C18:1/SM C26:1	28.13	7.96	0.11	$9.08\text{x}10^{-09}$	$1.30\text{x}10^{-06}$	0.13	$6.29\text{x}10^{+04}$
SM (OH) C22:1/SM C18:1	1.26	0.26	-0.11	$7.11\text{x}10^{-08}$	$1.02\text{x}10^{-05}$	0.07	$2.74\text{x}10^{+04}$
SM C18:1/SM C26:0	66.47	24.74	0.09	$1.58\text{x}10^{-07}$	$2.26\text{x}10^{-05}$	0.24	$1.87\text{x}10^{+03}$
SM (OH) C24:1/SM C18:1	0.12	0.03	-0.10	$1.62\text{x}10^{-07}$	$2.32\text{x}10^{-05}$	0.08	$5.50\text{x}10^{+03}$
SM C18:1/SM C24:1	0.21	0.04	0.09	$6.49\text{x}10^{-07}$	$9.28\text{x}10^{-05}$	0.18	$3.81\text{x}10^{+04}$
SM C18:0/SM C26:1	58.18	14.21	0.10	$7.30\text{x}10^{-07}$	$1.04\text{x}10^{-04}$	0.10	$7.82\text{x}10^{+02}$
SM (OH) C22:1/SM C24:0	0.63	0.09	-0.09	$2.79\text{x}10^{-06}$	$3.99\text{x}10^{-04}$	0.22	$6.97\text{x}10^{+02}$
SM (OH) C22:1/SM C18:0	0.60	0.11	-0.09	$3.82\text{x}10^{-06}$	$5.46\text{x}10^{-04}$	0.07	$5.09\text{x}10^{+02}$
SM (OH) C24:1/SM C18:0	0.06	0.01	-0.09	$4.93\text{x}10^{-06}$	$7.05\text{x}10^{-04}$	0.07	$1.81\text{x}10^{+02}$
SM C16:1/SM C18:1	1.45	0.19	-0.09	$1.19\text{x}10^{-05}$	$1.71\text{x}10^{-03}$	0.05	$2.59\text{x}10^{+03}$
H1	5005.34	670.72	0.10	$3.34\text{x}10^{-07}$	$4.77\text{x}10^{-05}$	0.13	

[a] Fat Free Mass Index; [b] for multiple testing adjusted p-value; [c] adjusted R^2 of the linear model; [d] p-gain, fold decrease in the p-value of association for the pair of metabolites, compared to the lowest of two p-values for the single metabolites; AAs amino acids; Σ aromatic amino acids is the sum of tyrosine, phenylalanine, and tryptophan; Σ BCAAs is the sum of valine, isoleucine, and leucine; Σ glucogenic amino acids is the sum of alanine, glycine, and serine.

Table B4: List of selected SNPs, which were significantly associated in genome wide association studies with anthropometric characteristic as outcomes and tested in the present study for associations with metabolomics data *(Jourdan et al., 2012)*.

rs6265	rs988748	rs2568958	rs4923457	rs7635103	rs10871777
rs12321	rs991790	rs2605097	rs4923460	rs7647305	rs10913469
rs29941	rs1011731	rs2605100	rs4923461	rs7766106	rs10938397
rs29942	rs1052486	rs2736172	rs4929949	rs7828207	rs10968576
rs206936	rs1055144	rs2736176	rs6054427	rs7832552	rs11030107
rs368794	rs1077393	rs2815752	rs6499640	rs7928842	rs11075987
rs464553	rs1294420	rs2815752	rs6548238	rs8044769	rs11075989
rs487720	rs1294421	rs2820446	rs6784615	rs8049439	rs11075990
rs506589	rs1350341	rs2844479	rs6795735	rs8050136	rs11084753
rs543874	rs1421085	rs2867125	rs6861681	rs8051591	rs11127491
rs545608	rs1443512	rs2890652	rs6864049	rs8055982	rs11165643
rs571312	rs1460943	rs2893221	rs6874626	rs9491696	rs11664883
rs633265	rs1514175	rs3101336	rs6905288	rs9816226	rs11721286
rs663129	rs1514176	rs3101336	rs7081678	rs9826482	rs11785269
rs713586	rs1555543	rs3751812	rs7085067	rs9931989	rs11847697
rs713587	rs1558902	rs3810291	rs7132908	rs9939609	rs12016871
rs718314	rs1800437	rs3817334	rs7138803	rs10145154	rs12324805
rs734597	rs1813006	rs3888190	rs7178753	rs10150332	rs12444979
rs747472	rs1822438	rs4074134	rs7187333	rs10184004	rs12446228
rs763712	rs1900273	rs4752857	rs7187776	rs10195252	rs12446554
rs887912	rs2049045	rs4771122	rs7189927	rs10501087	rs12641981
rs925946	rs2076529	rs4776375	rs7190492	rs10767658	rs12970134
rs925947	rs2076530	rs4788102	rs7203521	rs10767664	rs13078807
rs939582	rs2112347	rs4804023	rs7359397	rs10769908	rs13107325
rs975918	rs2145270	rs4823006	rs7428936	rs10835211	rs13393304
rs984222	rs2206277	rs4836133	rs7498665	rs10838738	rs16892496
rs984225	rs2241423	rs4846567	rs7561317	rs10840077	rs16912921
rs987237	rs2260000	rs4854344	rs7601028	rs10842703	rs17782313
rs987237	rs2287019				

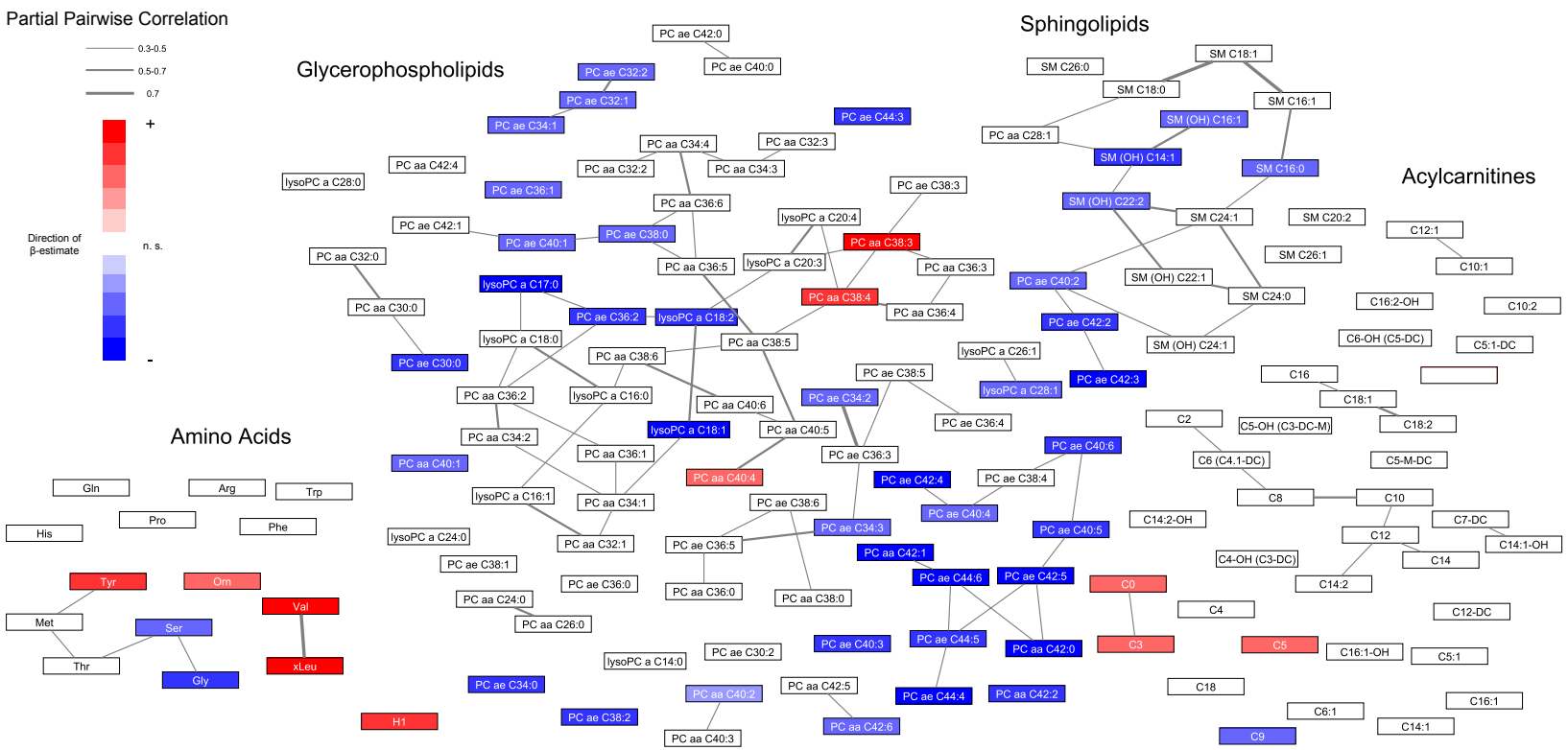

Figure B1: Gaussian graphical model of serum metabolite concentrations of KORA F4. Each node represents a metabolite, whereas edges represent significant partial correlations. Nodes were coloured according to the β-estimate and the p-value from the linear models (red = positive association with fat free mass index; blue = negative association with fat free mass index; white = not significant association with fat free mass index).

C Supplementary Material - Metabolomics and Thyroid Hormones

Table C1: Full biochemical names, abbreviation, mean ± standard deviation of all metabolite concentrations measured in µmol/l with the Biocrates Absolute*IDQ* kit p150 for KORA F4 ($n = 1469$) and the KORA F4 weight-stable[a] subset (WS, $n = 621$).

Abbrevation	Full biochemical name	KORA F4 Mean ± SD	KORA F4 WS Mean ± SD
C0	Carnitine	35.39 ± 7.59	35.36 ± 7.33
C2	Acetylcarnitine	7.86 ± 2.77	8.22 ± 2.93
C3	Propionylcarnitine	0.39 ± 0.12	0.38 ± 0.12
C3-OH	Hydroxypropionylcarnitine	*	*
C3:1	Propenonylcarnitine	*	*
C4	Butyrylcarnitine	0.22 ± 0.10	0.22 ± 0.10
C4-OH (C3-DC)	Hydroxybutyrylcarnitine	0.09 ± 0.05	0.09 ± 0.05
C4:1	Butenylcarnitine	*	*
C5	Valerylcarnitine	0.12 ± 0.04	0.12 ± 0.04
C5-DC (C6-OH)	Glutarylcarnitine	0.03 ± 0.01	0.03 ± 0.01
C5-M-DC	Methylglutarylcarnitine	0.03 ± 0.01	0.03 ± 0.01
C5-OH (C3-DC-M)	Hydroxyvalerylcarnitine (Methylmalonylcarnitine)	0.04 ± 0.02	0.04 ± 0.02
C5:1	Tiglylcarnitine	0.03 ± 0.01	0.03 ± 0.01
C5:1-DC	Glutaconylcarnitine	0.02 ± 0.01	0.02 ± 0.01
C6 (C4:1-DC)	Hexanoylcarnitine	0.07 ± 0.02	0.07 ± 0.03
C6:1	Hexenoylcarnitine	0.02 ± 0.01	0.02 ± 0.01
C7-DC	Pimelylcarnitine	0.04 ± 0.02	0.05 ± 0.02
C8	Octanoylcarnitine	0.21 ± 0.09	0.22 ± 0.09
C8:1	Octenoylcarnitine	0.09 ± 0.04	0.09 ± 0.04
C9	Nonaylcarnitine	0.05 ± 0.02	0.05 ± 0.02
C10	Decanoylcarnitine	0.34 ± 0.16	0.35 ± 0.15
C10:1	Decenoylcarnitine	0.16 ± 0.06	0.17 ± 0.06
C10:2	Decadienylcarnitine	0.04 ± 0.01	0.04 ± 0.01
C12	Dodecanoylcarnitine	0.13 ± 0.05	0.13 ± 0.05
C12-DC	Dodecanedioylcarnitine	0.06 ± 0.01	0.06 ± 0.01
C12:1	Dodecenoylcarnitine	0.14 ± 0.05	0.15 ± 0.05
C14	Tetradecanoylcarnitine	0.04 ± 0.01	0.05 ± 0.01
C14:1	Tetradecenoylcarnitine	0.14 ± 0.05	0.15 ± 0.05
C14:1-OH	Hydroxytetradecenoylcarnitine	0.01 ± 0.00	0.01 ± 0.00
C14:2	Tetradecadienylcarnitine	0.03 ± 0.01	0.03 ± 0.01
C14:2-OH	Hydroxytetradecadienylcarnitine	0.01 ± 0.00	0.01 ± 0.00
C16	Hexadecanoylcarnitine	0.12 ± 0.03	0.12 ± 0.03
C16-OH	Hydroxyhexadecanoylcarnitine	*	*
C16:1	Hexadecenoylcarnitine	0.04 ± 0.01	0.04 ± 0.01
C16:1-OH	Hydroxyhexadecenoylcarnitine	0.01 ± 0.00	0.01 ± 0.00
C16:2	Hexadecadienylcarnitine	*	*
C16:2-OH	Hydroxyhexadecadienylcarnitine	0.01 ± 0.00	0.01 ± 0.00
C18	Octadecanoylcarnitine	0.05 ± 0.01	0.05 ± 0.01
C18:1	Octadecenoylcarnitine	0.13 ± 0.04	0.13 ± 0.04
C18:1-OH	Hydroxyoctadecenoylcarnitine	*	*
C18:2	Octadecadienylcarnitine	0.05 ± 0.01	0.05 ± 0.01
Arg	Arginine	115.36 ± 18.30	115.92 ± 17.14

Abbrevation	Full biochemical name	KORA F4	KORA F4 WS
		Mean ± SD	Mean ± SD
Gln	Glutamine	615.65 ± 95.73	628.17 ± 88.52
Gly	Glycine	311.88 ± 81.53	314.48 ± 82.98
His	Histidine	101.79 ± 17.07	100.80 ± 16.22
Met	Methionine	31.83 ± 6.06	32.07 ± 5.65
Orn	Ornithine	79.80 ± 18.99	81.77 ± 18.61
Phe	Phenylalanine	61.61 ± 10.68	61.36 ± 10.48
Pro	Proline	174.95 ± 52.78	173.83 ± 50.94
Ser	Serine	129.71 ± 24.66	131.28 ± 24.13
Thr	Threonine	108.75 ± 26.37	108.03 ± 23.89
Trp	Tryptophan	83.95 ± 10.45	83.66 ± 10.07
Tyr	Tyrosine	85.12 ± 18.24	85.04 ± 17.68
Val	Valine	272.65 ± 58.67	274.27 ± 59.16
xLeu	Leucine/Isoleucine	213.31 ± 45.27	213.69 ± 44.87
PC aa C24:0	Phosphatidylcholine diacyl C24:0	0.15 ± 0.09	0.15 ± 0.09
PC aa C26:0	Phosphatidylcholine diacyl C26:0	1.10 ± 0.55	1.08 ± 0.52
PC aa C28:1	Phosphatidylcholine diacyl C28:1	3.33 ± 0.78	3.38 ± 0.80
PC aa C30:0	Phosphatidylcholine diacyl C30:0	4.75 ± 1.55	4.80 ± 1.55
PC aa C30:2	Phosphatidylcholine diacyl C30:2	*	*
PC aa C32:0	Phosphatidylcholine diacyl C32:0	15.13 ± 3.28	15.45 ± 3.48
PC aa C32:1	Phosphatidylcholine diacyl C32:1	21.69 ± 11.29	21.96 ± 11.57
PC aa C32:2	Phosphatidylcholine diacyl C32:2	4.01 ± 1.66	4.00 ± 1.70
PC aa C32:3	Phosphatidylcholine diacyl C32:3	0.48 ± 0.12	0.48 ± 0.12
PC aa C34:1	Phosphatidylcholine diacyl C34:1	244.39 ± 62.55	245.49 ± 63.35
PC aa C34:2	Phosphatidylcholine diacyl C34:2	405.97 ± 91.46	403.1 ± 91.63
PC aa C34:3	Phosphatidylcholine diacyl C34:3	18.17 ± 5.39	18.34 ± 5.47
PC aa C34:4	Phosphatidylcholine diacyl C34:4	2.26 ± 0.83	2.27 ± 0.82
PC aa C36:0	Phosphatidylcholine diacyl C36:0	2.72 ± 0.82	2.76 ± 0.85
PC aa C36:1	Phosphatidylcholine diacyl C36:1	53.44 ± 13.59	54.13 ± 13.63
PC aa C36:2	Phosphatidylcholine diacyl C36:2	235.38 ± 44.17	235.45 ± 42.57
PC aa C36:3	Phosphatidylcholine diacyl C36:3	151.34 ± 32.52	150.96 ± 32.57
PC aa C36:4	Phosphatidylcholine diacyl C36:4	221.37 ± 56.11	221.63 ± 55.24
PC aa C36:5	Phosphatidylcholine diacyl C36:5	29.07 ± 13.77	30.12 ± 14.83
PC aa C36:6	Phosphatidylcholine diacyl C36:6	1.11 ± 0.45	1.14 ± 0.46
PC aa C38:0	Phosphatidylcholine diacyl C38:0	3.27 ± 0.86	3.30 ± 0.87
PC aa C38:1	Phosphatidylcholine diacyl C38:1	*	*
PC aa C38:3	Phosphatidylcholine diacyl C38:3	52.87 ± 12.89	52.76 ± 12.73
PC aa C38:4	Phosphatidylcholine diacyl C38:4	116.72 ± 29.35	117.65 ± 29.28
PC aa C38:5	Phosphatidylcholine diacyl C38:5	62.18 ± 15.28	63.4 ± 16.05
PC aa C38:6	Phosphatidylcholine diacyl C38:6	90.04 ± 26.79	91.32 ± 27.71
PC aa C40:1	Phosphatidylcholine diacyl C40:1	0.47 ± 0.10	0.48 ± 0.10
PC aa C40:2	Phosphatidylcholine diacyl C40:2	0.35 ± 0.10	0.36 ± 0.10
PC aa C40:3	Phosphatidylcholine diacyl C40:3	0.65 ± 0.15	0.66 ± 0.15
PC aa C40:4	Phosphatidylcholine diacyl C40:4	4.12 ± 1.21	4.13 ± 1.18
PC aa C40:5	Phosphatidylcholine diacyl C40:5	11.38 ± 3.16	11.52 ± 3.24
PC aa C40:6	Phosphatidylcholine diacyl C40:6	27.79 ± 9.07	28.25 ± 9.51
PC aa C42:0	Phosphatidylcholine diacyl C42:0	0.60 ± 0.17	0.61 ± 0.17
PC aa C42:1	Phosphatidylcholine diacyl C42:1	0.30 ± 0.08	0.30 ± 0.08
PC aa C42:2	Phosphatidylcholine diacyl C42:2	0.21 ± 0.06	0.22 ± 0.06
PC aa C42:4	Phosphatidylcholine diacyl C42:4	0.22 ± 0.05	0.22 ± 0.05

Abbrevation	Full biochemical name	KORA F4	KORA F4 WS
		Mean ± SD	Mean ± SD
PC aa C42:5	Phosphatidylcholine diacyl C42:5	0.42 ± 0.12	0.43 ± 0.13
PC aa C42:6	Phosphatidylcholine diacyl C42:6	0.63 ± 0.14	0.63 ± 0.14
PC ae C30:0	Phosphatidylcholine acyl-akyl C30:0	52.87 ± 12.89	52.76 ± 12.73
PC ae C30:1	Phosphatidylcholine acyl-akyl C30:1	*	*
PC ae C30:2	Phosphatidylcholine acyl-akyl C30:2	0.48 ± 0.14	0.48 ± 0.14
PC ae C32:1	Phosphatidylcholine acyl-akyl C32:1	0.16 ± 0.04	0.16 ± 0.04
PC ae C32:2	Phosphatidylcholine acyl-akyl C32:2	2.90 ± 0.61	2.94 ± 0.60
PC ae C34:0	Phosphatidylcholine acyl-akyl C34:0	0.75 ± 0.17	0.76 ± 0.17
PC ae C34:1	Phosphatidylcholine acyl-akyl C34:1	1.72 ± 0.46	1.76 ± 0.47
PC ae C34:2	Phosphatidylcholine acyl-akyl C34:2	10.62 ± 2.39	10.76 ± 2.41
PC ae C34:3	Phosphatidylcholine acyl-akyl C34:3	13.07 ± 3.45	13.15 ± 3.42
PC ae C36:0	Phosphatidylcholine acyl-akyl C36:0	8.59 ± 2.42	8.70 ± 2.44
PC ae C36:1	Phosphatidylcholine acyl-akyl C36:1	1.05 ± 0.33	1.07 ± 0.34
PC ae C36:2	Phosphatidylcholine acyl-akyl C36:2	8.21 ± 1.96	8.41 ± 1.98
PC ae C36:3	Phosphatidylcholine acyl-akyl C36:3	15.3 ± 3.96	15.58 ± 3.95
PC ae C36:4	Phosphatidylcholine acyl-akyl C36:4	8.86 ± 2.15	8.85 ± 2.10
PC ae C36:5	Phosphatidylcholine acyl-akyl C36:5	21.41 ± 5.58	21.34 ± 5.42
PC ae C38:0	Phosphatidylcholine acyl-akyl C38:0	13.92 ± 3.50	14.13 ± 3.56
PC ae C38:1	Phosphatidylcholine acyl-akyl C38:1	2.48 ± 0.76	2.54 ± 0.77
PC ae C38:2	Phosphatidylcholine acyl-akyl C38:2	0.81 ± 0.28	0.83 ± 0.28
PC ae C38:3	Phosphatidylcholine acyl-akyl C38:3	2.14 ± 0.49	2.18 ± 0.50
PC ae C38:4	Phosphatidylcholine acyl-akyl C38:4	4.26 ± 0.96	4.30 ± 0.93
PC ae C38:5	Phosphatidylcholine acyl-akyl C38:5	15.79 ± 3.38	15.92 ± 3.32
PC ae C38:6	Phosphatidylcholine acyl-akyl C38:6	20.29 ± 4.48	20.42 ± 4.45
PC ae C40:0	Phosphatidylcholine acyl-akyl C40:0	8.73 ± 2.13	8.84 ± 2.17
PC ae C40:1	Phosphatidylcholine acyl-akyl C40:1	10.27 ± 1.63	10.35 ± 1.66
PC ae C40:2	Phosphatidylcholine acyl-akyl C40:2	1.69 ± 0.40	1.73 ± 0.40
PC ae C40:3	Phosphatidylcholine acyl-akyl C40:3	2.05 ± 0.48	2.10 ± 0.48
PC ae C40:4	Phosphatidylcholine acyl-akyl C40:4	1.13 ± 0.23	1.15 ± 0.23
PC ae C40:5	Phosphatidylcholine acyl-akyl C40:5	2.58 ± 0.50	2.61 ± 0.48
PC ae C40:6	Phosphatidylcholine acyl-akyl C40:6	3.55 ± 0.66	3.62 ± 0.65
PC ae C42:0	Phosphatidylcholine acyl-akyl C42:0	5.06 ± 1.26	5.15 ± 1.27
PC ae C42:1	Phosphatidylcholine acyl-akyl C42:1	0.51 ± 0.12	0.51 ± 0.11
PC ae C42:2	Phosphatidylcholine acyl-akyl C42:2	0.38 ± 0.09	0.38 ± 0.09
PC ae C42:3	Phosphatidylcholine acyl-akyl C42:3	0.68 ± 0.15	0.69 ± 0.15
PC ae C42:4	Phosphatidylcholine acyl-akyl C42:4	0.88 ± 0.20	0.90 ± 0.20
PC ae C42:5	Phosphatidylcholine acyl-akyl C42:5	1.02 ± 0.24	1.04 ± 0.24
PC ae C44:3	Phosphatidylcholine acyl-akyl C44:3	2.39 ± 0.49	2.41 ± 0.48
PC ae C44:4	Phosphatidylcholine acyl-akyl C44:4	0.11 ± 0.03	0.11 ± 0.03
PC ae C44:5	Phosphatidylcholine acyl-akyl C44:5	0.43 ± 0.11	0.44 ± 0.11
PC ae C44:6	Phosphatidylcholine acyl-akyl C44:6	2.15 ± 0.55	2.18 ± 0.54
lysoPC a C14:0	lysoPhosphatidylcholine acyl C14:0	3.23 ± 0.84	3.24 ± 0.86
lysoPC a C16:0	lysoPhosphatidylcholine acyl C16:0	95.47 ± 20.39	97.05 ± 20.04
lysoPC a C16:1	lysoPhosphatidylcholine acyl C16:1	2.92 ± 1.00	2.99 ± 1.03
lysoPC a C17:0	lysoPhosphatidylcholine acyl C17:0	1.73 ± 0.51	1.80 ± 0.53
lysoPC a C18:0	lysoPhosphatidylcholine acyl C18:0	26.47 ± 6.22	26.94 ± 6.10
lysoPC a C18:1	lysoPhosphatidylcholine acyl C18:1	19.77 ± 5.79	20.49 ± 5.82
lysoPC a C18:2	lysoPhosphatidylcholine acyl C18:2	28.98 ± 9.98	29.86 ± 9.82
lysoPC a C6:0	lysoPhosphatidylcholine acyl C6:0	*	*

Abbrevation	Full biochemical name	KORA F4	KORA F4 WS
		Mean ± SD	Mean ± SD
lysoPC a C20:3	lysoPhosphatidylcholine acyl C20:3	2.42 ± 0.71	2.49 ± 0.73
lysoPC a C20:4	lysoPhosphatidylcholine acyl C20:4	6.94 ± 2.18	7.10 ± 2.18
lysoPC a C24:0	lysoPhosphatidylcholine acyl C24:0	0.37 ± 0.11	0.37 ± 0.11
lysoPC a C26:0	lysoPhosphatidylcholine acyl C26:0	*	*
lysoPC a C26:1	lysoPhosphatidylcholine acyl C26:1	2.00 ± 0.23	2.01 ± 0.24
lysoPC a C28:0	lysoPhosphatidylcholine acyl C28:0	0.50 ± 0.23	0.50 ± 0.22
lysoPC a C28:1	lysoPhosphatidylcholine acyl C28:1	0.62 ± 0.23	0.62 ± 0.23
SM C16:0	Sphingomyelin C16:0	104.63 ± 20.10	106.72 ± 21.40
SM C16:1	Sphingomyelin C16:1	15.55 ± 3.32	15.78 ± 3.55
SM C18:0	Sphingomyelin C18:0	22.7 ± 4.76	22.85 ± 4.94
SM C18:1	Sphingomyelin C18:1	10.87 ± 2.70	10.99 ± 2.89
SM C20:2	Sphingomyelin C20:2	0.39 ± 0.13	0.38 ± 0.12
SM C22:3	Sphingomyelin C22:3	*	*
SM C24:0	Sphingomyelin C24:0	21.62 ± 4.97	21.88 ± 5.07
SM C24:1	Sphingomyelin C24:1	51.98 ± 11.37	52.70 ± 12.00
SM C26:0	Sphingomyelin C26:0	0.18 ± 0.05	0.18 ± 0.05
SM C26:1	Sphingomyelin C26:1	0.41 ± 0.12	0.42 ± 0.13
SM (OH) C14:1	Hydroxysphingomyelin C14:1	6.03 ± 1.73	6.21 ± 1.83
SM (OH) C16:1	Hydroxysphingomyelin C16:1	3.28 ± 0.84	3.34 ± 0.88
SM (OH) C22:1	Hydroxysphingomyelin C22:1	13.30 ± 3.31	13.52 ± 3.43
SM (OH) C22:2	Hydroxysphingomyelin C22:2	11.24 ± 2.94	11.46 ± 3.11
SM (OH) C24:1	Hydroxysphingomyelin C24:1	1.31 ± 0.34	1.34 ± 0.35
H1	Hexose	4960.71 ± 627.09	4991.31 ± 628.32

[a] weight-stable subjects of KORA F4, whose weight gain or loss did not exceed more than 0.5% per year since their body weight was measured in KORA S4 (seven years prior); Metabolites excluded from the analyses are marked with * and their mean and standard deviation are not given.

Table C2: Metabolic traits significantly associated with FT4 in a linear regression model adjusted for age, sex, BMI, and batch in the KORA F4 sample.

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj.^{c} R^2	P-Gain^d
His/Ser	0.81	0.18	-0.08	$6.60\text{x}10^{-09}$	0.20	$3.26\text{x}10^{+04}$
His/Phe	1.68	0.29	-0.07	$3.07\text{x}10^{-07}$	0.20	$3.34\text{x}10^{+03}$
Phe/Trp	0.73	0.09	0.08	$4.79\text{x}10^{-07}$	0.08	$7.02\text{x}10^{+04}$
Σ AC-DC	0.38	0.10	0.06	$3.95\text{x}10^{-05}$	0.10	
Σ AC	10.81	3.24	0.11	$3.15\text{x}10^{-13}$	0.14	
Σ even AC	9.97	3.16	0.11	$3.27\text{x}10^{-13}$	0.14	
Σ long AC	0.40	0.09	0.11	$3.34\text{x}10^{-13}$	0.21	
Σ med. AC	1.12	0.36	0.09	$9.88\text{x}10^{-09}$	0.14	
Σ mono AC	1.73	0.46	0.10	$6.71\text{x}10^{-11}$	0.16	
Σ poly AC	8.32	2.85	0.11	$6.09\text{x}10^{-13}$	0.13	
C18:1	0.13	0.04	0.12	$1.80\text{x}10^{-16}$	0.18	
C16:1	0.04	0.01	0.11	$1.50\text{x}10^{-13}$	0.17	
C2	7.86	2.77	0.11	$1.13\text{x}10^{-12}$	0.13	
C14:2	0.03	0.01	0.11	$1.25\text{x}10^{-12}$	0.14	
C18:2	0.05	0.01	0.09	$2.48\text{x}10^{-09}$	0.18	
C14:1-OH	0.01	0.00	0.09	$2.85\text{x}10^{-09}$	0.13	
C12:1	0.14	0.05	0.09	$3.86\text{x}10^{-09}$	0.12	
C16:2-OH	0.01	0.00	0.09	$4.01\text{x}10^{-09}$	0.15	
C6 (C4:1-DC)	0.07	0.02	0.09	$4.34\text{x}10^{-09}$	0.13	
C12	0.13	0.05	0.09	$5.96\text{x}10^{-09}$	0.12	
C16:1-OH	0.01	0.00	0.08	$6.29\text{x}10^{-08}$	0.20	
C14	0.04	0.01	0.08	$7.60\text{x}10^{-08}$	0.20	
C10	0.34	0.16	0.08	$1.30\text{x}10^{-07}$	0.10	
C16	0.12	0.03	0.07	$7.36\text{x}10^{-07}$	0.19	
C10:1	0.16	0.06	0.07	$9.50\text{x}10^{-07}$	0.14	
C14:2-OH	0.01	0.00	0.06	$9.93\text{x}10^{-07}$	0.36	
C5-DC (C6-OH)	0.03	0.01	0.06	$4.69\text{x}10^{-05}$	0.05	
C14:1	0.14	0.05	0.06	$5.56\text{x}10^{-05}$	0.25	
C5:1:DC	0.02	0.01	0.06	$6.37\text{x}10^{-05}$	0.09	
C7:DC	0.04	0.02	0.06	$8.65\text{x}10^{-05}$	0.12	
C8	0.21	0.09	0.06	$8.93\text{x}10^{-05}$	0.10	
C2/C0	0.23	0.08	0.11	$7.61\text{x}10^{-13}$	0.15	
(C2+C3)/C0	0.24	0.08	0.11	$4.15\text{x}10^{-13}$	0.14	
CTP1	0.001	0.001	0.06	$8.23\text{x}10^{-05}$	0.07	
PCs						
Σ PCs	1985.9	355.32	-0.11	$1.28\text{x}10^{-13}$	0.14	
Σ mono PCs	348.23	86.27	-0.11	$3.77\text{x}10^{-13}$	0.07	
Σ poly PCs	1593.43	279.51	-0.11	$3.30\text{x}10^{-12}$	0.15	
Σ sat. PCs	44.23	7.91	-0.09	$9.88\text{x}10^{-09}$	0.12	
Σ sat. mono PCs	348.23	86.27	-0.11	$3.77\text{x}10^{-13}$	0.07	
Σ short PCs	759.58	161.54	-0.11	$1.25\text{x}10^{-13}$	0.25	
PC aa						
Σ PC aa	1788.09	333.4	-0.12	$2.91\text{x}10^{-14}$	0.14	
Σ long PC aa	47.14	12.35	-0.06	$4.33\text{x}10^{-05}$	0.07	
Σ mono PC aa	323.62	83.10	-0.11	$4.36\text{x}10^{-13}$	0.07	

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj.[c] R^2	P-Gain[d]
Σ poly PC aa	1436.75	261.65	-0.11	$7.81x10^{-13}$	0.15	
Σ sat. PC aa	27.72	5.60	-0.08	$3.32x10^{-08}$	0.11	
Σ short PC aa	721.28	156.91	-0.11	$1.04x10^{-13}$	0.25	
PC aa C34:4	2.26	0.83	-0.14	$7.28x10^{-19}$	0.07	
PC aa C32:2	4.01	1.66	-0.13	$1.53x10^{-18}$	0.15	
PC aa C36:1	53.44	13.59	-0.13	$4.29x10^{-17}$	0.10	
PC aa C34:3	18.17	5.39	-0.13	$2.29x10^{-16}$	0.13	
PC aa C30:0	4.75	1.55	-0.12	$1.35x10^{-15}$	0.12	
PC aa C36:2	235.38	44.17	-0.12	$1.35x10^{-14}$	0.10	
PC aa C36:6	1.11	0.45	-0.11	$2.57x10^{-12}$	0.06	
PC aa C36:3	151.34	32.52	-0.11	$4.48x10^{-12}$	0.10	
PC aa C38:5	62.18	15.28	-0.11	$4.97x10^{-12}$	0.05	
PC aa C32:1	21.69	11.29	-0.11	$5.61x10^{-12}$	0.07	
PC aa C36:5	29.07	13.77	-0.11	$7.91x10^{-12}$	0.05	
PC aa C34:1	244.39	62.55	-0.10	$1.87x10^{-11}$	0.10	
PC aa C42:6	0.63	0.14	-0.10	$2.37x10^{-10}$	0.05	
PC aa C34:2	405.97	91.46	-0.08	$1.62x10^{-09}$	0.34	
PC aa C40:5	11.38	3.16	-0.09	$2.27x10^{-09}$	0.06	
PC aa C40:4	4.12	1.21	-0.09	$3.21x10^{-08}$	0.05	
PC aa C36:4	221.37	56.11	-0.08	$2.24x10^{-07}$	0.09	
PC aa C32:0	15.13	3.28	-0.08	$3.37x10^{-07}$	0.10	
PC aa C38:3	52.87	12.89	-0.07	$1.03x10^{-06}$	0.13	
PC aa C32:3	0.48	0.12	-0.07	$1.91x10^{-06}$	0.16	
PC aa C40:2	0.35	0.10	-0.07	$2.45x10^{-05}$	0.07	
PC aa C42:5	0.42	0.12	-0.07	$3.94x10^{-05}$	0.04	
PC aa C40:3	0.65	0.15	-0.06	$5.15x10^{-05}$	0.05	
PC ae						
Σ mono PC ae	24.61	5.00	-0.07	$2.63x10^{-06}$	0.17	
Σ sat. PC ae	16.51	2.81	-0.08	$2.88x10^{-07}$	0.12	
Σ short PC ae	38.30	8.25	-0.06	$3.23x10^{-05}$	0.19	
PC ae C40:1	1.69	0.40	-0.11	$6.43x10^{-13}$	0.08	
PC ae C38:2	2.14	0.49	-0.10	$1.21x10^{-11}$	0.17	
PC ae C42:2	0.68	0.15	-0.09	$1.88x10^{-09}$	0.12	
PC ae C38:0	2.48	0.76	-0.09	$3.78x10^{-08}$	0.06	
PC ae C38:1	0.81	0.28	-0.07	$4.36x10^{-06}$	0.05	
PC ae C34:0	1.72	0.46	-0.07	$6.95x10^{-06}$	0.13	
PC ae C36:1	8.21	1.96	-0.07	$9.39x10^{-06}$	0.15	
PC ae C36:0	1.05	0.33	-0.07	$1.18x10^{-05}$	0.04	
PC ae C42:1	0.38	0.09	-0.07	$1.51x10^{-05}$	0.02	
PC ae C40:0	10.27	1.63	-0.06	$2.89x10^{-05}$	0.11	
PC ae C34:3	8.59	2.42	-0.06	$4.55x10^{-05}$	0.13	
lysoPC a						
Σ lysoPCs	191.41	40.73	-0.08	$2.42x10^{-07}$	0.19	
Σ sat. lysoPCs	127.77	26.44	-0.07	$8.15x10^{-06}$	0.14	
Σ unsat. lysoPCs	63.64	17.36	-0.08	$1.03x10^{-07}$	0.23	
lysoPC a C14:0	3.23	0.84	-0.09	$9.92x10^{-09}$	0.04	
lysoPC a C20:3	2.42	0.71	-0.08	$3.44x10^{-08}$	0.16	
lysoPC a C16:1	2.92	1.00	-0.08	$7.64x10^{-08}$	0.06	
lysoPC a C18:1	19.77	5.79	-0.08	$1.34x10^{-07}$	0.21	

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj.^{c} R^2	P-Gain^{d}
lysoPC a C18:2	28.98	9.98	-0.07	$3.57\text{x}10^{-06}$	0.23	
lysoPC a C18:0	26.47	6.22	-0.07	$1.37\text{x}10^{-05}$	0.09	
lysoPC a C16:0	95.47	20.39	-0.06	$2.80\text{x}10^{-05}$	0.15	
PC aa/PC aa Ratios						
PC aa C36:6/PC aa C42:0	1.95	0.80	-0.14	$5.06\text{x}10^{-18}$	0.06	$5.08\text{x}10^{+05}$
PC aa C36:5/PC aa C42:0	51.17	24.93	-0.13	$1.93\text{x}10^{-16}$	0.10	$4.10\text{x}10^{+04}$
PC aa C36:6/PC aa C38:0	0.35	0.12	-0.13	$2.62\text{x}10^{-16}$	0.06	$9.81\text{x}10^{+03}$
PC aa C36:6/PC aa C42:1	3.84	1.52	-0.13	$6.48\text{x}10^{-16}$	0.05	$3.97\text{x}10^{+03}$
PC aa C42:0/PC aa C42:2	2.90	0.64	0.12	$4.10\text{x}10^{-14}$	0.09	$4.72\text{x}10^{+09}$
PC aa C42:1/PC aa C42:2	1.45	0.27	0.11	$5.58\text{x}10^{-12}$	0.07	$3.46\text{x}10^{+07}$
PC aa C36:0/PC aa C38:0	0.83	0.13	-0.11	$9.76\text{x}10^{-12}$	0.04	$1.51\text{x}10^{+08}$
PC aa C36:0/PC aa C42:0	4.70	1.30	-0.10	$1.77\text{x}10^{-10}$	0.10	$8.36\text{x}10^{+06}$
PC aa C40:2/PC aa C42:0	0.62	0.18	-0.10	$1.91\text{x}10^{-10}$	0.09	$1.28\text{x}10^{+05}$
PC aa C40:2/PC aa C42:1	1.22	0.30	-0.09	$7.26\text{x}10^{-09}$	0.07	$3.38\text{x}10^{+03}$
PC aa C40:3/PC aa C42:0	1.15	0.32	-0.09	$7.28\text{x}10^{-09}$	0.10	$7.07\text{x}10^{+03}$
PC aa C40:1/PC aa C42:0	0.82	0.16	-0.08	$4.30\text{x}10^{-08}$	0.12	$1.74\text{x}10^{+05}$
PC aa C42:0/PC aa C42:4	2.80	0.75	0.08	$1.37\text{x}10^{-07}$	0.08	$4.34\text{x}10^{+03}$
PC aa C36:0/PC aa C42:1	9.28	2.37	-0.08	$1.50\text{x}10^{-07}$	0.08	$9.86\text{x}10^{+03}$
PC ae/PC ae Ratios						
PC ae C42:2/PC ae C42:5	0.29	0.06	-0.15	$4.31\text{x}10^{-22}$	0.07	$4.37\text{x}10^{+12}$
PC ae C40:1/PC ae C42:5	0.73	0.18	-0.15	$2.55\text{x}10^{-21}$	0.09	$2.53\text{x}10^{+08}$
PC ae C40:1/PC ae C40:5	0.48	0.10	-0.14	$6.88\text{x}10^{-20}$	0.09	$9.35\text{x}10^{+06}$
PC ae C38:2/PC ae C42:5	0.92	0.22	-0.14	$1.33\text{x}10^{-18}$	0.08	$9.04\text{x}10^{+06}$
PC ae C40:5/PC ae C42:2	5.35	0.92	0.13	$1.58\text{x}10^{-18}$	0.15	$1.19\text{x}10^{+09}$
PC ae C38:2/PC ae C40:3	1.90	0.27	-0.13	$1.27\text{x}10^{-17}$	0.08	$9.49\text{x}10^{+05}$
PC ae C42:2/PC ae C44:5	0.33	0.08	-0.13	$7.13\text{x}10^{-17}$	0.06	$2.64\text{x}10^{+07}$
PC ae C40:1/PC ae C44:5	0.82	0.25	-0.13	$1.02\text{x}10^{-16}$	0.06	$6.28\text{x}10^{+03}$
PC ae C38:2/PC ae C40:5	0.61	0.12	-0.13	$4.12\text{x}10^{-16}$	0.09	$2.92\text{x}10^{+04}$
PC ae C42:2/PC ae C42:4	0.68	0.15	-0.12	$6.30\text{x}10^{-15}$	0.08	$2.99\text{x}10^{+05}$
PC ae C38:0/PC ae C40:6	0.50	0.12	-0.12	$1.47\text{x}10^{-14}$	0.07	$2.58\text{x}10^{+06}$
PC ae C40:4/PC ae C42:2	3.88	0.70	0.12	$1.80\text{x}10^{-14}$	0.08	$1.04\text{x}10^{+05}$
PC ae C42:3/PC ae C42:5	0.37	0.07	-0.12	$3.11\text{x}10^{-14}$	0.07	$3.57\text{x}10^{+10}$
PC ae C42:2/PC ae C44:4	1.61	0.37	-0.12	$4.22\text{x}10^{-14}$	0.07	$4.47\text{x}10^{+04}$
PC ae C42:2/PC ae C44:6	0.51	0.13	-0.12	$7.54\text{x}10^{-14}$	0.07	$2.50\text{x}10^{+04}$
PC ae C38:0/PC ae C42:5	1.07	0.34	-0.11	$5.42\text{x}10^{-13}$	0.05	$6.97\text{x}10^{+04}$
PC ae C42:3/PC ae C44:5	0.42	0.09	-0.11	$9.46\text{x}10^{-12}$	0.05	$1.22\text{x}10^{+08}$
PC ae C34:0/PC ae C42:5	0.74	0.20	-0.11	$1.67\text{x}10^{-11}$	0.06	$4.17\text{x}10^{+05}$
PC ae C38:1/PC ae C42:5	0.35	0.13	-0.10	$4.44\text{x}10^{-11}$	0.05	$9.83\text{x}10^{+04}$
PC ae C34:3/PC ae C42:5	3.66	1.00	-0.10	$6.52\text{x}10^{-11}$	0.05	$6.98\text{x}10^{+05}$
PC ae C42:1/PC ae C42:5	0.16	0.05	-0.10	$1.29\text{x}10^{-10}$	0.05	$1.17\text{x}10^{+05}$
PC ae C36:1/PC ae C42:5	3.53	0.95	-0.10	$1.51\text{x}10^{-10}$	0.09	$6.24\text{x}10^{+04}$
PC ae C34:1/PC ae C42:5	4.54	1.05	-0.10	$1.94\text{x}10^{-10}$	0.07	$9.42\text{x}10^{+05}$
PC ae C36:0/PC ae C42:5	0.45	0.15	-0.10	$3.43\text{x}10^{-10}$	0.04	$3.43\text{x}10^{+04}$
PC ae C42:3/PC ae C44:6	0.65	0.14	-0.10	$3.65\text{x}10^{-10}$	0.03	$3.17\text{x}10^{+06}$
PC ae C34:0/PC ae C40:5	0.49	0.11	-0.09	$1.32\text{x}10^{-09}$	0.09	$5.26\text{x}10^{+03}$
PC ae C36:3/PC ae C42:5	3.79	0.93	-0.10	$1.74\text{x}10^{-09}$	0.04	$3.10\text{x}10^{+05}$
PC ae C34:3/PC ae C44:5	4.15	1.26	-0.10	$1.85\text{x}10^{-09}$	0.05	$2.46\text{x}10^{+04}$
PC ae C42:3/PC ae C42:4	0.87	0.16	-0.09	$3.27\text{x}10^{-09}$	0.03	$3.54\text{x}10^{+05}$
PC ae C42:1/PC ae C44:5	0.18	0.06	-0.09	$3.28\text{x}10^{-09}$	0.03	$4.60\text{x}10^{+03}$

Trait	Mean (µmol/l)	SD	Beta	P-Value	Adj.[c] R^2	P-Gain[d]
PC ae C32:1/PC ae C42:5	1.23	0.22	-0.09	$4.10\text{x}10^{-09}$	0.06	$2.71\text{x}10^{+05}$
PC ae C34:3/PC ae C44:6	6.41	1.84	-0.09	$5.09\text{x}10^{-09}$	0.04	$8.95\text{x}10^{+03}$
PC ae C36:5/PC ae C42:5	5.95	1.54	-0.09	$5.54\text{x}10^{-09}$	0.12	$2.00\text{x}10^{+05}$
PC ae C34:2/PC ae C42:5	5.58	1.45	-0.09	$2.76\text{x}10^{-08}$	0.04	$4.02\text{x}10^{+04}$
PC ae C42:3/PC ae C44:4	2.08	0.43	-0.09	$3.04\text{x}10^{-08}$	0.03	$3.80\text{x}10^{+04}$
PC ae C40:3/PC ae C42:5	0.48	0.09	-0.08	$4.75\text{x}10^{-08}$	0.12	$2.33\text{x}10^{+04}$
PC ae C34:1/PC ae C44:5	5.16	1.48	-0.09	$4.77\text{x}10^{-08}$	0.07	$3.83\text{x}10^{+03}$
PC ae C36:3/PC ae C44:5	4.30	1.26	-0.09	$8.32\text{x}10^{-08}$	0.05	$6.48\text{x}10^{+03}$
PC ae C36:5/PC ae C44:5	6.75	2.02	-0.08	$1.38\text{x}10^{-07}$	0.08	$2.13\text{x}10^{+04}$
PC ae C34:2/PC ae C44:5	6.34	1.93	-0.08	$4.78\text{x}10^{-07}$	0.05	$4.05\text{x}10^{+03}$
PC ae C32:1/PC ae C44:5	1.40	0.32	-0.08	$5.33\text{x}10^{-07}$	0.06	$9.60\text{x}10^{+03}$
SM C18:1	10.87	2.70	0.07	$4.15\text{x}10^{-06}$	0.24	
SM C20:2	0.39	0.13	0.05	$3.96\text{x}10^{-05}$	0.39	
SM (OH) C16:1	3.28	0.84	0.06	$1.19\text{x}10^{-04}$	0.17	
SM C18:0	22.70	4.76	0.06	$1.32\text{x}10^{-04}$	0.12	
SM C24:0/SM C24:1	0.42	0.06	-0.09	$9.48\text{x}10^{-09}$	0.04	$3.37\text{x}10^{+04}$

[a] adjusted R^2 of the linear model; [b] p-gain, fold decrease in the p-value association for the pair of metabolites, compared to the lowest of two p-values for the single metabolites; AC, acylcarnitines; CPT1, carnitine palmitoyltransferase I; even, even numbered; long, long-chain; med., medium-chain; short, short-chain; sat., saturated; unsat., unsaturated.

Table C3: Metabolic traits significantly associated with FT4 in linear regression models adjusted for age, sex, batch, and FFMI[a] next to the significantly associated traits from linear models adjusted for age, sex, batch, and BMI the in the KORA F4 weight-stable[b] subsample ($n = 621$).

	Adjusted for FFMI				Adjusted for BMI			
Trait	Beta	P-Value	Adj.[c] R^2	P-Gain[d]	Beta	P-Value	Adj.[c] R^2	P-Gain[d]
His	-0.09	$1.62\text{x}10^{-05}$	0.38		-0.09	$9.41\text{x}10^{-06}$	0.38	
Ser/Trp	0.12	$3.74\text{x}10^{-07}$	0.20	$2.86\text{x}10^{+03}$	0.12	$1.27\text{x}10^{-07}$	0.20	$4.36\text{x}10^{+03}$
His/Ser					-0.14	$1.69\text{x}10^{-09}$	0.25	$5.56\text{x}10^{+03}$
Σ long AC	0.09	$5.06\text{x}10^{-05}$	0.20		0.10	$2.38\text{x}10^{-05}$	0.20	
Σ mono AC	0.09	$1.72\text{x}10^{-04}$	0.15		0.09	$9.31\text{x}10^{-05}$	0.15	
C18:1	0.11	$7.90\text{x}10^{-06}$	0.16		0.11	$3.74\text{x}10^{-06}$	0.17	
C14:1-OH	0.09	$1.73\text{x}10^{-04}$	0.11		0.09	$9.89\text{x}10^{-05}$	0.11	
C16:2-OH	0.13	$6.68\text{x}10^{-08}$	0.13		0.13	$4.30\text{x}10^{-08}$	0.13	
C6 (C4:1-DC)	0.10	$5.80\text{x}10^{-05}$	0.11		0.10	$2.92\text{x}10^{-05}$	0.12	
C10	0.10	$8.16\text{x}10^{-05}$	0.10		0.10	$4.22\text{x}10^{-05}$	0.10	
C14:2-OH					0.09	$1.02\text{x}10^{-04}$	0.12	
PCs								
Σ PCs	-0.12	$4.78\text{x}10^{-07}$	0.14		-0.12	$1.93\text{x}10^{-07}$	0.14	
Σ mono PCs	-0.12	$3.00\text{x}10^{-06}$	0.07		-0.12	$1.31\text{x}10^{-06}$	0.07	
Σ poly PCs	-0.11	$1.95\text{x}10^{-06}$	0.15		-0.12	$8.65\text{x}10^{-07}$	0.15	
Σ sat. PCs	-0.10	$5.93\text{x}10^{-05}$	0.14		-0.10	$4.96\text{x}10^{-05}$	0.14	
Σ sat. mono PCs	-0.12	$3.00\text{x}10^{-06}$	0.07		-0.12	$1.31\text{x}10^{-06}$	0.07	
Σ short PCs	-0.11	$7.90\text{x}10^{-07}$	0.26		-0.11	$3.52\text{x}10^{-07}$	0.26	
PC aa								
Σ PC aa	-0.12	$3.68\text{x}10^{-07}$	0.14		-0.13	$1.45\text{x}10^{-07}$	0.14	
Σ mono PC aa	-0.12	$3.18\text{x}10^{-06}$	0.07		-0.12	$1.40\text{x}10^{-06}$	0.07	
Σ poly PC aa	-0.11	$1.75\text{x}10^{-06}$	0.15		-0.12	$7.98\text{x}10^{-07}$	0.15	
Σ sat. PC aa	-0.09	$2.37\text{x}10^{-04}$	0.13					
Σ short PC aa	-0.11	$8.32\text{x}10^{-07}$	0.27		-0.11	$3.84\text{x}10^{-07}$	0.27	
PC aa C34:4	-0.16	$3.22\text{x}10^{-10}$	0.08		-0.16	$1.31\text{x}10^{-10}$	0.08	
PC aa C32:2	-0.15	$3.77\text{x}10^{-10}$	0.15		-0.15	$2.06\text{x}10^{-10}$	0.15	
PC aa C36:1	-0.13	$3.21\text{x}10^{-07}$	0.09		-0.13	$1.34\text{x}10^{-07}$	0.10	
PC aa C34:3	-0.12	$4.15\text{x}10^{-07}$	0.10		-0.13	$1.39\text{x}10^{-07}$	0.10	
PC aa C30:0	-0.12	$5.50\text{x}10^{-07}$	0.12		-0.12	$5.73\text{x}10^{-07}$	0.12	
PC aa C36:2	-0.12	$4.67\text{x}10^{-07}$	0.10		-0.13	$2.11\text{x}10^{-07}$	0.10	
PC aa C36:6	-0.13	$2.79\text{x}10^{-07}$	0.08		-0.13	$1.74\text{x}10^{-07}$	0.08	
PC aa C36:3	-0.12	$3.00\text{x}10^{-06}$	0.08		-0.12	$1.03\text{x}10^{-06}$	0.08	
PC aa C38:5	-0.12	$3.37\text{x}10^{-06}$	0.05		-0.12	$1.62\text{x}10^{-06}$	0.06	
PC aa C32:1	-0.12	$2.18\text{x}10^{-06}$	0.06		-0.12	$1.58\text{x}10^{-06}$	0.06	
PC aa C36:5	-0.10	$4.73\text{x}10^{-05}$	0.05		-0.11	$2.51\text{x}10^{-05}$	0.05	
PC aa C34:1	-0.11	$1.04\text{x}10^{-05}$	0.11		-0.11	$4.41\text{x}10^{-06}$	0.11	
PC aa C42:6	-0.13	$2.21\text{x}10^{-07}$	0.06		-0.13	$1.94\text{x}10^{-07}$	0.06	
PC aa C34:2	-0.08	$4.38\text{x}10^{-05}$	0.37		-0.09	$2.37\text{x}10^{-05}$	0.37	
PC aa C40:5	-0.10	$7.82\text{x}10^{-05}$	0.06		-0.10	$5.11\text{x}10^{-05}$	0.06	
PC aa C40:4	-0.11	$1.79\text{x}10^{-05}$	0.06		-0.11	$9.96\text{x}10^{-06}$	0.07	
PC aa C36:4	-0.09	0.00012	0.09		-0.10	$6.43\text{x}10^{-05}$	0.09	
PC aa C42:2	-0.10	$5.52\text{x}10^{-05}$	0.09		-0.10	$6.39\text{x}10^{-05}$	0.09	

Trait	Beta	P-Value	Adj.[c] R^2	P-Gain[d]	Beta	P-Value	Adj.[c] R^2	P-Gain[d]
PC aa C38:3					-0.09	$1.27\text{x}10^{-04}$	0.15	
PC ae								
Σ sat. PC ae	-0.10	$3.02\text{x}10^{-05}$	0.12		-0.10	$2.00\text{x}10^{-05}$	0.13	
PC ae C40:1	-0.12	$1.65\text{x}10^{-06}$	0.05		-0.12	$1.08\text{x}10^{-06}$	0.07	
PC ae C38:2	-0.13	$1.39\text{x}10^{-07}$	0.15		-0.13	$6.11\text{x}10^{-08}$	0.17	
PC ae C42:2	-0.10	$1.86\text{x}10^{-05}$	0.11		-0.11	$1.27\text{x}10^{-05}$	0.13	
PC ae C38:0	-0.10	$2.59\text{x}10^{-05}$	0.07		-0.11	$1.56\text{x}10^{-05}$	0.07	
PC ae C42:1	-0.10	$4.35\text{x}10^{-05}$	0.03		-0.10	$6.10\text{x}10^{-05}$	0.03	
PC ae C40:0	-0.09	0.00015	0.12		-0.09	$9.62\text{x}10^{-05}$	0.13	
PC ae C34:3					-0.09	$1.44\text{x}10^{-04}$	0.14	
lysoPC a								
lysoPC a C16:1	-0.10	$4.35\text{x}10^{-05}$	0.07		-0.10	$3.90\text{x}10^{-05}$	0.07	
PC aa/PC aa								
PC aa C36:0/ PC aa C38:0	-0.12	$2.23\text{x}10^{-06}$	0.05	$5.05\text{x}10^{+03}$	-0.12	$1.10\text{x}10^{-06}$	0.05	$7.08\text{x}10^{+03}$
PC ae/PC ae								
Ratios								
PC ae C42:2/ PC ae C42:5	-0.15	$1.50\text{x}10^{-09}$	0.07	$1.24\text{x}10^{+04}$	-0.16	$6.15\text{x}10^{-10}$	0.07	$2.06\text{x}10^{+04}$
PC ae C42:3/ PC ae C42:5	-0.14	$2.92\text{x}10^{-08}$	0.05	$8.03\text{x}10^{+04}$	-0.14	$1.67\text{x}10^{-08}$	0.06	$1.33\text{x}10^{+05}$
PC ae C32:1/ PC ae C42:5	-0.11	$6.85\text{x}10^{-06}$	0.07	$3.50\text{x}10^{+03}$	-0.12	$3.55\text{x}10^{-06}$	0.07	$5.93\text{x}10^{+03}$

[a] fat free mass index, [b] weight-stable subjects of KORA F4, whose weight gain or loss did not exceed more than 0.5% per year since their body weight was measured in KORA S4 (seven years prior); [c] adjusted R^2 of the linear model; [d] p-gain, fold decrease in the p-value association for the pair of metabolites, compared to the lowest of two p-values for the single metabolites; AC, acylcarnitines; even, even numbered; long, long-chain; med., medium-chain; short, short-chain; sat., saturated; unsat., unsaturated.

Table C4: Metabolic traits significantly associated with FT4 in linear regression models adjusted for age, BMI, sex, batch and stratified by physical activity[a] in the KORA F4 sample.

	Active (n = 838)				Inactive (n = 631)			
Trait	Beta	P-Value	Adj.[b] R^2	P-Gain[c]	Beta	P-Value	Adj.[b] R^2	P-Gain[c]
Σ poly AC	0.1	$2.22\text{x}10^{-06}$	0.12		0.12	$3.01\text{x}10^{-08}$	0.14	
Σ even AC	0.1	$2.90\text{x}10^{-06}$	0.13		0.12	$1.22\text{x}10^{-08}$	0.15	
Σ AC	0.1	$4.12\text{x}10^{-06}$	0.13		0.13	$7.12\text{x}10^{-09}$	0.16	
Σ long AC	0.09	$2.32\text{x}10^{-05}$	0.18		0.13	$1.07\text{x}10^{-09}$	0.25	
Σ mono AC					0.12	$7.61\text{x}10^{-09}$	0.19	
Σ AC-DC					0.10	$9.94\text{x}10^{-06}$	0.13	
Σ AC-OH					0.08	$1.39\text{x}10^{-03}$	0.13	
C18:1	0.11	$1.25\text{x}10^{-07}$	0.16		0.14	$1.83\text{x}10^{-10}$	0.20	
C16:1	0.10	$1.22\text{x}10^{-06}$	0.16		0.12	$1.63\text{x}10^{-08}$	0.18	
C2	0.10	$2.76\text{x}10^{-06}$	0.12		0.12	$4.70\text{x}10^{-08}$	0.13	
C14:2	0.09	$2.85\text{x}10^{-05}$	0.14		0.13	$8.38\text{x}10^{-09}$	0.15	
C12:1					0.11	$1.36\text{x}10^{-06}$	0.14	
C14					0.09	$3.70\text{x}10^{-05}$	0.22	
C18:2					0.11	$4.08\text{x}10^{-07}$	0.19	
C16:1:OH					0.09	$2.17\text{x}10^{-05}$	0.21	
C12					0.11	$6.58\text{x}10^{-07}$	0.14	
C6 (C4:1-DC)					0.11	$2.31\text{x}10^{-07}$	0.15	
C14:1:OH					0.12	$8.53\text{x}10^{-08}$	0.14	
C16:2:OH					0.12	$1.07\text{x}10^{-08}$	0.17	
C10					0.11	$1.23\text{x}10^{-06}$	0.12	
C16					0.09	$1.10\text{x}10^{-05}$	0.22	
C10:1					0.11	$1.09\text{x}10^{-06}$	0.15	
C5:1-DC					0.09	$4.64\text{x}10^{-05}$	0.09	
C8					0.09	$7.02\text{x}10^{-05}$	0.14	
C14:2-OH					0.11	$2.08\text{x}10^{-08}$	0.35	
C7-DC					0.10	$5.10\text{x}10^{-06}$	0.14	
C5-DC (C6-OH)					0.12	$2.33\text{x}10^{-07}$	0.08	
C18					0.08	$1.67\text{x}10^{-04}$	0.22	
C2+C3/C0	0.11	$8.00\text{x}10^{-08}$	0.15		0.11	$5.59\text{x}10^{-07}$	0.14	
C2/C0	0.11	$9.91\text{x}10^{-08}$	0.15		0.11	$1.06\text{x}10^{-06}$	0.14	
PCs								
Σ mono PCs	-0.12	$1.50\text{x}10^{-08}$	0.07		-0.11	$3.95\text{x}10^{-06}$	0.08	
Σ sat. mono PCs	-0.12	$1.50\text{x}10^{-08}$	0.07		-0.11	$3.95\text{x}10^{-06}$	0.07	
Σ PCs	-0.12	$1.72\text{x}10^{-08}$	0.14		-0.11	$1.52\text{x}10^{-06}$	0.14	
Σ short. PCs	-0.11	$2.76\text{x}10^{-08}$	0.25		-0.10	$1.36\text{x}10^{-06}$	0.24	
Σ poly PCs	-0.11	$1.38\text{x}10^{-07}$	0.14		-0.10	$5.81\text{x}10^{-06}$	0.15	
Σ sat. PCs					-0.10	$8.95\text{x}10^{-06}$	0.145	
PC aa								
Σ PC aa	-0.12	$7.48\text{x}10^{-09}$	0.14		-0.11	$8.30\text{x}10^{-07}$	0.14	
Σ mono PC aa	-0.12	$1.52\text{x}10^{-08}$	0.07		-0.10	$4.27\text{x}10^{-06}$	0.07	
Σ short. PC aa	-0.11	$2.42\text{x}10^{-08}$	0.26		-0.10	$1.48\text{x}10^{-06}$	0.24	
Σ poly PC aa	-0.11	$6.30\text{x}10^{-08}$	0.15		-0.10	$3.27\text{x}10^{-06}$	0.15	
PC aa C36:1	-0.15	$8.78\text{x}10^{-13}$	0.11		-0.11	$2.04\text{x}10^{-06}$	0.09	

Trait	Beta	P-Value	Adj.[b] R^2	P-Gain[c]	Beta	P-Value	Adj.[b] R^2	P-Gain[c]
PC aa C36:2	-0.14	$4.86\text{x}10^{-11}$	0.11		-0.10	$1.40\text{x}10^{-05}$	0.09	
PC aa C34:4	-0.14	$2.94\text{x}10^{-10}$	0.07		-0.14	$6.15\text{x}10^{-10}$	0.07	
PC aa C32:2	-0.13	$7.15\text{x}10^{-10}$	0.16		-0.14	$6.79\text{x}10^{-10}$	0.14	
PC aa C34:3	-0.13	$7.91\text{x}10^{-10}$	0.14		-0.12	$1.12\text{x}10^{-07}$	0.11	
PC ae C38:2	-0.11	$5.08\text{x}10^{-08}$	0.18		-0.09	$6.76\text{x}10^{-05}$	0.15	
PC aa C36:3	-0.12	$5.20\text{x}10^{-08}$	0.10		-0.10	$1.93\text{x}10^{-05}$	0.08	
PC aa C30:0	-0.11	$8.21\text{x}10^{-08}$	0.11		-0.13	$2.50\text{x}10^{-09}$	0.13	
PC aa C34:1	-0.11	$2.46\text{x}10^{-07}$	0.10		-0.10	$1.54\text{x}10^{-05}$	0.10	
PC ae C40:1	-0.11	$5.97\text{x}10^{-07}$	0.07		-0.11	$4.28\text{x}10^{-07}$	0.08	
PC aa C32:1	-0.11	$1.13\text{x}10^{-06}$	0.06		-0.11	$1.42\text{x}10^{-06}$	0.07	
PC aa C34:2	-0.09	$2.82\text{x}10^{-06}$	0.36					
PC aa C40:4	-0.10	$2.90\text{x}10^{-06}$	0.05		-0.08	$7.80\text{x}10^{-04}$	0.04	
PC aa C36:6	-0.10	$3.18\text{x}10^{-06}$	0.06		-0.12	$3.17\text{x}10^{-07}$	0.06	
PC aa C38:5	-0.10	$3.98\text{x}10^{-06}$	0.04		-0.12	$3.55\text{x}10^{-07}$	0.06	
PC aa C40:5	-0.10	$6.24\text{x}10^{-06}$	0.06		-0.09	$4.39\text{x}10^{-05}$	0.05	
PC aa C38:3	-0.09	$9.96\text{x}10^{-06}$	0.14					
PC aa C36:5	-0.10	$1.58\text{x}10^{-05}$	0.03		-0.12	$1.33\text{x}10^{-07}$	0.07	
PC aa C32:3	-0.08	$4.13\text{x}10^{-05}$	0.17					
PC aa C42:6	-0.09	$6.35\text{x}10^{-05}$	0.05		-0.11	$7.94\text{x}10^{-07}$	0.05	
PC aa C36:4					-0.09	$1.03\text{x}10^{-04}$	0.10	
PC aa C32:0					-0.09	$1.07\text{x}10^{-04}$	0.12	
PC ae								
PC ae C38:1	-0.09	$1.54\text{x}10^{-05}$	0.07					
PC ae C34:3	-0.08	$8.84\text{x}10^{-05}$	0.14					
PC ae C38:0					-0.09	$7.13\text{x}10^{-05}$	0.05	
PC ae C42:2					-0.11	$9.87\text{x}10^{-07}$	0.12	
lysoPC								
Σ lysoPCs	-0.09	$3.75\text{x}10^{-06}$	0.20					
Σ sat. lysoPCs	-0.09	$1.41\text{x}10^{-05}$	0.16					
lysoPC a C14:0	-0.10	$4.51\text{x}10^{-06}$	0.04		-0.08	$5.91\text{x}10^{-04}$	0.05	
lysoPC a C16:1	-0.09	$1.69\text{x}10^{-05}$	0.06					
lysoPC a C18:0	-0.09	$2.57\text{x}10^{-05}$	0.10					
lysoPC a C16:0	-0.08	$3.75\text{x}10^{-05}$	0.17					
lysoPC a C18:1	-0.08	$4.16\text{x}10^{-05}$	0.21					
lysoPC a C20:3	-0.08	$9.00\text{x}10^{-05}$	0.17		-0.09	$6.81\text{x}10^{-05}$	0.14	
lysoPC a C18:2	-0.08	$1.03\text{x}10^{-04}$	0.23					
PC aa/PC aa Ratios								
PC ae C38:2/ PC ae C42:5	-0.15	$1.55\text{x}10^{-12}$	0.09	$3.28\text{x}10^{+04}$				
PC ae C40:1/ PC ae C42:5	-0.15	$6.50\text{x}10^{-12}$	0.08	$9.19\text{x}10^{+04}$				
PC aa C42:1/ PC ae C40:1	0.15	$1.05\text{x}10^{-11}$	0.08	$5.67\text{x}10^{+04}$				
PC aa C42:0/ PC ae C40:1	0.15	$1.67\text{x}10^{-11}$	0.09	$3.58\text{x}10^{+04}$				
PC ae C42:2/ PC ae C42:5	-0.14	$1.17\text{x}10^{-10}$	0.05	$3.46\text{x}10^{+06}$	-0.16	$1.76\text{x}10^{-12}$	0.09	$5.61\text{x}10^{+05}$
PC ae C38:2/ PC ae C40:3					-0.13	$1.20\text{x}10^{-08}$	0.08	$5.62\text{x}10^{+03}$

Trait	Beta	P-Value	Adj.[b] R^2	P-Gain[c]	Beta	P-Value	Adj.[b] R^2	P-Gain[c]
PC ae C40:1/ PC ae C44:5	-0.14	$1.44\text{x}10^{-10}$	0.05	$4.15\text{x}10^{+03}$				
PC aa C36:6/ PC aa C42:0	-0.14	$3.03\text{x}10^{-10}$	0.06	$1.05\text{x}10^{+04}$				
PC ae C40:1/ PC ae C40:5					-0.15	$9.98\text{x}10^{-11}$	0.10	$4.29\text{x}10^{+03}$
PC aa C36:6/ PC ae C40:6	-0.14	$3.47\text{x}10^{-10}$	0.07	$9.18\text{x}10^{+03}$				
PC ae C42:2/ PC ae C44:5	-0.13	$1.45\text{x}10^{-09}$	0.05	$2.80\text{x}10^{+05}$				
PC ae C38:1/ PC ae C42:5	-0.13	$2.30\text{x}10^{-09}$	0.06	$6.71\text{x}10^{+03}$				
PC aa C42:0/ PC ae C42:2	0.13	$4.29\text{x}10^{-09}$	0.08	$9.44\text{x}10^{+04}$				
PC ae C34:3/ PC ae C42:5	-0.13	$7.23\text{x}10^{-09}$	0.06	$1.22\text{x}10^{+04}$				
PC aa C42:0/ PC ae C38:0	0.13	$1.01\text{x}10^{-08}$	0.05	$3.50\text{x}10^{+04}$				
PC ae C34:3/ PC ae C44:5	-0.13	$1.33\text{x}10^{-08}$	0.06	$6.64\text{x}10^{+03}$				
PC aa C42:0/ PC aa C42:2	0.12	$3.31\text{x}10^{-08}$	0.09	$4.60\text{x}10^{+05}$	0.12	$1.77\text{x}10^{-07}$	0.10	$1.30\text{x}10^{+04}$
PC ae C38:0/ PC ae C40:6	-0.12	$3.60\text{x}10^{-08}$	0.05	$9.87\text{x}10^{+03}$				
PC aa C42:0/ PC ae C42:3	0.12	$5.38\text{x}10^{-08}$	0.04	$2.83\text{x}10^{+05}$	0.12	$2.74\text{x}10^{-07}$	0.04	$1.10\text{x}10^{+04}$
PC ae C40:5/ PC ae C42:2	0.11	$8.31\text{x}10^{-08}$	0.16	$4.88\text{x}10^{+03}$	0.15	$2.93\text{x}10^{-12}$	0.15	$3.37\text{x}10^{+05}$
PC aa C42:1/ PC ae C42:2	0.12	$9.47\text{x}10^{-08}$	0.08	$4.28\text{x}10^{+03}$				
PC aa C42:1/ PC ae C38:0	0.12	$1.02\text{x}10^{-07}$	0.04	$3.50\text{x}10^{+03}$				
PC ae C36:3/ PC ae C42:5	-0.12	$1.43\text{x}10^{-07}$	0.05	$5.29\text{x}10^{+03}$				
PC aa C42:1/ PC aa C42:2	0.11	$1.65\text{x}10^{-07}$	0.07	$1.72\text{x}10^{+05}$				
PC aa C32:0/ PC ae C42:5	-0.11	$3.30\text{x}10^{-07}$	0.10	$3.18\text{x}10^{+03}$				
PC aa C40:2/ PC aa C42:0	-0.11	$4.09\text{x}10^{-07}$	0.08	$4.83\text{x}10^{+03}$				
PC ae C42:3/ PC ae C44:5	-0.11	$5.96\text{x}10^{-07}$	0.05	$1.89\text{x}10^{+04}$				
PC ae C34:1/ PC ae C42:5	-0.11	$6.16\text{x}10^{-07}$	0.06	$5.70\text{x}10^{+03}$				
PC aa C40:2/ PC aa C42:1	-0.11	$6.91\text{x}10^{-07}$	0.07	$2.86\text{x}10^{+03}$				
PC ae C42:3/ PC ae C42:5	-0.11	$7.64\text{x}10^{-07}$	0.06	$9.45\text{x}10^{+03}$	-0.13	$1.39\text{x}10^{-08}$	0.07	$2.16\text{x}10^{+05}$
PC ae C34:2/ PC ae C42:5	-0.11	$9.51\text{x}10^{-07}$	0.04	$3.34\text{x}10^{+03}$				

Trait	Beta	P-Value	Adj.^{b} R^2	P-Gain^{c}	Beta	P-Value	Adj.^{b} R^2	P-Gain^{c}
PC ae C40:3/ PC ae C42:5	-0.10	$2.40\text{x}10^{-06}$	0.13	$3.00\text{x}10^{+03}$				
PC ae C42:3/ PC ae C44:6	-0.10	$9.58\text{x}10^{-06}$	0.02	$4.30\text{x}10^{+03}$				
PC aa C42:1/ PC ae C42:3	0.10	$1.26\text{x}10^{-05}$	0.03	$7.83\text{x}10^{+03}$				
PC aa C36:0/ PC aa C38:0					-0.13	$2.86\text{x}10^{-08}$	0.07	$1.73\text{x}10^{+05}$
SM C18:1					0.09	$1.17\text{x}10^{-05}$	0.25	
SM C24:1					0.09	$4.66\text{x}10^{-05}$	0.13	
SM C16:0					0.09	$2.67\text{x}10^{-05}$	0.21	

[a] physical activity (active: $\geq$ 1h sport per week on a regular basis; inactive: less than 1h sport per week); [b] adjusted R^2 of the linear model; [c] p-gain, fold decrease in the p-value association for the pair of metabolites, compared to the lowest of two p-values for the single metabolites; AC, acylcarnitines; even, even numbered; long, long-chain; med., medium-chain; short, short-chain; sat., saturated; unsat., unsaturated.

Table C5: Metabolic traits significantly associated with FT4 in linear regression models adjusted for age, BMI, batch and stratified by gender in the KORA F4 sample.

	Male (n = 792)				Female (n = 677)			
Trait	Beta	P-Value	Adj.[a] R^2	P-Gain[b]	Beta	P-Value	Adj.[a] R^2	P-Gain[b]
Σ AC	0.11	2.36x10^{-08}	0.13		0.11	2.46x10^{-06}	0.16	
Σ even AC	0.11	2.72x10^{-08}	0.13		0.11	2.14x10^{-06}	0.15	
Σ long AC	0.11	2.76x10^{-08}	0.16		0.11	3.60x10^{-06}	0.16	
Σ med. AC	0.10	3.54x10^{-06}	0.10					
Σ mono AC	0.11	1.74x10^{-07}	0.11		0.09	1.29x10^{-04}	0.16	
Σ poly AC	0.11	6.70x10^{-08}	0.12		0.11	2.18x10^{-06}	0.14	
C18:1	0.12	1.91x10^{-09}	0.16		0.13	8.35x10^{-09}	0.13	
C14:2	0.11	4.62x10^{-08}	0.10		0.10	1.56x10^{-05}	0.14	
C18:2	0.08	1.58x10^{-04}	0.12		0.11	7.49x10^{-06}	0.10	
C14:1-OH	0.10	3.52x10^{-07}	0.09					
C12:1	0.10	2.86x10^{-06}	0.10					
C16:2-OH	0.11	3.71x10^{-08}	0.14					
C6 (4:1-DC)	0.10	6.43x10^{-07}	0.09					
C12	0.10	3.05x10^{-06}	0.08					
C16:1-OH	0.09	7.37x10^{-06}	0.15					
C14	0.09	1.32x10^{-05}	0.15					
C10	0.09	8.88x10^{-06}	0.06					
C16	0.09	1.07x10^{-05}	0.12					
C10:1	0.08	1.13x10^{-04}	0.09					
C14:2-OH	0.08	4.78x10^{-06}	0.36					
C2/C0	0.11	1.59x10^{-07}	0.15		0.13	5.81x10^{-08}	0.08	
(C2+C3)/C0	0.11	1.09x10^{-07}	0.15		0.13	4.85x10^{-08}	0.08	
PCs								
Σ PCs	-0.11	2.64x10^{-08}	0.14		-0.11	1.11x10^{-06}	0.12	
Σ mono PCs	-0.10	1.02x10^{-06}	0.08		-0.13	3.56x10^{-08}	0.07	
Σ poly PCs	-0.11	5.46x10^{-08}	0.15		-0.10	1.72x10^{-05}	0.13	
Σ sat. mono PCs	-0.10	1.02x10^{-06}	0.08		-0.13	3.56x10^{-08}	0.07	
Σ sat. PCs	-0.08	3.51x10^{-05}	0.10		-0.09	1.27x10^{-04}	0.11	
Σ short PCs	-0.10	1.86x10^{-07}	0.24		-0.11	1.23x10^{-07}	0.25	
PC aa								
Σ mono PC aa	-0.10	9.22x10^{-07}	0.08		-0.13	4.92x10^{-08}	0.07	
Σ PC aa	-0.11	1.52x10^{-08}	0.14		-0.12	4.17x10^{-07}	0.13	
Σ poly PC aa	-0.11	3.20x10^{-08}	0.16		-0.10	7.51x10^{-06}	0.14	
Σ sat. PC aa	-0.08	4.72x10^{-05}	0.10					
Σ short PC aa	-0.10	1.55x10^{-07}	0.24		-0.11	1.46x10^{-07}	0.26	
PC aa C34:4	-0.16	1.18x10^{-13}	0.07		-0.13	3.04x10^{-07}	0.04	
PC aa C32:2	-0.14	4.82x10^{-11}	0.09		-0.14	6.42x10^{-09}	0.11	
PC aa C36:1	-0.13	1.81x10^{-09}	0.07		-0.14	7.82x10^{-10}	0.15	
PC aa C34:3	-0.12	4.42x10^{-08}	0.06		-0.15	5.10x10^{-10}	0.08	
PC aa C30:0	-0.13	1.87x10^{-09}	0.08		-0.12	3.19x10^{-07}	0.10	
PC aa C36:2	-0.12	1.46x10^{-09}	0.11		-0.12	8.57x10^{-07}	0.07	
PC aa C36:6	-0.11	5.76x10^{-07}	0.04		-0.12	5.71x10^{-07}	0.06	
PC aa C36:3	-0.09	4.87x10^{-06}	0.08		-0.12	1.73x10^{-07}	0.09	
PC aa C38:5	-0.10	1.10x10^{-06}	0.04		-0.12	3.64x10^{-07}	0.07	

Trait	Beta	P-Value	Adj.[a] R^2	P-Gain[b]	Beta	P-Value	Adj.[a] R^2	P-Gain[b]
PC aa C32:1	-0.10	$2.28\text{x}10^{-06}$	0.06		-0.12	$1.07\text{x}10^{-06}$	0.06	
PC aa C36:5	-0.09	$1.22\text{x}10^{-05}$	0.03		-0.13	$5.69\text{x}10^{-08}$	0.06	
PC aa C34:1	-0.09	$7.93\text{x}10^{-06}$	0.11		-0.12	$4.61\text{x}10^{-07}$	0.10	
PC aa C42:6	-0.10	$2.75\text{x}10^{-06}$	0.03		-0.10	$5.47\text{x}10^{-05}$	0.07	
PC aa C34:2	-0.08	$7.36\text{x}10^{-06}$	0.33		-0.08	$1.08\text{x}10^{-04}$	0.34	
PC aa C40:5	-0.09	$8.44\text{x}10^{-06}$	0.05		-0.10	$3.83\text{x}10^{-05}$	0.08	
PC aa C40:4	-0.09	$9.50\text{x}10^{-06}$	0.06					
PC aa C36:4	-0.09	$3.74\text{x}10^{-06}$	0.11					
PC aa C32:3	-0.08	$1.63\text{x}10^{-04}$	0.02					
PC aa C42:5	-0.08	$1.47\text{x}10^{-04}$	0.07					
PC ae								
Σ mono PC ae					-0.09	$7.57\text{x}10^{-05}$	0.10	
Σ sat. PC ae					-0.09	$1.54\text{x}10^{-04}$	0.10	
PC ae C40:1	-0.11	$1.58\text{x}10^{-07}$	0.07		-0.12	$2.94\text{x}10^{-07}$	0.11	
PC ae C38:2	-0.10	$4.69\text{x}10^{-07}$	0.08		-0.11	$3.08\text{x}10^{-06}$	0.11	
PC ae C42:2	-0.09	$5.81\text{x}10^{-06}$	0.11		-0.10	$2.87\text{x}10^{-05}$	0.10	
PC ae C38:0	-0.08	$1.30\text{x}10^{-04}$	0.04		-0.10	$3.50\text{x}10^{-05}$	0.06	
lysoPC a								
Σ unsat lysoPCs	-0.08	$1.07\text{x}10^{-04}$	0.18		-0.10	$2.93\text{x}10^{-05}$	0.16	
lysoPC a C14:0	-0.10	$4.52\text{x}10^{-06}$	0.05					
lysoPC a C20:3					-0.12	$1.97\text{x}10^{-07}$	0.10	
lysoPC a C16:1	-0.08	$1.11\text{x}10^{-04}$	0.04		-0.09	$1.36\text{x}10^{-04}$	0.06	
lysoPC a C18:1					-0.10	$1.78\text{x}10^{-05}$	0.17	
lysoPC a C18:2					-0.09	$1.31\text{x}10^{-04}$	0.15	
lysoPC a C18:0	-0.08	$4.75\text{x}10^{-05}$	0.07					
PC aa/PC aa Ratios								
PC aa C36:6/ PC aa C42:0					-0.15	$1.91\text{x}10^{-10}$	0.07	$2.99\text{x}10^{+03}$
PC aa C42:0/ PC aa C42:2	0.11	$1.38\text{x}10^{-07}$	0.05	$7.53\text{x}10^{+03}$	0.13	$5.19\text{x}10^{-08}$	0.06	$1.59\text{x}10^{+05}$
PC aa C42:1/ PC aa C42:2					0.13	$1.43\text{x}10^{-07}$	0.06	$2.95\text{x}10^{+05}$
PC aa C36:0/ PC aa C38:0					-0.13	$8.51\text{x}10^{-08}$	0.06	$5.78\text{x}10^{+05}$
PC aa C36:0/ PC aa C42:0					-0.12	$4.83\text{x}10^{-07}$	0.06	$1.71\text{x}10^{+04}$
PC aa C36:0/ PC aa C42:1					-0.11	$5.16\text{x}10^{-06}$	0.06	$8.19\text{x}10^{+03}$
PC ae/PC ae Ratios								
PC ae C42:2/ PC ae C42:5	-0.14	$5.52\text{x}10^{-11}$	0.07	$1.05\text{x}10^{+05}$	-0.18	$1.27\text{x}10^{-13}$	0.09	$2.25\text{x}10^{+08}$
PC ae C40:1/ PC ae C42:5					-0.18	$1.90\text{x}10^{-13}$	0.10	$1.55\text{x}10^{+06}$
PC ae C40:1/ PC ae C40:5					-0.16	$1.28\text{x}10^{-11}$	0.08	$2.29\text{x}10^{+04}$
PC ae C38:2/ PC ae C42:5					-0.16	$4.45\text{x}10^{-12}$	0.11	$6.92\text{x}10^{+05}$

Trait	Beta	P-Value	Adj.[a] R^2	P-Gain[b]	Beta	P-Value	Adj.[a] R^2	P-Gain[b]
PC ae C40:5/ PC ae C42:2	0.12	$1.19\text{x}10^{-09}$	0.16	$4.87\text{x}10^{+03}$	0.15	$7.68\text{x}10^{-11}$	0.14	$3.73\text{x}10^{+05}$
PC ae C38:2/ PC ae C40:3					-0.15	$1.53\text{x}10^{-10}$	0.08	$2.02\text{x}10^{+04}$
PC ae C42:2/ PC ae C44:5					-0.15	$1.72\text{x}10^{-10}$	0.07	$1.67\text{x}10^{+05}$
PC ae C38:2/ PC ae C40:5					-0.15	$8.16\text{x}10^{-10}$	0.05	$3.78\text{x}10^{+03}$
PC ae C42:2/ PC ae C42:4					-0.15	$7.37\text{x}10^{-10}$	0.08	$3.89\text{x}10^{+04}$
PC ae C38:2/ PC ae C40:4					-0.15	$6.03\text{x}10^{-10}$	0.07	$5.12\text{x}10^{+03}$
PC ae C38:2/ PC ae C42:4					-0.14	$1.84\text{x}10^{-09}$	0.10	$1.68\text{x}10^{+03}$
PC ae C38:0/ PC ae C40:6					-0.15	$1.30\text{x}10^{-09}$	0.07	$2.68\text{x}10^{+04}$
PC ae C40:4/ PC ae C42:2					0.15	$1.49\text{x}10^{-09}$	0.07	$1.93\text{x}10^{+04}$
PC ae C42:3/ PC ae C42:5	-0.10	$1.79\text{x}10^{-06}$	0.06	$6.38\text{x}10^{+03}$	-0.15	$1.45\text{x}10^{-09}$	0.08	$7.01\text{x}10^{+05}$
PC ae C42:2/ PC ae C44:6					-0.15	$1.25\text{x}10^{-09}$	0.07	$2.29\text{x}10^{+04}$
PC ae C38:0/ PC ae C42:5					-0.14	$4.57\text{x}10^{-09}$	0.07	$7.65\text{x}10^{+03}$
PC ae C42:3/ PC ae C44:5					-0.13	$1.05\text{x}10^{-07}$	0.05	$5.48\text{x}10^{+04}$
PC ae C34:0/ PC ae C42:5					-0.13	$1.11\text{x}10^{-08}$	0.11	$2.51\text{x}10^{+04}$
PC ae C38:1/ PC ae C42:5					-0.12	$1.94\text{x}10^{-07}$	0.08	$5.22\text{x}10^{+03}$
PC ae C38:0/ PC ae C42:0					-0.13	$1.19\text{x}10^{-08}$	0.20	$2.93\text{x}10^{+03}$
PC ae C34:3/ PC ae C42:5					-0.14	$5.46\text{x}10^{-09}$	0.07	$1.56\text{x}10^{+05}$
PC ae C36:1/ PC ae C42:5					-0.13	$2.32\text{x}10^{-08}$	0.15	$9.23\text{x}10^{+03}$
PC ae C34:1/ PC ae C42:5					-0.14	$2.33\text{x}10^{-09}$	0.08	$2.45\text{x}10^{+05}$
PC ae C42:3/ PC ae C44:6					-0.13	$1.12\text{x}10^{-07}$	0.04	$6.73\text{x}10^{+04}$
PC ae C36:3/ PC ae C42:5					-0.13	$1.47\text{x}10^{-07}$	0.04	$6.92\text{x}10^{+03}$
PC ae C34:3/ PC ae C44:5					-0.13	$1.22\text{x}10^{-07}$	0.05	$6.98\text{x}10^{+03}$
PC ae C42:3/ PC ae C42:4					-0.12	$2.15\text{x}10^{-06}$	0.03	$2.37\text{x}10^{+04}$
PC ae C32:1/ PC ae C42:5					-0.15	$8.65\text{x}10^{-10}$	0.07	$1.17\text{x}10^{+06}$
PC ae C34:3/ PC ae C44:6					-0.14	$2.90\text{x}10^{-08}$	0.05	$2.94\text{x}10^{+04}$

Trait	Beta	P-Value	Adj.[a] R^2	P-Gain[b]	Beta	P-Value	Adj.[a] R^2	P-Gain[b]
PC ae C32:1/ PC ae C44:5					-0.12	5.25×10^{-07}	0.06	$1.10 \times 10^{+04}$

[a] adjusted R^2 of the linear model; [b] p-gain, fold decrease in the p-value association for the pair of metabolites, compared to the lowest of two p-values for the single metabolites; AC, acylcarnitines; even, even numbered; long, long-chain; med., medium-chain; short, short-chain; sat., saturated; unsat., unsaturated.

Table C6: Metabolic traits significantly associated with FT4 in linear regression models adjusted for age, BMI, batch and stratified by obesity status in the KORA F4 sample.

	Obese (BMI = 30 kg/m^2) (n = 286)				Non-Obese (BMI < 30 kg/m^2) (n = 1182)			
Trait	Beta	P-Value	Adj.^{a} R^2	P-Gain^b	Beta	P-Value	Adj.^{a} R^2	P-Gain^b
Σ AC					0.11	$5.18\text{x}10^{-10}$	0.10	
Σ even AC					0.11	$5.83\text{x}10^{-10}$	0.10	
Σ long AC	0.13	$7.86\text{x}10^{-05}$	0.20		0.10	$1.40\text{x}10^{-09}$	0.20	
Σ med. AC					0.08	$1.14\text{x}10^{-06}$	0.10	
Σ mono AC					0.09	$1.89\text{x}10^{-08}$	0.20	
Σ poly AC					0.10	$1.38\text{x}10^{-09}$	0.10	
C18:1	0.13	$7.29\text{x}10^{-05}$	0.18		0.12	$1.47\text{x}10^{-12}$	0.17	
C16:1	0.15	$7.62\text{x}10^{-06}$	0.20		0.10	$1.06\text{x}10^{-09}$	0.15	
C2					0.10	$2.21\text{x}10^{-09}$	0.11	
C14:2	0.14	$7.12\text{x}10^{-05}$	0.15		0.10	$4.84\text{x}10^{-09}$	0.14	
C18:2					0.08	$1.21\text{x}10^{-06}$	0.19	
C14:1-OH	0.13	$1.04\text{x}10^{-04}$	0.17		0.08	$3.27\text{x}10^{-06}$	0.11	
C12:1					0.08	$1.48\text{x}10^{-06}$	0.11	
C16:2-OH					0.08	$2.70\text{x}10^{-06}$	0.15	
C6 (C4:1-DC)					0.09	$7.89\text{x}10^{-08}$	0.11	
C12					0.08	$2.53\text{x}10^{-06}$	0.12	
C16:1-OH					0.08	$1.01\text{x}10^{-06}$	0.20	
C14					0.07	$1.40\text{x}10^{-05}$	0.20	
C10					0.08	$2.86\text{x}10^{-06}$	0.09	
C10:1					0.07	$2.77\text{x}10^{-05}$	0.13	
C2/C0					0.11	$6.77\text{x}10^{-11}$	0.10	
(C2+C3)/C0					0.11	$3.20\text{x}10^{-11}$	0.10	
PCs								
Σ PCs					-0.10	$2.72\text{x}10^{-11}$	0.10	
Σ mono PCs					-0.10	$6.32\text{x}10^{-11}$	0.10	
Σ poly PCs					-0.10	$3.04\text{x}10^{-10}$	0.10	
Σ sat. PCs					-0.10	$3.32\text{x}10^{-07}$	0.10	
Σ sat. mono PCs					-0.10	$6.32\text{x}10^{-11}$	0.10	
Σ short PCs					-0.10	$2.25\text{x}10^{-10}$	0.20	
PC aa								
Σ PC aa					-0.10	$6.13\text{x}10^{-12}$	0.10	
Σ long PC aa					-0.10	$3.25\text{x}10^{-05}$	0.10	
Σ mono PC aa					-0.10	$7.39\text{x}10^{-11}$	0.10	
Σ poly PC aa					-0.10	$8.31\text{x}10^{-11}$	0.10	
Σ sat. PC aa					-0.10	$1.50\text{x}10^{-06}$	0.10	
Σ short PC aa					-0.10	$1.67\text{x}10^{-10}$	0.20	
PC aa C34:4	-0.14	$7.37\text{x}10^{-05}$	0.07		-0.14	$1.76\text{x}10^{-14}$	0.07	
PC aa C32:2	-0.15	$8.56\text{x}10^{-06}$	0.16		-0.12	$2.02\text{x}10^{-13}$	0.15	
PC aa C36:1					-0.13	$1.15\text{x}10^{-14}$	0.11	
PC aa C34:3	-0.14	$5.98\text{x}10^{-05}$	0.14		-0.12	$4.04\text{x}10^{-12}$	0.13	
PC aa C30:0					-0.12	$1.42\text{x}10^{-12}$	0.11	
PC aa C36:2					-0.12	$2.34\text{x}10^{-11}$	0.09	

Trait	Beta	P-Value	Adj.[a] R^2	P-Gain[b]	Beta	P-Value	Adj.[a] R^2	P-Gain[b]
PC aa C36:6					-0.11	$1.99\text{x}10^{-10}$	0.07	
PC aa C36:3					-0.11	$1.16\text{x}10^{-09}$	0.08	
PC aa C38:5					-0.11	$8.45\text{x}10^{-11}$	0.06	
PC aa C32:1					-0.11	$2.44\text{x}10^{-10}$	0.06	
PC aa C36:5					-0.12	$4.14\text{x}10^{-11}$	0.06	
PC aa C34:1					-0.10	$2.22\text{x}10^{-09}$	0.09	
PC aa C42:6					-0.11	$2.87\text{x}10^{-09}$	0.05	
PC aa C34:2					-0.07	$1.09\text{x}10^{-06}$	0.35	
PC aa C40:5					-0.10	$5.65\text{x}10^{-09}$	0.06	
PC aa C40:4					-0.10	$3.46\text{x}10^{-08}$	0.03	
PC aa C36:4					-0.08	$5.79\text{x}10^{-06}$	0.08	
PC aa C32:0					-0.08	$7.09\text{x}10^{-06}$	0.10	
PC aa C38:3					-0.09	$9.12\text{x}10^{-07}$	0.05	
PC aa C32:3					-0.07	$5.26\text{x}10^{-05}$	0.16	
PC aa C42:5					-0.07	$1.41\text{x}10^{-04}$	0.05	
PC aa C40:3					-0.08	$1.39\text{x}10^{-05}$	0.06	
PC ae								
Σ mono PC ae					-0.10	$5.31\text{x}10^{-05}$	0.10	
Σ sat. PC ae					-0.10	$1.38\text{x}10^{-06}$	0.10	
PC ae C40:1					-0.12	$9.56\text{x}10^{-11}$	0.04	
PC ae C38:2					-0.09	$2.91\text{x}10^{-08}$	0.14	
PC ae C42:2					-0.10	$3.85\text{x}10^{-08}$	0.08	
PC ae C38:0					-0.09	$1.47\text{x}10^{-07}$	0.06	
PC ae C38:1					-0.07	$7.70\text{x}10^{-05}$	0.04	
PC ae C34:0					-0.07	$1.34\text{x}10^{-04}$	0.11	
PC ae C36:0					-0.08	$2.65\text{x}10^{-05}$	0.03	
PC ae C42:1					-0.07	$5.03\text{x}10^{-05}$	0.02	
PC ae C40:0					-0.07	$6.98\text{x}10^{-05}$	0.09	
lysoPC a								
Σ lysoPCs					-0.10	$5.38\text{x}10^{-07}$	0.20	
Σ sat. lysoPCs					-0.10	$4.57\text{x}10^{-06}$	0.10	
Σ unsat. lysoPCs					-0.10	$2.27\text{x}10^{-06}$	0.10	
lysoPC a C14:0					-0.10	$1.39\text{x}10^{-08}$	0.05	
lysoPC a C20:3					-0.09	$2.28\text{x}10^{-08}$	0.17	
lysoPC a C16:1					-0.10	$4.72\text{x}10^{-08}$	0.07	
lysoPC a C18:1					-0.08	$1.20\text{x}10^{-06}$	0.13	
lysoPC a C18:2					-0.07	$1.18\text{x}10^{-04}$	0.12	
lysoPC a C18:0					-0.08	$9.36\text{x}10^{-06}$	0.09	
lysoPC a C16:0					-0.07	$1.59\text{x}10^{-05}$	0.15	
PC aa/PC aa Ratios								
PC aa C42:0/ PC aa C42:2					0.11	$1.49\text{x}10^{-10}$	0.08	$2.62\text{x}10^{+06}$
PC aa C42:1/ PC aa C42:2					0.11	$5.16\text{x}10^{-10}$	0.06	$7.59\text{x}10^{+05}$
PC aa C36:0/ PC aa C38:0					-0.10	$4.26\text{x}10^{-08}$	0.03	$2.13\text{x}10^{+05}$
PC aa C36:0/ PC aa C42:0					-0.09	$1.09\text{x}10^{-06}$	0.06	$8.28\text{x}10^{+03}$

Trait	Beta	P-Value	Adj.[a] R^2	P-Gain[b]	Beta	P-Value	Adj.[a] R^2	P-Gain[b]
PC aa C40:1/ PC aa C42:0					-0.08	$7.74\text{x}10^{-06}$	0.08	$1.05\text{x}10^{+04}$
PC ae/PC ae Ratios								
PC ae C42:2/ PC ae C42:5	-0.17	$2.03\text{x}10^{-06}$	0.09	$3.00\text{x}10^{+03}$	-0.15	$6.47\text{x}10^{-17}$	0.07	$5.94\text{x}10^{+08}$
PC ae C40:1/ PC ae C42:5					-0.14	$4.55\text{x}10^{-16}$	0.09	$2.10\text{x}10^{+05}$
PC ae C40:1/ PC ae C40:5					-0.14	$2.77\text{x}10^{-15}$	0.07	$3.45\text{x}10^{+04}$
PC ae C38:2/ PC ae C42:5	-0.19	$1.47\text{x}10^{-07}$	0.09	$1.39\text{x}10^{+04}$	-0.12	$2.31\text{x}10^{-12}$	0.08	$1.26\text{x}10^{+04}$
PC ae C40:5/ PC ae C42:2					0.13	$3.96\text{x}10^{-15}$	0.15	$9.71\text{x}10^{+06}$
PC ae C38:2/ PC ae C40:3	-0.19	$1.47\text{x}10^{-07}$	0.13	$1.40\text{x}10^{+04}$	-0.12	$4.01\text{x}10^{-11}$	0.05	$7.27\text{x}10^{+02}$
PC ae C42:2/ PC ae C44:5					-0.12	$4.09\text{x}10^{-12}$	0.05	$9.41\text{x}10^{+03}$
PC ae C38:2/ PC ae C40:5	-0.18	$3.14\text{x}10^{-07}$	0.12	$6.53\text{x}10^{+03}$				
PC ae C38:0/ PC ae C40:6					-0.12	$1.89\text{x}10^{-12}$	0.07	$7.77\text{x}10^{+04}$
PC ae C42:3/ PC ae C42:5					-0.12	$5.37\text{x}10^{-11}$	0.05	$3.04\text{x}10^{+07}$
PC ae C42:3/ PC ae C44:5					-0.10	$4.28\text{x}10^{-08}$	0.04	$3.82\text{x}10^{+04}$
PC ae C34:0/ PC ae C42:5					-0.10	$3.63\text{x}10^{-08}$	0.06	$3.68\text{x}10^{+03}$
PC ae C34:3/ PC ae C42:5					-0.09	$4.27\text{x}10^{-07}$	0.04	$3.46\text{x}10^{+03}$
PC ae C34:1/ PC ae C42:5					-0.09	$3.00\text{x}10^{-07}$	0.06	$5.96\text{x}10^{+03}$
PC ae C36:3/ PC ae C42:5	-0.18	$9.55\text{x}10^{-07}$	0.09	$6.37\text{x}10^{+03}$				
PC ae C42:3/ PC ae C42:4					-0.09	$5.38\text{x}10^{-07}$	0.03	$3.04\text{x}10^{+03}$
PC ae C32:1/ PC ae C42:5					-0.08	$4.01\text{x}10^{-06}$	0.04	$3.47\text{x}10^{+03}$
PC ae C36:5/ PC ae C42:5					-0.08	$3.07\text{x}10^{-06}$	0.10	$2.90\text{x}10^{+03}$
PC ae C34:2/ PC ae C42:5	-0.19	$1.90\text{x}10^{-07}$	0.10	$2.43\text{x}10^{+04}$				
PC ae C40:3/ PC ae C42:5					-0.08	$3.84\text{x}10^{-06}$	0.12	$3.62\text{x}10^{+03}$
PC ae C34:2/ PC ae C44:5	-0.18	$8.01\text{x}10^{-07}$	0.10	$5.75\text{x}10^{+03}$				
PC ae C34:2/ PC ae C44:6	-0.18	$5.28\text{x}10^{-07}$	0.11	$8.73\text{x}10^{+03}$				
SM C16:0/ SM C24:0					0.08	$2.60\text{x}10^{-06}$	0.10	$8.80\text{x}10^{+03}$

Trait	Beta	P-Value	Adj.[a] R^2	P-Gain[b]	Beta	P-Value	Adj.[a] R^2	P-Gain[b]
SM C24:0/ SM C24:1					-0.09	2.04×10^{-07}	0.04	$9.58 \times 10^{+04}$

[a] adjusted R^2 of the linear model; [b] p-gain, fold decrease in the p-value association for the pair of metabolites, compared to the lowest of two p-values for the single metabolites; AC, acylcarnitines; even, even numbered; long, long-chain; med., medium-chain; short, short-chain; sat., saturated; unsat., unsaturated.

Acknowledgements

First, I thank my supervisor Prof. Dr. Dr. Wichmann who provided me with the possibility to conduct this PhD project. Special thanks go to my co-supervisor PD Dr. Jakob Linseisen for his continuous support, invaluable advice, and his encouraging words throughout all stages of this work. I like to thank my co-authors, in particular Gabi and Jan, for their help and many fruitful discussions.
I thank my friends and colleagues, especially Sigrid, Ann-Kristin, Nina, Inke, Guido, and Julia, for their help, ideas, open ears, and many good memories.
A special thank you goes to David without whom I probably would not have started this PhD project in the first place.
Most importantly, I am grateful for my wonderful family and I thank them for believing in me. Their continuing love, support, trust, and understanding gave me the strength to complete this PhD project. I would not know what to do without them.