Institut für Ernährungs- und Lebensmittelwissenschaften

Abteilung Ernährungsphysiologie

Acute impact of dietary pattern and walking on postprandial metabolism, attention, and mood in older adults with a cardiovascular disease risk phenotype

Dissertation

zur Erlangung des Grades

Doktorin der Ernährungs- und Lebensmittelwissenschaften (Dr. troph.)

der Landwirtschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

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Bonn 2020

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Tag der mündlichen Prüfung: 14.01.2020

Angefertigt mit Genehmigung der Landwirtschaftlichen Fakultät der Universität Bonn

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List of abbreviations

AD	Alzheimer's disease
ADP	Adenosine diphosphate
AMPK	5`adenosine monophosphate-activated protein kinase
ANOVA	Analysis of variance
ApoE	Apolipoprotein E
ATP	Adenosine triphosphate
BDNF	Brain-derived neurotrophic factor
CaMK	Ca^{2+}/calmodulin-dependent protein kinase
CRP	C-reactive protein
CVD	Cardiovascular diseases
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
FAIR-2	Frankfurt Attention Inventory 2
GL	Glycemic load
GLUT-4	Glucose transporter-4
HDL	High-density lipoprotein
HOMA-IR	Homeostasis model assessment for insulin resistance
HPA	Hypothalamic-pituitary-adrenal axis
HR_{max}	Maximal heart rate
Hs	High sensitivity
iAUC	Incremental area under the curve
IGF1	Insulin-like growth factor

IL	Interleukin
IR	Insulin receptor
IRS-1	Insulin receptor substrate-1
LDL	Low-density lipoprotein
LPL	Lipoprotein lipase
MAPK	Mitogen-activated protein kinase
MD	Mediterranean-type diet meal
MDMQ	Multidimensional Mood state Questionnaire
MD-R	Mediterranean-type diet meal plus postprandial resting
MD-W	Mediterranean-type diet meal plus postprandial walking
MUFA	Monounsaturated fatty acid
NEFA	Non-esterified fatty acid
NF-κB	Nuclear factor 'kappa-light-chain-enhancer' of activated B-cells
NO	Nitric oxide
oxLDL	Oxidized low density lipoprotein
PAL	Physical activity level
PI-3K	Phosphatidylinositol 3-kinase
PUFA	Polyunsaturated fatty acid
ROS	Reactive oxygen species
SD	Standard deviation
SEM	Standard error of the mean
sE-selectin	Soluble endothelial selectin
SFA	Saturated fatty acid
sICAM-1	Soluble intercellular adhesion molecule-1

sVCAM-1	Soluble vascular cell adhesion molecule-1
TEAC	Trolox equivalent antioxidative capacity
TNF-α	Tumor Necrosis Factor-α
TRL	Triglyceride rich lipoproteins
VAS	Visual analogue scales
VLDL	Very-low density lipoprotein
VO_{2max}	Maximal oxygen uptake
WD	Western diet high-fat meal
WD-R	Western diet high-fat meal plus postprandial resting
WD-W	Western diet high-fat meal plus postprandial walking

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CHAPTER 1: GENERAL INTRODUCTION

Postprandial metabolism and cardiovascular diseases

The postprandial state is a dynamic period of metabolic processes that occur following the digestion and absorption of a meal (Jackson et al. 2012; Burton-Freeman 2010; Lopez-Miranda et al. 2007). Physiologically, meal intake results in a postprandial increase in plasma glucose, serum insulin, and serum triglyceride concentrations. Depending on the quantity of dietary fat and carbohydrate, fatty acid composition, and type of carbohydrate, these metabolic events vary in extent and duration and can be measured for up to eight hours after a single meal intake (Jackson et al. 2012; Lacroix et al. 2012; Calder et al. 2011). During this period, nearly every major physiological system is responding with compensatory and adaptive mechanisms to restore homeostasis, which, under physiological conditions, leads to a rapid recovery (Sottero et al. 2015; Burton-Freeman 2010). However, the dietary habits of Western societies, characterized by a frequent intake of energy-dense meals (≥ 3 meals / day with less than 6 hours in-between), are responsible for the fact, that many people spend the majority of their day (up to 18 hours) in the postprandial state (Teeman et al. 2016a; Burton-Freeman 2010) (**Figure 1-1**). Current research suggests that a chronic oversupply of macronutrients and total energy and the resulting prolonged and exaggerated postprandial metabolic events (hyperglycemia, hyperinsulinemia, and hyperlipidemia) that repeat multiple times each day, lead to a short-term oxidative imbalance, a status referred to as postprandial oxidative stress (Sottero et al. 2015). In the long term, this may lead to increased susceptibility to the development of cardiovascular diseases (CVD) (O'Keefe and Bell 2007).

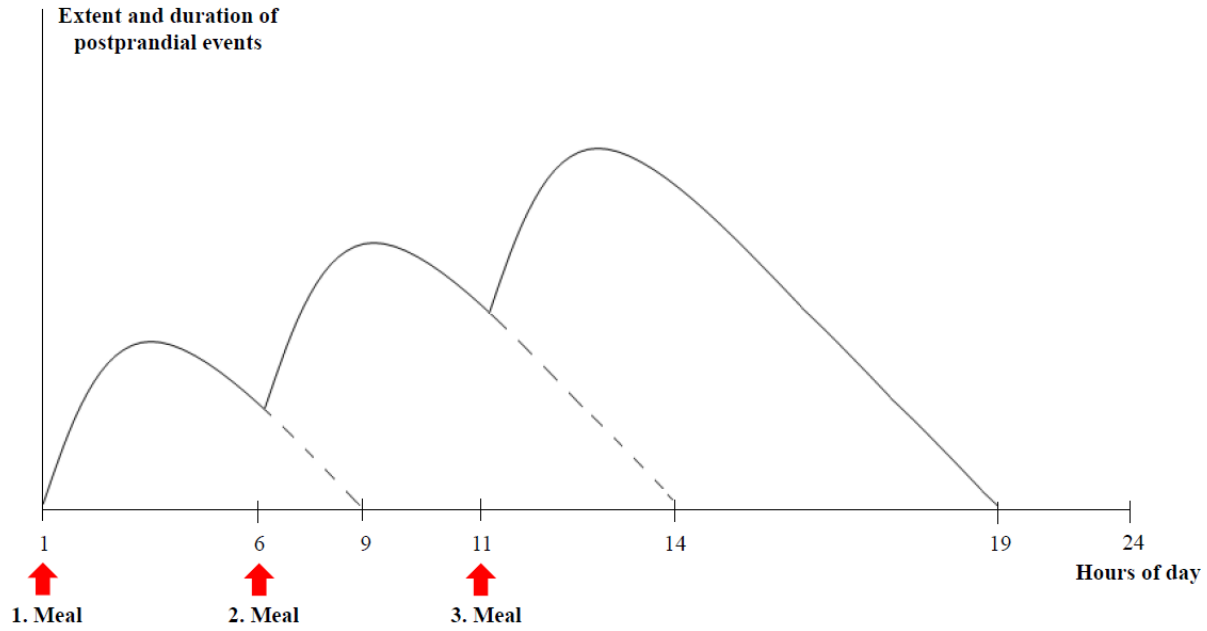

Figure 1-1 Extent and duration of postprandial events in the case of multiple meal consumption. Depending on the quantity of dietary fat and carbohydrate, fatty acid composition, and type of carbohydrate, postprandial events can be measured up to eight hours after a single meal intake. In the case of multiple meals (here: consumption of three meals every five hours), the postprandial events of the individual meals overlap and add up, resulting in people spending up to 18 hours in the postprandial state (own figure).

The oxidative degradation of dietary fat and carbohydrate during energy metabolism results in acetyl CoA formation and the synthesis of superoxide anions in the respiratory chain in the mitochondria. These intermediate compounds can further react to form reactive oxygen species (ROS) in the cytoplasm (e.g., hydrogen peroxide or hydroxyl radicals), which have the ability to oxidize mitochondrial proteins, deoxyribonucleic acid, and unsaturated fatty acids (Quijano et al. 2016; Ott et al. 2007). Moreover, this pro-oxidant state can promote non-enzymatic glycation of low-density lipoprotein (LDL) (Younis et al. 2008) and triggers LDL-oxidation, leading to an increased formation of oxidized LDL (oxLDL) (Gradinaru et al. 2015; Sies et al. 2005). The altered redox balance in the cells triggers the activation of numerous redox-sensitive transcription factors, including the nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NF-κB), which is the main mediator of inflammatory response (Muñoz and Costa 2013). The transcription factor NF-κB mediates the release of inflammatory cytokines (e.g., tumor necrosis factor α, TNF-α; interleukin-6, IL-6; and IL-8), and acute phase reactants like C-reactive protein (CRP), linking the food-induced increase in oxidative stress to a postprandial inflammatory response (Muñoz and Costa 2013). In endothelial cells the postprandial pro-oxidant state impacts cell function through a reduction of endothelial nitric oxide (NO) synthase activity and an increase in peroxynitrite formation. This leads to a reduced NO availability and a defective endothelial dependent vasodilation, also referred to as endothelial dysfunction (Gradinaru et al. 2015; Muñoz and Costa 2013). The formation of NO

is further impaired by the release of endothelial adhesion molecules (e.g., soluble intercellular adhesion molecule-1, sICAM-1; soluble vascular cell adhesion molecule-1, sVCAM-1; and soluble endothelial selectin, sE-selectin) through ROS-mediated endothelial activation (Lacroix et al. 2012). sICAM-1 and sVCAM-1 enable the adhesion and penetration of leukocytes across the vascular endothelium resulting in an increased recruitment of monocytes, which become macrophages by scavenging oxLDL. These macrophages differentiate in foam cells by accumulating lipid, initiating the formation of atherosclerotic plaque (Teeman et al. 2016a). Altogether, the postprandial metabolic response is thus associated with low-grade oxidative stress, low-grade inflammation and low-grade endothelial dysfunction. **Figure 1-2** summarizes the events caused by postprandial hyperglycemia, hyperinsulinemia, and hyperlipidemia.

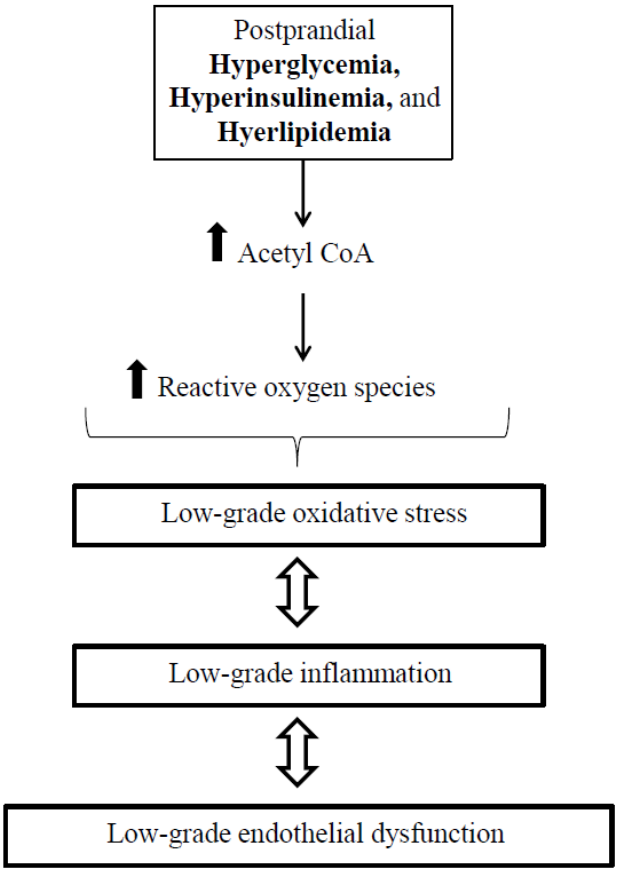

Figure 1-2 Overview of the downstream effects mediated by nutrient overload. Excessive intake of dietary fat and carbohydrates leads to an increased acetyl CoA formation, which stimulates the formation of superoxide in the electron transport chain in the mitochondria. The subsequent conversion of superoxide to hydrogen peroxides results in an increase of reactive oxygen species within the cell. This change in redox status activates numerous redox-sensitive transcription factors, including the nuclear factor 'kappa-light-chain-enhancer' of activated B-cells, which is the main mediator of inflammatory responses. Furthermore, endothelial cell function is impaired through a reduction of endothelial nitric oxide synthase activity and an increase in peroxynitrite formation. Modified according to (Muñoz and Costa 2013).

The extent and duration of all postprandial events are influenced by several meal dependent and meal independent factors, which are summarized in **Figure 1-3.**

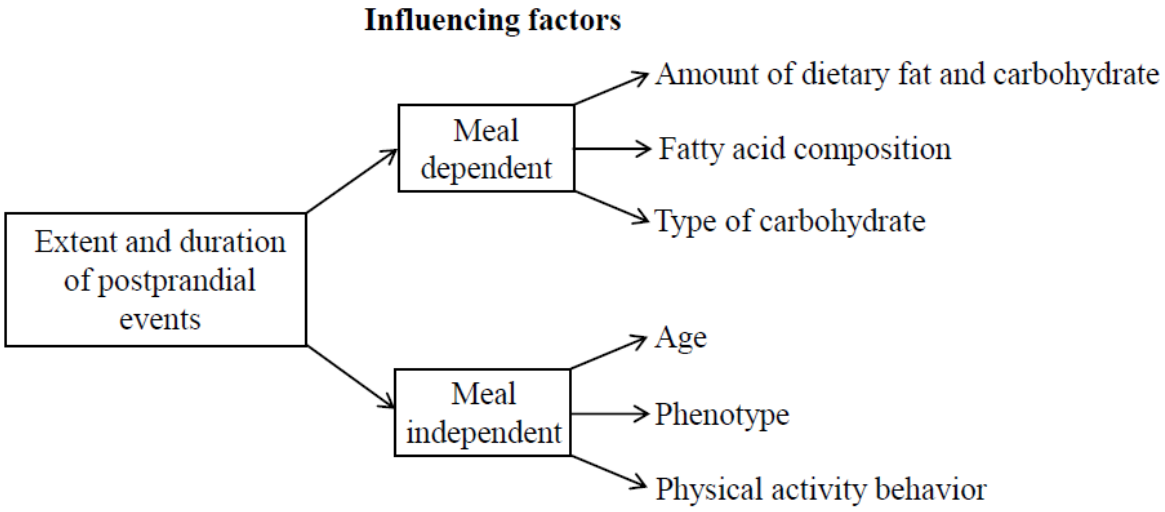

Figure 1-3 Overview of meal dependent and meal independent factors influencing postprandial metabolic, oxidative, and inflammatory events. Modified according to (Margioris 2009).

The quantitative nutrient dependent factor influencing the extent and duration of postprandial events is the total energy content of a meal and therefore its total amount of macronutrients (Margioris 2009). In this context, the amount of dietary carbohydrate and dietary fat is of particular importance, since an excessive consumption of these macronutrients results in postprandial hyperglycemia/hyperinsulinemia and hyperlipidemia.

Research suggests that both for normal-weight and obese individuals an amount of 30 – 50 g of dietary fat seems to be required to observe a relevant increase in serum triglycerides and up to approximately 80 g of dietary fat the magnitude of the postprandial lipemic response seems to be dose-dependent (Dias et al. 2017; Lopez-Miranda et al. 2007). Regarding the fatty acid composition of high-fat meals (defined as >30 energy-% fat), it appears that the saturated fatty acid (SFA) content in particular plays an important role in the extent of the postprandial lipemic and inflammatory response, but the available research data are equivocal (Dias et al. 2017; Monfort-Pires et al. 2016; Teeman et al. 2016a; Teng et al. 2015; Margioris 2009; Jackson et al. 2007). Furthermore, especially regarding the postprandial inflammatory response, the amount of dietary long chain n-3 polyunsaturated fatty acids (PUFA) like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are of importance, due to their potent anti-inflammatory effects. In contrast to the long chain n-3 PUFAs, the n-6 PUFAs (e.g., arachidonic acid) are precursors of pro-

inflammatory mediators (e.g., series-4 leukotrienes and series-2 prostaglandins). Research suggests that in addition to being influenced by the fatty acid composition of the ingested meal, the postprandial lipemic response after a high-fat meal seems to be influenced by the fatty acid composition of an individual's habitual diet as well (Dias et al. 2017; Weintraub et al. 1988). In this context, Weintraub and colleagues demonstrated, that a n-6 PUFA challenge following chronic consumption of a diet rich in n-6 PUFA resulted in a more pronounced postprandial lipemic response compared to the lipemic response observed following a n-3 PUFA challenge after the chronic consumption of a diet rich in n-3 PUFAs (Weintraub et al. 1988).

The glycemic response to a meal is dependent on multiple factors, including meal specific (e.g., dose and digestibility of carbohydrate, food matrix) and metabolic factors (e.g., neuroendocrine responses such as the secretion and action of insulin) (Burton-Freeman 2010). Chronic hyperglycemia and consequently hyperinsulinemia promote insulin resistance, which represents a primary metabolic disturbance in the metabolic syndrome (Cordain et al. 2005; Cordain et al. 2003; Reaven 1995). Therefore, postprandial hyperglycemia/hyperinsulinemia are described to be independent risk factors for the development of CVD (Gerich 2006). Research suggests, that it is of special importance to avoid the occurrence of high postprandial glucose and insulin peaks, both in type 2 diabetic and metabolically healthy individuals, and to rather ensure a steady glucose and concomitant insulin release. This might protect against type 2 diabetes progression and the development of its associated cardiovascular complications (Heden and Kanaley 2019; Rozendaal et al. 2018). The glycemic load (GL), which combines the quality (glycemic index) and quantity of dietary carbohydrates, is an established parameter for assessing the carbohydrate quality of a meal, as it is better suited to predicting postprandial glucose and insulin concentrations, than the total amount of carbohydrates alone (Rozendaal et al. 2018).

A major nutrient independent factor influencing postprandial events is the obese phenotype since it has been demonstrated that the postprandial oxidative stress response and its associated inflammatory and endothelial events are exaggerated and prolonged in these individuals (Telle-Hansen et al. 2017). Since the adipose tissue releases a spectrum of inflammatory mediators, obese persons (BMI > 30 kg/m^2) have up to 10-fold higher circulating concentrations of different inflammation-associated markers (e.g., CRP, TNF-α, IL-6) compared to normal-weight individuals. This makes a state of chronic, low-grade systemic inflammation characteristic of the overweight-to-obese phenotype (Calder et al. 2011; Gregor and Hotamisligil 2011). According to current models it can be assumed that, due to their elevated inflammatory indices in the fasting state, obese individuals have an accentuated inflammatory response in the postprandial state as well. This seems

to additionally intensify the obesity-induced chronic low-grade systemic inflammation and, in the long run, results in a failure to recover physiological homeostasis (maladaptation) (Calder 2011; Margioris 2009). Research suggests that the ability of a person to metabolically adapt to food intake, measured by the time frame within which metabolic homeostasis recovers, can be used as an indicator of the persons health state (phenotypic flexibility) (Kardinaal et al. 2015; Stroeve et al. 2015; van Ommen et al. 2014). It can therefore be assumed that the described 'dysmetabolism' characteristic for the obese phenotype contributes to its increased CVD risk (**Figure 1-4**).

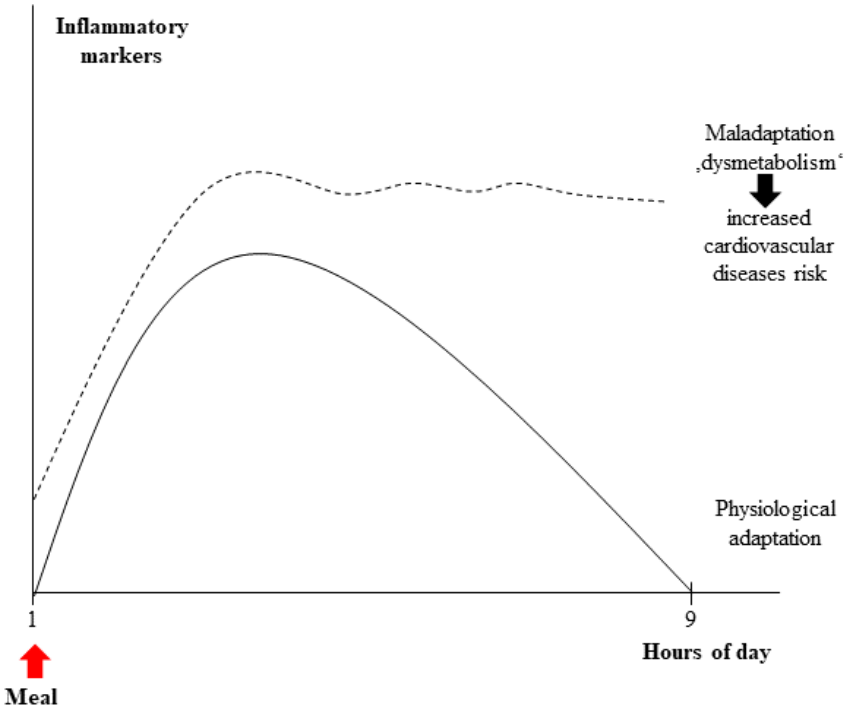

Figure 1-4 Model of the postprandial inflammatory response in normal-weight individuals (physiological adaptation) and obese individuals (maladaptation). Along with their already elevated inflammatory indices in the fasting state, obese individuals show exaggerated and prolonged postprandial inflammatory responses. In the long run this results in a failure to recover physiological homeostasis (= maladaptation/'dysmetabolism'), which leads to an increased cardiovascular disease risk. Modified according to (Margioris 2009).

Zilversmit (1979) was the first to postulate the concept of atherogenesis being a postprandial phenomenon (Zilversmit 1979), triggered by the prolonged elevation of triglycerides in the blood stream and the concomitant inflammatory response in the blood vessels wall (Teeman et al. 2016a; Libby 2012; Ross 1999). Scientific interest in postprandial metabolic and associated oxidative, and inflammatory events as risk factors for CVD are still focus of current human intervention studies, especially considering the fact that the postprandial phase predominates over the course of a day, compared to the fasting state (Higgins and Adeli 2017; Burton-Freeman 2010; Tushuizen et al.

2005). Accumulating research suggests that even acute postprandial responses following the consumption of single high-carbohydrate or high-fat meals contribute to the CVD risk, with postprandial hyperglycemia and hyperlipidemia being independent cardio metabolic risk factors (Jiang et al. 2017; Jacome-Sosa et al. 2016; Nakamura et al. 2016; Pirillo et al. 2014). Therefore, attenuating the postprandial stress response and in this context its associated inflammatory and endothelial events through specific nutritional and lifestyle interventions, seems to be a promising approach to facilitate the recovery of metabolic homeostasis and to provide resistance to pathology. This might be especially relevant in the CVD risk phenotype (Teeman et al. 2016a).

The epidemiological concept of dietary patterns

Over the last few decades researchers have shifted focus from the analysis of single foods or even nutrients to the evaluation of the effects of the whole diet and regular meals on different health outcomes (Hu 2002). This holistic approach takes into account the interactive, synergistic, or antagonistic interplay between the variety of the consumed nutrients. Furthermore, it considers the fact, that the physiological effect of the food matrix differs from the physiological effect of individual food items or nutrients (Drake et al. 2018; Gu and Scarmeas 2011; Hu 2002). In order to examine the joint effects of single foods and nutrients on clinical outcomes (e.g., CVD risk), the epidemiological concept of dietary patterns, which describe an individual's habitual diet, gains scientific interest, not only in observational studies but also in controlled human intervention trials (Gu and Scarmeas 2011; Jacobs and Steffen 2003). The variety of differently composed dietary patterns allows these intervention studies to examine and evaluate the impact of different nutrient compositions in the context of holistic meals (realistic approach), leading to a high public health relevance of research results.

Western dietary pattern

The main dietary components of today's Western societies comprise sizable portions of energy dense, nutrient poor, highly processed convenience foods such as salty snacks, sweets, and soft drinks, as well as animal products such as red meat, processed meats and high-fat dairy products (Hu 2002). Accordingly, the Western dietary pattern is characterized by a high intake of total fat and saturated fatty acids, as well as by a high GL, attributable to the regular consumption of large amounts of simple sugars (Teeman et al. 2016a; Cordain et al. 2005). Furthermore, the Western dietary pattern is higher in sodium and lower in potassium than plant-based dietary patterns such as the Mediterranean dietary pattern. Moreover, it contains a lower proportion of vitamins, minerals, dietary fiber, and antioxidants, which are characteristic nutrients of plant foods, particularly fruits and vegetables (Burton-Freeman 2010; Margioris 2009; Cordain et al. 2005). Due to its nutritional characteristics described above, the Western dietary pattern, which has become commonplace in developed countries around the world, is associated with an increased risk of developing metabolic and cardiovascular diseases in the long term. This is especially the case when combined with specific lifestyle factors (e.g., sedentary lifestyle) and genetic susceptibility (Drake et al. 2018; Cordain et al. 2005).

Mediterranean dietary pattern

The definition of the traditional Mediterranean dietary pattern is based on the dietary habits of the Mediterranean countries (e.g., Greece, Spain, south Italy) in the early 1960s (Boucher 2017; Willett et al. 1995). It is a plant-based diet mainly characterized by the consumption of minimally processed, seasonally fresh, and locally grown foods of vegetable origin. These include in particular fruit, vegetables, legumes, nuts, and seeds. On the other hand, the traditional Mediterranean diet contains only limited amounts of animal foods, such as cheese, yogurt, eggs and poultry. Other common characteristics of this dietary pattern are a moderate consumption of red wine during meals, a frequent intake of fish, dependent on the proximity of the country's distance from the Mediterranean Sea, and the use of olive oil as the principle source of fat (Lorgeril and Salen 2011; Bach et al. 2006; Willett et al. 1995; Kromhout et al. 1989; Keys et al. 1986). The described food selection results in a low intake of saturated fatty acids, animal protein, and sodium, as well as in a high intake of unsaturated fatty acids (especially oleic acid), dietary fibers, vitamins, minerals and polyphenols. Keys et al. were the first to associate the Mediterranean dietary pattern with different health benefits (Keys et al. 1986). In recent decades various observational and intervention studies have confirmed this assumption, demonstrating the association of the Mediterranean diet with a reduced risk for metabolic and cardiovascular diseases, cancer, and neurodegenerative diseases, as well as a reduced overall mortality (Dinu et al. 2018; Eleftheriou et al. 2018; Estruch et al. 2018; Sofi et al. 2014). In this context, plant foods, especially fruits and vegetables, appear to be the key components mainly due to their inherent antioxidant properties and potential to modulate cellular reductive-oxidant balance (Burton-Freeman 2010).

Effects of physical exercise on postprandial metabolism

Evidence is emerging that regular aerobic exercise entails anti-inflammatory effects. Therefore, the integration of activity sessions into everyday life (lifestyle interventions) represents a cornerstone in the primary prevention of several chronic conditions such as metabolic diseases (e.g., metabolic syndrome), CVD (e.g., coronary heart disease), psychiatric diseases (e.g., depression), neurological diseases (e.g., dementia), pulmonary diseases (e.g., asthma), musculo-skeletal disorders (e.g., osteoporosis), and cancer (Pedersen and Saltin 2015; Flynn et al. 2007). In this context, aerobic activities that are rhythmic in nature like walking, jogging, biking, or swimming are particularly recommended, since they require all large muscle groups (Fletcher et al. 2013). Research suggests that a minimum of 30 minutes of moderate-intensity aerobic activity [64–76% of maximal heart rate ($\%HR_{max}$); 46-63% of maximal oxygen uptake (VO_{2max})], performed on at least five days of the week are required to reduce the overall risk of cardiovascular events and to promote and maintain health throughout the age span (Fletcher et al. 2013; Garber et al. 2011; Haskell et al. 2007). Since this physical exercise session can be carried out either continuously or in 10-minute increments accumulated throughout the day, it can easily be incorporated into daily routines (e.g., walking or cycling to work). Furthermore, it is easy to implement and thus feasible for older, currently inactive, or physically more restricted individuals (Füzéki and Banzer 2018; Fletcher et al. 2013).

Current postprandial intervention trials focus primarily on the acute impact of aerobic training (single exercise sessions) on postprandial hyperlipidemia, as one of the major independent cardiovascular risk factors (Nakamura et al. 2016; Pirillo et al. 2014). Research substantially suggests that acute exercise effectively attenuates the postprandial lipemic response following a high-fat meal when performed in the timeframe between 18 hours pre-meal, until 90 min post-meal (Teeman et al. 2016a). However, the majority of human intervention studies performed in metabolically healthy adults suggest that exercise-induced reductions in postprandial triglycerides are more profound if the exercise session is performed before, rather than after meal intake (Edinburgh et al. 2017; Haxhi et al. 2013). It appears that the effects of an exercise session on postprandial hyperlipidemia are measurable up to 24 hours after exercise and are mainly due to acute metabolic responses rather than a long-term adaptation to regular training (Plaisance and Fisher 2014; Katsanos 2006; Malkova and Gill 2006).

Different possible mechanisms acting alone or in combination are discussed to be responsible for the exercise-induced attenuation of the postprandial lipemic response. Mechanisms include increased lipolysis and fatty acid oxidation in adipose tissue and skeletal muscle, increased clearance of intestinally derived triglyceride-rich chylomicrons from circulation and reduced

hepatic secretion of very-low density lipoprotein (VLDL) (Peddie et al. 2012; Malkova and Gill 2006). An upregulation of lipoprotein lipase (LPL) expression and activity in skeletal muscle (stimulated by exercise) and to a lesser extent in adipose tissue (stimulated by insulin) is proposed to be involved in the increased clearance of postprandial triglycerides from systemic circulation (Plaisance and Fisher 2014; Fielding 2011). In response to exercise, the muscle LPL expression on the surface of the vascular endothelium appears to be increased between 4 – 8 hours post exercise and returns to baseline around 20 hours post exercise (Plaisance and Fisher 2014; Herd et al. 2001; Seip and Semenkovich 1998). In addition, the higher blood flow through the vasculature during exercise and thus the extended contact time between LPL and the circulating triglycerides contributes to increased triglyceride hydrolysis and the associated triglyceride clearance from the circulation (Teeman et al. 2016a; Hurren et al. 2011). Overall, the described processes lead to a reduction of postprandial lipidemia, of resident time of triglyceride-rich lipoproteins in the circulation, and of LDL oxidation. On the other hand, the concentration of serum high-density lipoprotein (HDL) is increased (Wang and Xu 2017; Teeman et al. 2016a; Jackson et al. 2012). At the same time, anti-inflammatory cytokines are released during the training session such as IL-6, which is produced and released by the working muscle as a myokine with anti-inflammatory properties (Pal et al. 2014; Pedersen and Fischer 2007). The release of IL-6 during exercise is transient and increases exponentially with exercise duration, returning to resting levels approximately 1 hour after the exercise session (Gleeson et al. 2011). IL-6 stimulates the synthesis of further anti-inflammatory cytokines such as IL-10 and suppresses the production of various pro-inflammatory cytokines such as TNF-α and IL-1 (Teeman et al. 2016a; Pedersen and Fischer 2007). **Figure 1-5** summarizes the main mechanisms that are proposed to be involved in the exercise-induced attenuation of the postprandial lipemic and inflammatory response following a high-fat meal.

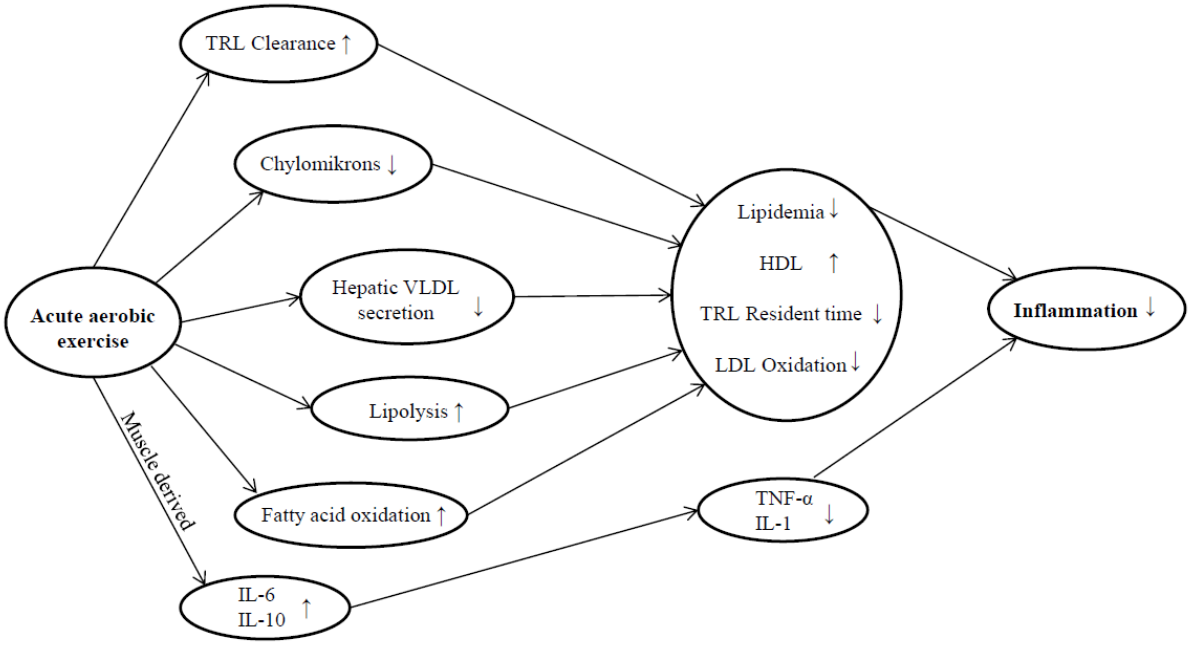

Figure 1-5 Mechanisms of exercise-induced attenuation of the postprandial lipemic response following a high-fat meal. Acute aerobic exercise leads to an increased TRL clearance from circulation, a decreased appearance of triglyceride-rich chylomicrons from the small intestine, a decreased hepatic VLDL-secretion, and to an increased lipolysis and fat oxidation. This results in an attenuation of postprandial lipidemia, an increase in serum HDL concentration, a decrease in LDL oxidation, and a decrease in TRL resident time in the circulation. All processes contribute to a less inflammatory environment within the vasculature through the release of anti-inflammatory cytokines (IL-6; IL-10) and the inhibition of pro-inflammatory cytokines (TNF-α; IL-1). Modified according to (Teeman et al. 2016a). HDL, High-density lipoprotein; IL, Interleukin; LDL, Low-density lipoprotein; TNF-α, Tumor Necrosis Factor-α; TRL, Triglyceride rich lipoproteins; VLDL, Very-low density lipoprotein.

Interventional trials point out that the effect of endurance exercise on postprandial events is influenced by several factors related to exercise (e.g., intensity and duration) or meal characteristics (e.g., moderate-fat- vs. high-fat meals), as well as the time interval between them (pre- vs. post-meal exercise) (Haxhi et al. 2013). In addition, the energy deficit created by the exercise session, which can be modulated equally by exercise duration and intensity, seems to be a major factor determining the extent to which the postprandial lipemic response is attenuated. Furthermore, an energy replacement of exercise energy expenditure after the training session seems to revise the hypolipemic effects of exercise (Plaisance and Fisher 2014; Haxhi et al. 2013; Cox-York et al. 2012; Peddie et al. 2012). Research suggests that in metabolically healthy adults, favorable effects can be attained by aerobic exercise resulting in an energy expenditure of at least 500 kcal. In individuals with increased cardiovascular disease risk a lower energy expenditure appears to be sufficient to achieve similar effects (Teeman et al. 2016b; Maraki and Sidossis 2013; Cox-York et al. 2012; Mestek et al. 2008).

In addition to the modulation of the postprandial lipemic response, acute aerobic exercise is widely acknowledged as a strong modulator of the postprandial glycemic response as well. In this context aerobic exercise is recognized to increase insulin sensitivity and to improve postprandial glucose control (Edinburgh et al. 2017; Haxhi et al. 2013). The mechanisms involved in the exercise-induced attenuation of postprandial glycemia are driven by an enhancement of the glucose transport from the circulation into the skeletal muscle. This is primarily triggered by an increased expression and translocation of the glucose transporter GLUT-4 from intracellular stores to the plasma membrane of the musculature. In this context, exercise is able to regulate different molecular pathways that have an additive effect on glucose uptake (Pereira et al. 2017; DiPietro et al. 2013): Even single exercise sessions activate the insulin signaling pathway (phosphoinositide 3-kinase pathway), which is the key regulator of the glucose transport into the muscle in the conditions of rest (insulin dependent mechanism), and further stimulate the GLUT-4 translocation via the contraction of skeletal muscle. The stimulation of GLUT-4 translocation via skeletal muscle contraction is an insulin independent glucose uptake which seems to be initiated by the release of calcium from the sarcoplasmic reticulum. It may involve the activation of several molecular signaling pathways irrespective of the exercise modality (Pereira et al. 2017; Röhling et al. 2016; Röckl et al. 2008; Hayashi et al. 1997). **Figure 1-6** provides an overview of the postulated mechanisms involved in the insulin dependent and insulin independent uptake of glucose into the skeletal muscle.

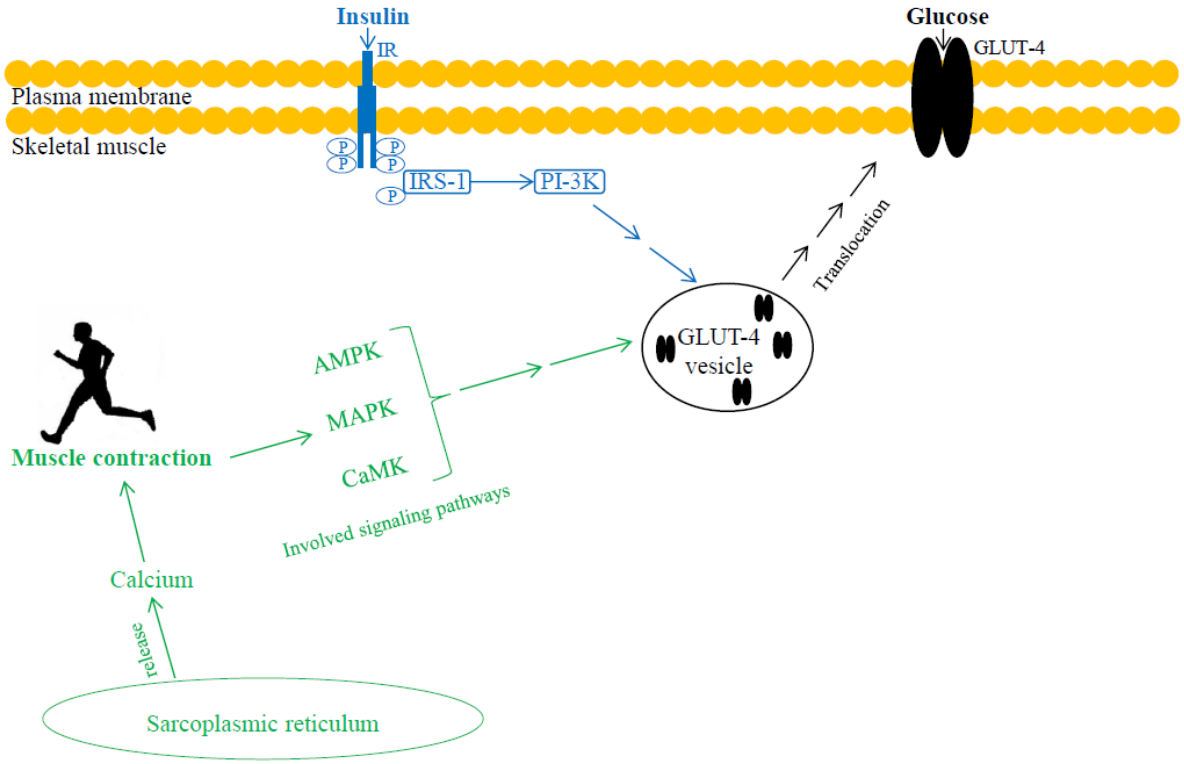

Figure 1-6 Postulated insulin dependent (blue) and insulin independent (green) mechanisms involved in skeletal muscle glucose uptake. Insulin and muscle contractions cause translocation of the glucose transporter GLUT-4 to the plasma membrane initiating an increase of glucose uptake from plasma into muscle. Insulin stimulated GLUT-4 translocation involves the PI-3-kinase signaling pathway. The exercise-induced GLUT-4 translocation is triggered by the release of calcium from the sarcoplasmic reticulum and is postulated to involve different molecular signaling pathways (e.g., AMPK, MAPK, CaMK). Modified according to (Pereira et al. 2017; Hayashi et al. 1997). AMPK; 5`adenosine monophosphate-activated protein kinase; CaMK; Ca^{2+}/calmodulin-dependent protein kinase; GLUT-4; Glucose transporter-4; IR, Insulin receptor; IRS-1, Insulin receptor substrate-1; MAPK, Mitogen-activated protein kinase; P, Phosphate; PI-3K, Phosphatidylinositol 3-kinase.

Human intervention trials substantially established that plasma glucose concentrations are sensitive to exercise timing, intensity, duration, and frequency. Research suggests that both in healthy adults and individuals with impaired glucose metabolism (e.g., manifested type 2 diabetes mellitus), post-meal aerobic exercise seems to result in a greater attenuation of postprandial glycemia compared to exercise performed in the pre-prandial or fasted state (Borror et al. 2018; Erickson et al. 2017; Reynolds et al. 2016; Aadland and Hostmark 2008). The hypoglycemic effects of exercise can be realized immediately after just a single exercise session and thus no long-term training adaptations are needed for beneficial effects on blood glucose to occur (Erickson et al. 2017). The benefit of postprandial exercise on plasma glucose concentrations is due to the synergy between insulin and muscular contraction, which in combination stimulate skeletal muscle glucose uptake to a greater extent than either stimulus alone (Wallis and Gonzalez 2019).

Effects of diet and physical exercise on cognitive and emotional functioning

The term "cognition" is a collective term combining processes and structures based on the recording, processing, and storing of information by the brain. A person's cognitive abilities are diverse and include, among other things, perception, attention, memory, language, thinking, problem solving, as well as intelligence (Hänsel et al. 2016). Research substantially shows that cognitive capacity is strongly influenced by lifestyle modulators such as diet and physical activity behavior, even in individuals with genetic susceptibility for the development of Alzheimer's disease (AD) (e.g., Apolipoprotein E4 carriers) (Plourde 2018; Phillips 2017).

Numerous epidemiological studies suggest that an adherence to plant-based dietary patterns, especially the Mediterranean dietary pattern, is associated with improved cognitive performance, slower age-related cognitive decline and lower risk of cognitive impairment and neurodegenerative disease in older adults (Chen et al. 2019; Shannon et al. 2019; Abbatecola et al. 2018; Smith and Blumenthal 2016). By contrast, the number of randomized, controlled intervention trials in this field of research is limited (Radd-Vagenas et al. 2018). Different supplementation studies suggest an association between single nutrients (especially DHA) and increased cognitive performance, mediated by neurotrophic and neuroendocrine factors. In this context, the brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF1) seem to play an important role. These factors regulate the transcription of genes involved in brain structure and brain function via different cell signaling pathways (Weiser et al. 2016; Dauncey 2009; Gómez-Pinilla 2008b). Furthermore, long chain n-3 PUFAs seem to modulate mood-related behaviors via the endocannabinoid system and the hypothalamic-pituitary-adrenal (HPA) axis (Larrieu and Layé 2018). On the other hand, nutrients such as refined carbohydrates, saturated and trans fatty acids have been associated with cognitive deficits (Hawkins et al. 2018; Barnard et al. 2014). The neuroprotective effects of single nutrients such as DHA in the context of whole meals reflecting different dietary patterns (holistic approach) have not yet been sufficiently investigated and are examined by current ongoing human intervention trials (Bundy and Minihane 2018).

Research reveals beneficial effects of physical activity on emotional and cognitive function and especially regular aerobic exercise is described to exert neuroprotective effects (Strasser and Fuchs 2015). The cellular and molecular mechanisms that underlie the association between physical activity and cognition are not fully elucidated. However, regular exercise seems to affect synaptic plasticity and cognitive function through its involvement in neurotrophic signaling, neurogenesis, and the HPA axis, as well as its anti-inflammatory and anti-oxidative capacities (Phillips and Fahimi 2018; Mandolesi et al. 2018). Furthermore, physical exercise seems to upregulate the

synthesis of several neurotransmitters (e.g., serotonin, dopamine) associated with mood enhancement and reduced depressive symptoms (Basso and Suzuki 2017; Strasser and Fuchs 2015). Current research results regarding the effects of an acute session of aerobic exercise on cognitive performance are inconsistent with modulators of effect size being exercise intensity, temporal sequencing of cognitive assessment in relation to exercise (e.g., following exercise session or during exercise session), modality of aerobic training (e.g., cycling or running), and cognitive parameters measured (e.g., memory or processing speed) (Basso and Suzuki 2017; Lambourne and Tomporowski 2010). Postprandial intervention trials examining the interactive effects of physical activity and meal composition on emotional and cognitive functioning are limited (Veasey et al. 2013; Veasey et al. 2015). However, research suggests that the effects of particular diets on the activation of molecular systems that are involved in synaptic plasticity and cognitive function interact with the effects of exercise (Gómez-Pinilla 2008b). **Figure 1-7** summarizes the hypothetical mechanism by which the interaction of exercise and the consumption of neuroprotective nutrients seem to affect cognitive abilities (simplified overview).

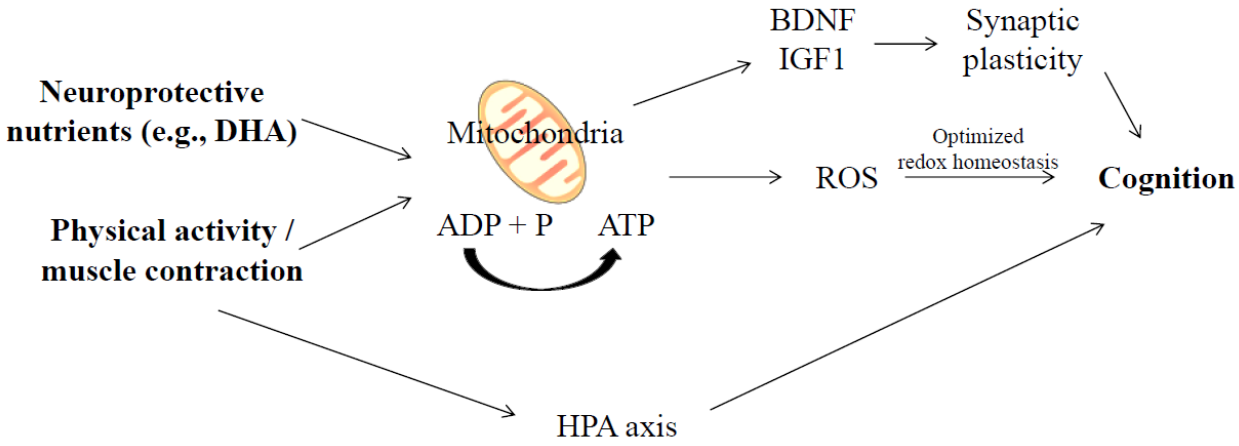

Figure 1-7 The role of specific nutrients and physical activity in maintaining mental health (simplified overview). Specific nutrients and physical activity show individual and additive effects on synaptic plasticity and cognition through the activation of different pathways: The molecules BDNF and IGF1 support synaptic plasticity and their activation might be triggered by energy metabolism (ATP production) in the mitochondria. Long-term physical activity optimizes redox homeostasis by buffering ROS formation during energy metabolism (anti-oxidative capacity of exercise), which helps to maintain cognitive function even under challenging situations. Physical activity also affects cognitive function through its role in the endocrine stress-regulation system (HPA axis), leading to an optimized stress response in trained individuals, characterized by a stronger reactivity and quicker regeneration. Modified according to (Gómez-Pinilla 2008a; Phillips 2017). ADP, Adenosine diphosphate; ATP, Adenosine triphosphate; BDNF, Brain-derived neurotrophic factor; DHA, Docosahexaenoic acid; HPA, Hypothalamic-pituitary-adrenal axis; IGF1, Insulin-like growth factor; P, Phosphate; ROS, Reactive oxygen species.

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OBJECTIVES

Recent postprandial intervention studies focused on the examination of the effects of aerobic exercise performed prior or after the consumption of high-fat or high-carbohydrate challenges on selected physiological parameters, in particular postprandial hyperlipidemia or hyperglycemia. Currently, little is known regarding the postprandial effects of exercise after the consumption of true-to-life meals with different nutrient composition. Also, further intervention studies are necessary to evaluate the efficacy of physical activity sessions of low-to-moderate intensity that can easily be incorporated into daily routines, even by inactive or physically more restricted individuals. Furthermore, only a limited number of studies address populations with higher metabolic risk, such as individuals with advanced age, metabolic syndrome traits and a sedentary lifestyle. Mainly for individuals with increased susceptibility to the development of CVD, formulating exercise-oriented therapeutic measures might be of special clinical importance.

The purpose of the present study was to examine the acute postprandial effects of a 30-minutes moderate walking program suitably for everyday use in older subjects (60-80 years) with a risk phenotype for cardiovascular and neurodegenerative disease. The duration of the walking program was chosen to be in accordance with the current recommendations for the minimum of moderate-intensity physical activity required on most days of the week to reduce overall risk of cardiovascular events and to promote and maintain health throughout the age span. In contrast to current postprandial intervention trials, the present study focused on the administration of realistic, regular meals, to be able to evaluate the joint effects of single foods and nutrients on postprandial events. With the purpose of examining the postprandial impact of different nutrient compositions, two iso-energetic meals were designed to compare common dietary patterns; the Mediterranean dietary pattern and the typical Western dietary pattern. Next to metabolic outcomes (lipemic and glycemic responses) the present study included selected oxidative (oxLDL), endothelial (sICAM, sVCAM, sE-selectin), and inflammatory (IL-6) parameters, with the intention of reflecting all major postprandial systems involved. Since only a limited number of postprandial intervention studies exist that focus on the interactive effects of physical activity and meal composition on neuropsychological parameters, additional outcome measures (attention, mood, and the feeling of hunger and satiety) were included in the present trial.

The study was performed as a randomized, controlled, crossover trial. In order to evaluate the interactive effects of walking and meal composition on the postprandial outcome measures, the participants were randomly assigned to four intervention groups, each lasting 4.5 h from morning until afternoon: (i) Mediterranean-type diet meal plus 30 min postprandial walking; (ii) Mediterranean-type diet meal plus 30 min postprandial resting; (iii) Western-diet high-fat meal plus 30 min postprandial walking and (iv) Western-diet high fat meal plus 30 min postprandial resting.

The study tested the following hypotheses regarding physiological outcome measures:

1. A Mediterranean-type diet meal generates a lower postprandial response than a Western diet high-fat meal.

2. Moderate walking in the postprandial period as compared to remaining sedentary, results in attenuated postprandial events.

The study tested the following hypotheses regarding psychological outcome measures:

1. A Mediterranean-type diet meal generates higher postprandial satiety, postprandial attention, and a better subjective mood than a Western diet high-fat meal.

2. Moderate walking in the postprandial period as compared to remaining sedentary, results in increased postprandial attention and a better subjective mood.

CHAPTER 2: MANUSCRIPT 1

Moderate post-meal walking has no beneficial effects over resting on postprandial lipemia, glycemia, insulinemia, and selected oxidative and inflammatory parameters in older adults with a cardiovascular disease risk phenotype: A randomized crossover trial

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Keywords: Postprandial metabolism, physical activity, walking, metabolic syndrome, randomized controlled trial, crossover design, inflammation, adhesion molecules.

Published in *The Journal of Nutrition* (J Nutr. 2019 Nov 1;149(11):1930-1941. doi: 10.1093/jn/nxz148).

ABSTRACT

Background: Research suggests that postprandial events as risk factors for cardiovascular diseases (CVD) are influenced by meal composition and exercise.

Objective: We investigated the effect of walking versus rest on postprandial metabolic, inflammatory, and oxidative events following the consumption of test meals reflecting two different dietary patterns in older adults with increased CVD risk.

Design: A randomized crossover trial was conducted in 26 men and women (age 70±5 y; BMI 30.3 ± 2.3 kg/m^2). Each adult participated in four treatments combining one of two isoenergetic (4300 kJ) meals [Western diet high-fat meal (WD): total fat, 59.4 g; saturated fatty acids, 32.0 g, dietary fiber, 4.2 g; Mediterranean-type diet meal (MD): total fat, 40.1 g; saturated fatty acids, 5.1 g; dietary fiber, 14.5 g] with 30 min walking (4.6 ± 0.1 km/h) or rest. Primary (serum triglycerides) and secondary (serum non-esterified fatty acids, NEFAs; parameters of glucose metabolism, inflammation, endothelial activation, oxidation; blood pressure/heart rate) outcomes were measured at fasting and 1.5, 3.0, 4.5 h postprandially. Data were analyzed by linear mixed models.

Results: Triglycerides were higher after WD compared to MD (AUC in mmol/L x min: WD-W 218 ± 15.2; WD-R 207 ± 12.6; MD-W 139 ± 9.83; MD-R 149±8.15, P<0.001). No meal or activity effect was observed for NEFAs based on AUC data (WD-W -43.5 ± 7.08; WD-R -49.2 ± 6.94; MD-W -48.0 ± 11.6; MD-R -67.6 ± 7.58). Plasma glucose was higher after MD compared to WD (WD-W 222 ± 34.9; WD-R 177 ± 32.8; MD-W 314 ± 44.4; MD-R 275 ± 57.8, P<0.001), as was serum insulin (AUC in ng/mL x min: WD-W 82.0 ± 10.3; WD-R 88.6 ± 12.8; MD-W 129 ± 14.7; MD-R 138 ± 20.5, P<0.001). Plasma interleukin-6 was higher after walking compared to resting (AUC in pg/mL x min: WD-W 72.0 ± 34.0; WD-R 14.3 ± 38.8; MD-W 70.8 ± 39.4; MD-R 5.60 ± 26.0, P<0.05). Plasma vitamin C was higher after MD compared to WD (P<0.001) and after walking compared to resting (P<0.05) (AUC in mg/L x min: WD-W -305 ± 59.6; WD-R -396 ± 84.0; MD-W 113 ± 56.4; MD-R -44.5 ± 48.1). We observed no meal or activity effects on parameters of oxidation and endothelial adhesion molecules. Our data revealed no significant meal x activity effects on all outcomes.

Conclusions: In older adults with increased CVD risk, the MD was associated with superior effects on several postprandial parameters (e.g., triglycerides) in comparison to the WD. Data revealed no relevant differences regarding the effects of post-meal walking and resting. None of the four treatments can be rated as superior regarding their acute effects on the shown postprandial metabolic, oxidative, and inflammatory parameters.

The trial was registered at German Clinical Trials Register (DRKS) (http://www.germanctr.de and http://www.drks.de) under identifier DRKS00012409.

INTRODUCTION

The postprandial state is the dynamic period of metabolic processes that occur following the digestion and absorption of a meal (1–3). In developed societies, modern lifestyle is characterized by an excessive food intake. As a result, many individuals spend the majority of their waking hours in the postprandial state, and experience exaggerated and prolonged postprandial metabolic (lipemia, glycemia/insulinemia), oxidative, and immune imbalances. This phenomenon is termed "postprandial oxidative stress". This prolonged pro-oxidative phase is accompanied by postprandial low-grade inflammation and impaired endothelial function, and can promote cellular dysfunction and cardiovascular disease (CVD) (1, 2). Scientific interest in postprandial metabolic events as risk factors for CVD is therefore increasing (4).

The magnitude and duration of postprandial responses is influenced by the quantity and quality of macronutrients in the consumed meal (2, 3). In contrast to the dietary pattern which is typically consumed in Western societies [high in total fat, saturated fatty acids (SFAs), simple carbohydrates and animal protein; low in dietary fiber, vitamins and minerals] (5, 6), the Mediterranean dietary pattern has been consistently associated with a lower CVD risk (7–13). Research suggests that these effects are attributable to the high-quality food choices (plant-based, minimally processed) and characteristic nutrients (e.g., antioxidants such as vitamins, polyphenols and n-3 PUFAs) of this eating pattern (11).

Independent of meal composition, postprandial metabolic events show wide inter-individual variation. For example, aging, physical activity status and metabolic status seem to affect postprandial metabolic responses (14). In addition to elevated inflammatory indices in the fasting state, overweight-to-obese patients with metabolic syndrome and insulin resistance show accentuated postprandial inflammatory responses compared to metabolically healthy, normal weight individuals (15, 16), which likely contributes to their increased CVD risk. This emphasizes the importance of attenuating postprandial metabolic events via lifestyle interventions, particularly in this high risk population (17). Current international guidelines recommend regular physical activity to lower CVD risk and previous studies suggest that even acute bouts of exercise have beneficial effects on cardio-metabolic risk factors (17, 18). Research has shown that the postprandial effects of a bout of exercise are influenced by several modulators. These include mode of exercise (aerobic or resistance), duration and intensity of exercise, total energy expenditure, meal composition, and the exercise meal sequence (pre- or post-meal exercise) (18). To date, the majority of studies have focused on the acute effect of a single bout of exercise (in particular aerobic exercise) on postprandial lipemia in metabolically healthy adults (19). To our knowledge, no previous human

study has investigated the acute effects of postprandial exercise suitable for daily implementation on metabolism following the consumption of meals reflecting different dietary patterns.

Therefore the aim of the present study was to determine the acute impact of dietary pattern and moderate walking on postprandial metabolic, inflammatory, and oxidative events in older adults with a CVD risk phenotype. In this context, the focus was set especially on the interactive effects of meal composition and postprandial activity behavior on these postprandial outcomes. The effects on serum triglycerides (postprandial lipemia) were the primary outcome measure, whereas all other parameters [serum non-esterified fatty acids (NEFAs), parameters of glucose metabolism, inflammation, endothelial activation, oxidation and blood pressure] were secondary outcome measures. The study tested two hypotheses: i) a Mediterranean-type diet meal (MD) generates a lower postprandial response than a Western diet high-fat meal (WD); and ii) acute postprandial walking has a more beneficial effect on postprandial parameters than a period of postprandial rest.

MARTERIALS AND METHODS

Participants

Between April 2017 and May 2017 volunteers (*n*=31) aged 60 to 80 y from Bonn (Germany) and the surrounding area attended a one hour screening session at the Department of Nutritional Physiology at the University of Bonn to determine eligibility for the present study. The screening session was conducted in the fasting state and comprised documentation of medical history and dietary habits, physical assessments (measurement of height, weight, fat mass, waist and hip circumference, resting blood pressure and heart rate) and clinical biochemistry and hematology assessments (liver and kidney function, serum lipids and lipoproteins, plasma glucose, high sensitivity C-reactive protein (hs-CRP), and hematology profile). The main study inclusion criteria were: i) excessive body weight or obesity stage 1 (BMI 27-34.9 kg/m^2), ii) visceral fat distribution (waist circumference ≥94 cm for men and ≥80 cm for women), and iii) prehypertension (≥120–139 mmHg systolic and/or ≥80–89 mmHg diastolic) or stage 1 hypertension (≥140–159 mmHg systolic and/or ≥90–99 mmHg diastolic). In addition, study eligibility required fulfillment of at least one of the following criteria: i) dyslipidemia (fasting serum triglycerides ≥1.7 mmol/L and/or serum HDL-cholesterol <1.0 mmol/L for men and <1.3 mmol/L for women), ii) increased plasma glucose (fasting plasma glucose ≥5.6 mmol/L) or iii) a pro-inflammatory state (hs-CRP ≥2.0 mg/L) (20, 21). The main exclusion criteria were: malabsorption syndromes, unmedicated thyroid disease, impaired kidney function, secondary hypertension, chronic liver diseases, heart insufficiency and prior myocardial infarction, insulin-treated Diabetes mellitus and untreated Diabetes insipidus, chronic inflammatory disease including rheumatoid arthritis, tumor diseases, immobility or use of walking aid, alcohol or medicine abuse, chronic intake of dietary-supplements and immune suppression medication.

A total of 26 adults (18 male and eight female) were included in the trial. All participants completed the entire postprandial study, and the respective data were included in the analysis. Participant flow from initial screening to final analysis is shown in **Figure 2-1**. Baseline characteristics are presented in **Table 2-1**. The study was conducted in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments. All study procedures were approved by the ethics committee of the Medical Faculty of the Rheinische Friedrich-Wilhelms-University of Bonn, Germany. Written informed consent was obtained from all adults prior to inclusion. The trial was registered at German Clinical Trials Register (DRKS) (http://www.germanctr.de and http://www.drks.de) under identifier DRKS00012409.

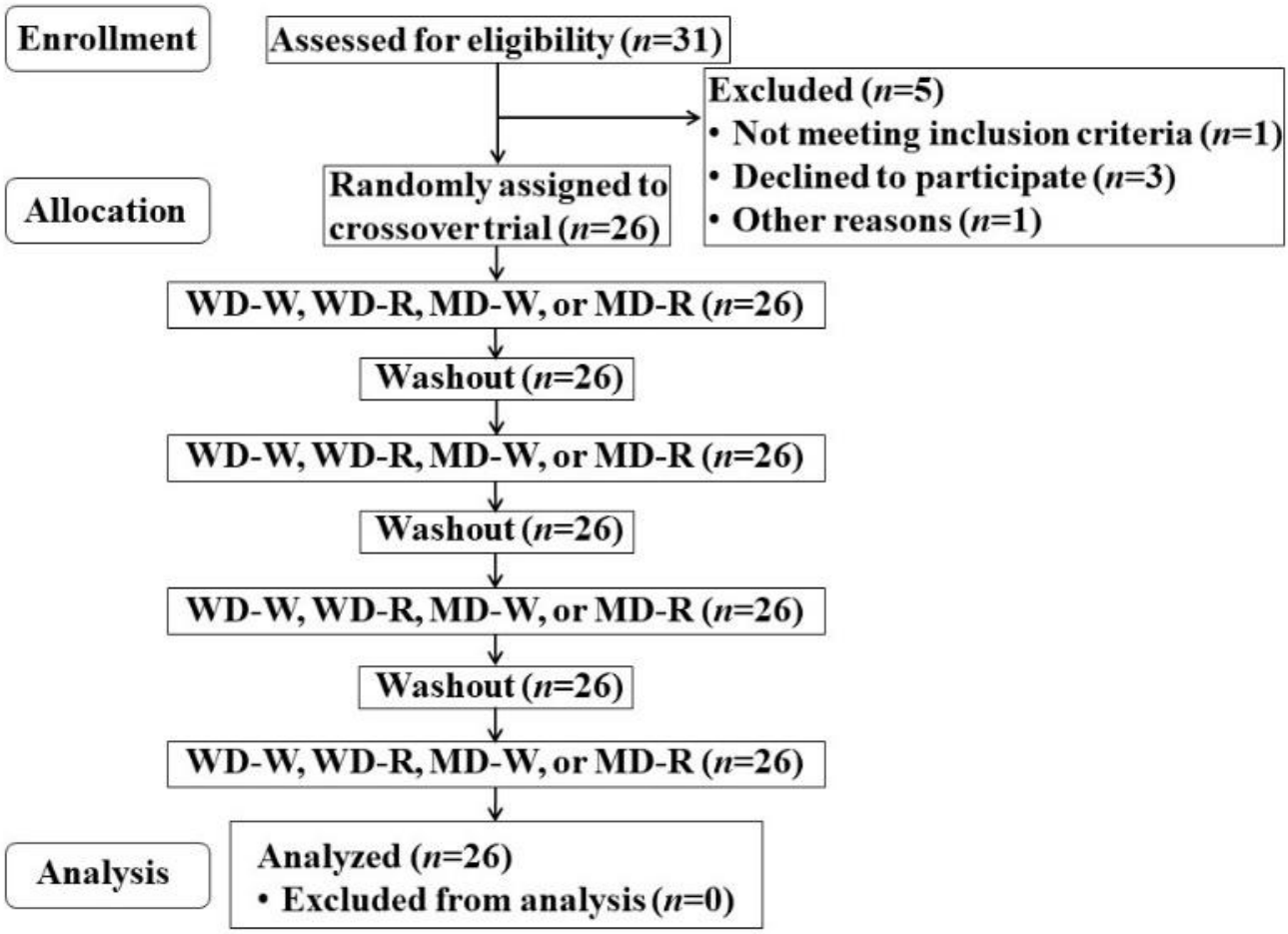

Figure 2-1 Flow chart of process of eligibility assessment, enrollment, and allocation. MD-R, Mediterranean-type diet meal plus postprandial resting; MD-W, Mediterranean-type diet meal plus postprandial walking; WD-R, Western diet high-fat meal plus postprandial resting; WD-W, Western diet high-fat meal plus postprandial walking.

Table 2-1 Baseline characteristics of participants at high risk of cardiovascular disease[1]

	Total (n = 26)	Female (n = 8)	Male (n = 18)	P-value[2]
Age (y)	69.9 ± 4.7	69.4 ± 5.6	70.8 ± 4.8	0.519
Height (cm)	171.4 ± 8.4	161.0 ± 5.0	176.0 ± 5.0	<0.001
Body weight (kg)	88.8 ± 8.2	82.2 ± 8.7	91.8 ± 6.1	0.003
BMI (kg/m^2)	30.3 ± 2.3	31.6 ± 3.0	29.7 ± 1.7	0.047
Body fat (%)	38.4 ± 8.1	40.6 ± 5.2	33.6 ± 3.7	<0.001
Waist circumference (cm)	104 ± 5.8	99.8 ± 7.5	106 ± 4.0	0.069
Hip circumference (cm)	106 ± 5.4	110 ± 6.2	105 ± 4.4	0.029
Waist-to-height ratio	0.61 ± 0.03	0.62 ± 0.04	0.60 ± 0.03	0.176
Systolic blood pressure (mmHg)	149 ± 16.4	150 ± 17.8	149 ± 16.4	0.982
Diastolic blood pressure (mmHg)	88.3 ± 7.3	91.3 ± 8.2	87.0 ± 6.8	0.184
Heart rate (min^{-1})	63.7 ± 8.9	65.8 ± 9.0	62.8 ± 8.8	0.453
Serum triglycerides (mmol/L)	1.76 ± 0.79	1.98 ± 0.64	1.67 ± 0.85	0.375
Serum total cholesterol (mmol/L)	4.86 ± 1.60	4.92 ± 0.89	5.23 ± 1.03	0.464
Serum HDL cholesterol (mmol/L)	1.61 ± 0.37	1.64 ± 0.22	1.60 ± 0.42	0.769
Serum LDL cholesterol (mmol/L)	3.19 ± 0.76	3.09 ± 0.59	3.23 ± 0.83	0.675
Plasma glucose (mmol/L)	5.64 ± 0.66	5.90 ± 1.02	5.52 ± 0.42	0.328
Serum hs-CRP (mg/L)	2.5 ± 3.0	2.7 ± 1.6	2.4 ± 3.4	0.833

[1]Shown as mean ± SD, n = 26.
[2]compared using independent samples t tests.
hs-CRP, high sensitivity C-reactive protein.

Study protocol

A randomized controlled crossover trial was performed at the Department of Nutritional Physiology (University of Bonn, Germany) from June 2017 until August 2017. All adults participated in four treatment conditions, each lasting 4.5 h from morning until afternoon. Study days were separated by 2 wk wash-out periods. The order of treatments was randomized for each subject via computer generated randomization tables (Microsoft Excel). The four treatment conditions were as follows: (i) MD plus 30 min postprandial walking (MD-W); (ii) MD plus 30 min postprandial resting (MD-R); (iii) WD plus 30 min postprandial walking (WD-W) and (iv) WD plus 30 min postprandial resting (WD-R). Venous blood sampling and measurements of blood pressure and heart rate were

taken at fasting (0 h) and 1.5, 3.0 and 4.5 h postprandially. The participants were instructed to maintain their habitual diet, body weight, body composition, and lifestyle across the entire study period. For the 24 h period prior to each treatment, the participants were instructed to abstain from alcohol and intense physical activity. For the purpose of standardization, the participants were also instructed to complete a 1-day food diary and activity log on the day prior to each treatment in order to monitor and identify possible variations in total energy intake, total intake of macronutrients, and physical activity level (PAL). Participants taking antihypertensive (n=19), lipid lowering (n=11), or thyroid (n=8) drugs were instructed to continue taking their medication throughout the study period as prescribed by their physician.

Test meals

The WD and MD test meals (challenges) were designed specifically for the purposes of the present study. The food items and nutrient composition of the test meals were based on published data on average nutrient profile and most commonly consumed foods in the respective dietary patterns (5, 6, 11, 12). Furthermore, the food selection focused on food items usually consumed in Germany. The main components of the WD were croissants, bread rolls, jam, butter, cold cuts, boiled eggs and cream yogurt. The main components of the MD were ciabatta, smoked salmon, muesli, fruit, and vegetables. Canola oil was used in the MD, since it has a similar fatty acid composition (except for alpha-linolenic acid), but a more neutral flavor than olive oil. The food items per serving WD and MD are summarized in **Table 2-2 and Table 2-3**. The meals were designed to be iso-energetic (4300 kJ per meal) and iso-nitrogenous. The WD was rich in total fat, SFAs, and animal protein. The MD was rich in unsaturated fatty acids, dietary fiber, and antioxidative compounds. The nutrient composition of the test meals were calculated by using the computer-based nutrient calculation program EBISpro based on the German nutrient database Bundeslebensmittelschlüssel, version 3.01 (Max Rubner-Institut) (**Table 2-4**). Both test meals were prepared at the study location by study personnel in accordance with a standardized protocol, which included the weighing of each food component to the nearest gram. During each meal, the participants consumed a glass of water. The participants were required to ingest the complete test meal within 20 min, under the observation of study personnel.

Table 2-2 Food items per serving of Western diet high-fat test meal

Food items	Amount (g)
Croissant	60
Bread roll	45
Butter	10
Strawberry jam	35
Cold cuts	50
Egg (chicken)	40
Cream yogurt (10% fat), strawberry flavor	150

Table 2-3 Food items per serving of Mediterranean-type diet test meal

Food items	Amount (g)
Smoothie[1]	290
Muesli[2]	178
Lentil spread[3]	41.5
Ciabatta bread	135
Smoked salmon	20
Cucumber	30
Tomato	30
Basil (fresh)	0.5
Kiwi fruit	50
Canola oil[4]	18

[1]Main components were apple, orange, carrot, lemon, banana and sweet potatoe.
[2]Main components were oats, walnut, hazelnut, yogurt, honey, and apple.
[3]Main components were lentils, olives, tomato paste, pine nuts, rosemary, and lemon juice.
[4]Incorporated into smoothie, lentil spread and ciabatta.

Table 2-4 Nutrient composition per serving of the two test meals[1]

	Western diet high-fat meal	Mediterranean-type diet meal
Energy (kJ)	4247	4251
Carbohydrates (g)	93.7	133
Mono- and disaccharides (g)	45.0	51.0
Polysaccharides (g)	47.0	78.9
Ratio mono- and disaccharides to polysaccharides	0.96	0.65
Dietary fiber (g)	4.2	14.5
Protein (g)	26.1	25.9
Total fat (g)	59.4	40.1
SFAs (g)	32.0	5.1
MUFAs (g)	19.7	20.0
n-6 PUFAs (g)	3.4	8.0
n-3 PUFAs (g)	0.7	2.9
Total EPA, DPA, DHA (g)	0.0	0.6
Cholesterol (mg)	306	14.4
ß-carotene (mg)	0.2	5.4
Vitamin A[1] (µg)	365	902
Vitamin E[2] (mg)	2.3	12.1
Vitamin C (mg)	9	102

[1]Retinol equivalent.
[2]α-Tocopherol equivalent.
EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

Physical activity

The assigned activity (walking or resting) was performed immediately after the consumption of the test meal. The 30 min walking program was performed outdoors on the University of Bonn campus in the company of study personnel. The 30 min duration was selected to reflect current recommendations for the minimum level of moderate-intensity physical activity required on most days of the week to reduce the risk of CVD events (22). During the first walking treatment, the participants were instructed to walk at a moderate pace, corresponding to their individual speed of comfort. For standardization purposes, this speed was then reproduced during the second walking session. For each participant, walking speed and distance were measured by study personnel using a measuring wheel (Berlan Measuring Wheel) equipped with a tachometer (Sigma BC 8.12). In addition, the number of steps was recorded using a pedometer (Omron walking style IV), while heart rate was measured using a heart rate monitor (Polar watch FT1). To classify and compare the metabolic state of the participants immediately after each walking session, the plasma lactate concentration in peripheral blood was measured by study personnel using a quick, commercially available test (Lactate SCOUT+). Perceived exertion was rated using the Borg Rating of Perceived Exertion scale (23). The resting (control) phase took place at the study location. The subject remained in a supine position, and was instructed to abstain from talking, reading, or sleeping for 30 min.

Measurements

Blood pressure and heart rate

Blood pressure and heart rate were measured twice under standardized conditions using an automatic blood pressure measurement device (Boso Carat Professional), in accordance with the recommendations of the American Heart Association Council on High Blood Pressure Research (24, 25).

Anthropometrics

All anthropometric measurements were obtained during screening for study eligibility. Body composition (fat mass and fat-free mass) was determined by air-displacement plethysmography using the BOD POD body composition system (Cosmed). Height was determined to the nearest 0.1 cm using a stadiometer (Seca scale 704). Waist circumference was measured midway between the lowest rib and the iliac crest with the subject at minimal respiration. Hip circumference was measured at the height of the greater trochanters.

Blood sample processing and analysis

Fasting and postprandial blood samples were taken using tubes containing EDTA, fluoride, or a coagulation activator (Sarstedt). Plasma and serum were obtained by centrifugation at 3000 g for 15 min at 8°C. Aliquots of plasma and serum were immediately frozen and stored in cryovials at -80°C until analysis for NEFAs, parameters of endothelial activation, inflammation, and oxidation. Fasting and postprandial triglycerides, insulin, and glucose (study data), as well as serum cholesterol, clinical biochemistry and hematology parameters, and hs-CRP (screening data), were assayed within 4 h of blood sampling.

Serum concentrations of triglycerides, total cholesterol, LDL-cholesterol, and HDL-cholesterol were measured using VIS photometry (cobas 8000 modular analyzer series, Roche Diagnostics).

Plasma concentration of glucose was measured using the enzymatic reference method with hexokinase and VIS photometry (cobas 8000 modular analyzer series). Serum insulin concentration was measured using a chemiluminescent immunometric assay (cobas 8000 modular analyzer series). Serum concentration of hs-CRP was determined using a turbidimetric immunoassay (cobas 8000 modular analyzer series).

Hematological parameters were determined by fluorescence flow cytometry, photometry, and the resistance measuring technique using a hematology analysis device (Sysmex XN9000, Sysmex XN1000 analyzer). Serum alanine transaminase, aspartate transaminase, gamma-glutamyl transpeptidase, and serum concentration of total bilirubin were measured using VIS photometry (cobas 8000 modular analyzer series). Serum creatinine was determined using the Jaffé bichromatic kinetic method (cobas 8000 modular analyzer series).

Serum concentration of NEFAs was analyzed in duplicate using an in vitro enzymatic colorimetric method assay (NEFA-HR(2), Wako Diagnostics).

Plasm/serum concentration of soluble endothelial selectin (sE-selectin), soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), high sensitivity interleukin-6 (IL-6) (R&D systems), and oxidized LDL (oxLDL) (Immundiagnostik AG) were determined in duplicate using commercially available enzyme-linked immunoassay kits.

The antioxidant capacity of plasma was measured as trolox equivalent antioxidant capacity (TEAC), in accordance with Miller et al. (26). Plasma retinol, α-tocopherol, and β-carotene were measured as described previously (27). For vitamin C analysis, metaphosphoric acid was added to

plasma samples for stabilization purposes. After centrifugation, the supernatant was poured into vials and analyzed using HPLC with ultraviolet detection.

Sample size calculation

Sample size was calculated *a priori* based on serum triglyceride concentration as primary outcome measure. Triglyceride data from a previous postprandial trial of similar design conducted in our research group (Schönknecht YB, Crommen S, Stoffel-Wagner B, Coenen M, Fimmers R, Stehle P, Egert S: unpublished results) and anticipated postprandial changes in triglycerides in the four treatment conditions (one sample *t* test; 2-sided; $P<0.05$) were used for calculation. The sample size calculation indicated that a minimum of $n=24$ individuals would provide a power of 80% to detect a difference of 0.14 mmol/L, assuming a standard deviation (SD) for the difference of 0.23 mmol/L. To account for a potential drop-out rate of 10%, a total of 26 participants were included.

Statistical analysis

All statistical analyses were performed using the IBM SPSS statistical software package (SPSS version 25, IBM Corporation, Somers, USA). Baseline characteristics of male and female adults (screening data) were compared using independent samples *t* tests.

To identify differences in total energy- and macronutrient intake (as recorded in the 1-day food diaries) and PAL (as recorded via the physical activity logs) between the four pre-treatment days, the data were compared using one-way ANOVA (**Table 2-5, Table 2-6**).

To compare the parameters measured during walking (heart rate, number of steps, distance, speed, lactate concentrations, and perceived exertion) after WD and MD, one- sample *t* tests were used (**Table 2-7**).

The linear mixed-models procedure was used to test the effects of the intervention (meal and activity), time points, and their interaction on all postprandial parameters (blood pressure, heart rate and blood parameters). Fixed factors comprised: meal type (WD and MD); activity (walking and resting); time points (1.5, 3.0 and 4.5 h postprandially); and interactions (meal x activity, meal x time, activity x time, and meal x activity x time). Subject identifier was set as a random factor. The respective baseline values (fasting measures) of the postprandial parameters were included as covariates in the corresponding tests. Furthermore, in all tests, the residuals were checked for relevant deviations from a normal distribution. In case of a significant interaction between meal and activity (meal x activity), the linear mixed models procedure was conducted separately for WD and

MD to demonstrate possible activity effects for both meals. Also, all postprandial time points were analyzed separately, to check for possible meal, activity, and meal x activity effects on each time point. Furthermore, incremental area under the curve (iAUC) was calculated for selected blood parameters (e.g., glucose and insulin) using the trapezoidal rule, and the linear mixed-models procedure was used to test meal, activity, and meal x activity effects. In all analyses, the significance level was set at $P<0.05$. Unless otherwise stated, descriptive data are presented as the arithmetic mean ± standard error of the mean (SEM).

RESULTS

Baseline characteristics

Baseline characteristics of the participants are presented in **Table 2-1.** All participants were overweight (46.2%) or obese (53.8%), had a visceral fat distribution, and were prehypertensive or displayed stage 1 hypertension. Significant sex differences were found for height, body weight, BMI, hip circumference, and body fat mass ($P<0.05$).

One-day food diaries and physical activity logs

For all participants, no significant difference was found in total energy and macronutrient intake and PAL between the four pre-treatment days. As instructed, the PAL data indicated that all participants had refrained from strenuous physical activity (mean PAL of 1.4) (**Table 2-5, Table 2-6**).

Table 2-5 Energy- and macronutrient intake of participants at high risk of cardiovascular disease before each treatment day[1]

	V 1	V 2	V 3	V 4	*P*-value[2]
Energy (kcal)	1771 ± 427	1906 ± 551	1874 ± 492	1837 ± 499	0.783
Fat (g)	79.9 ± 34.9	85.0 ± 34.4	86.3 ± 32.1	82.2 ± 34.2	0.908
Carbohydrate (g)	166 ± 39.3	179 ± 57.1	176 ± 53.4	173 ± 57.1	0.839
Protein (g)	70.5 ± 21.6	75.1 ± 29.7	71.0 ± 25.1	70.8 ± 21.0	0.895

[1]Data from 1-d food diaries; Shown as mean ± SD, $n = 26$.
[2]Compared using one-way ANOVA.

Table 2-6 Physical activity level of participants at high risk of cardiovascular disease before each treatment day[1]

	V 1	V 2	V 3	V 4	*P*-value[2]
PAL	1.40 ± 0.14	1.38 ± 0.21	1.37 ± 0.20	1.38 ± 0.19	0.923

[1]Data from 1-d physical activity logs; Shown as mean ± SD, *n* = 26.
[2]Compared using one-way ANOVA.
PAL; physical activity level.

Parameters measured during walking

For all participants, no significant difference was found between the two meal types in terms of parameters recorded during postprandial walking (heart rate, number of steps, distance, speed, lactate concentration, perceived exertion), indicating that physical stress was standardized across both walking sessions. Plasma lactate analysis indicated that the walking session represented a moderate bout of physical activity. Plasma lactate concentrations were 1.87 ± 0.49 mmol/L after WD-W, and 2.04 ± 0.57 mmol/L after MD-W. Ratings of perceived exertion were 12.1 ± 1.49 after WD-W and 12.0 ± 1.62 after MD-W. These scores indicate a rating of "moderately strenuous" (**Table 2-7**).

Table 2-7 Comparison of all parameters recorded during the walking sessions in participants at high risk of cardiovascular disease[1]

	WD-W	MD-W	*P*-value[2]
Number of steps	3428 ± 201	3441 ± 243	0.803
Distance (km)	2.33 ± 0.25	2.35 ± 0.25	0.857
Speed (km/h)	4.62 ± 0.49	4.62 ± 0.49	0.991
Heart rate (min^{-1})[3]	100 ± 12.2	97.8 ± 10.9	0.498
%Heart $rate_{max}$ (%)	63.6 ± 7.72	62.2 ± 6.73	0.490
Plasma lactate concentration (mmol/L)	1.87 ± 0.49	2.04 ± 0.57	0.237
Perceived exertion (points)[4]	12.1 ± 1.49	12.0 ± 1.62	0.860

[1]Shown as mean ± SD, *n* = 26.
[2]Compared using independent sample *t* tests.
[3]Mean heart rate during walking unit.
[4]Borg-RPE scale. Shown scores indicate moderate exertion.
MD-W, Mediterranean-type diet meal plus postprandial walking; WD-W, Western diet high-fat meal plus postprandial walking.

Serum lipids, glucose, and insulin

Serum triglycerides concentrations were higher after WD compared to MD (P<0.001). No activity effect was found for this parameter (**Figure 2-2**). Comparison of AUCs showed a significant effect for meal type (P<0.001) (AUC in mmol/L x min: WD-W 218 ± 15.2; WD-R 207 ± 12.6; MD-W 139 ± 9.83; MD-R 149±8.15).

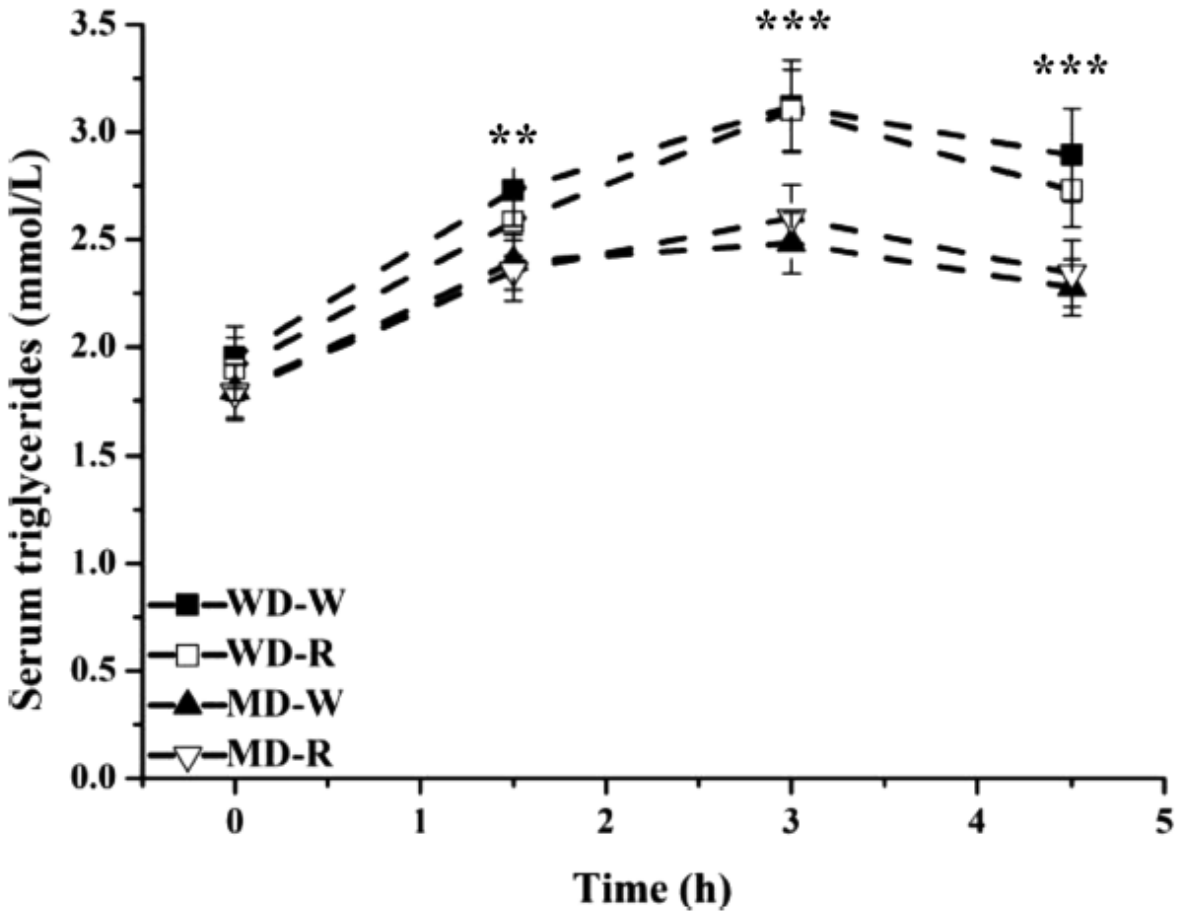

Figure 2-2 Fasting (0 h) and postprandial (1.5, 3.0, 4.5 h) serum triglyceride concentrations in the four treatments in participants at high risk of cardiovascular disease. Mean ± SEM, n = 26. ***P<0.001, **P<0.01 meal effect for specific time point. MD-R, Mediterranean-type diet meal plus postprandial resting; MD-W, Mediterranean-type diet meal plus postprandial walking; WD-R, Western diet high-fat meal plus postprandial resting; WD-W, Western diet high-fat meal plus postprandial walking.

Concentrations of serum NEFAs were higher after WD compared to MD (P<0.001), and after walking compared to resting (P<0.001) (**Figure 2-3).** Comparison of AUCs showed no effect for meal or activity (AUC in mmol/L x min: WD-W -43.5 ± 7.08; WD-R -49.2 ± 6.94; MD-W -48.0 ± 11.6; MD-R -67.6 ± 7.58).

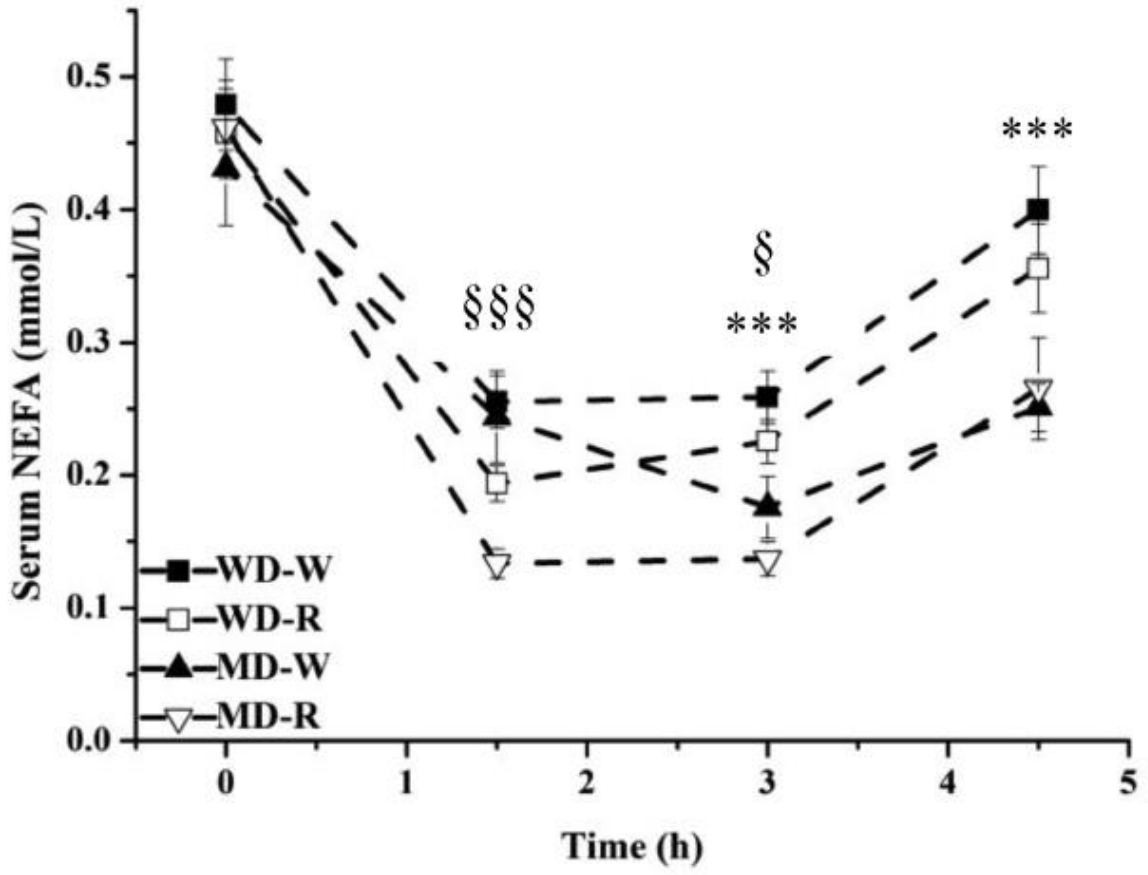

Figure 2-3 Fasting (0 h) and postprandial (1.5, 3.0, 4.5 h) serum NEFA concentrations in the four treatments in participants at high risk of cardiovascular disease. Mean ± SEM, n = 26. ***P<0.001 meal effect for specific time point. §§§P<0.001, §P<0.05 activity effect for specific time point. MD-R, Mediterranean-type diet meal plus postprandial resting; MD-W, Mediterranean-type diet meal plus postprandial walking; NEFA, non-esterified fatty acid; WD-R, Western diet high-fat meal plus postprandial resting; WD-W, Western diet high-fat meal plus postprandial walking

For plasma glucose a significant effect was found for meal but not for activity. Here, concentrations were higher after MD compared to WD (P=0.002). In addition, a significant interaction for activity x time (P=0.015) and meal x time (P=0.033) was observed: At 1.5 h postprandially, glucose concentrations were higher after walking for both meal types (P<0.001). At 3.0 h postprandially, no activity effect was observed. However, a significant effect was found for meal type (higher glucose concentrations after MD; P=0.003). No treatment effects were found at 4.5 h postprandially (**Figure 2-4**). Statistical analysis of AUC values revealed an effect for meal type (P<0.001) (AUC in mmol/L x min: WD-W 222 ± 34.9; WD-R 177 ± 32.8; MD-W 314 ± 44.4; MD-R 275 ± 57.8).

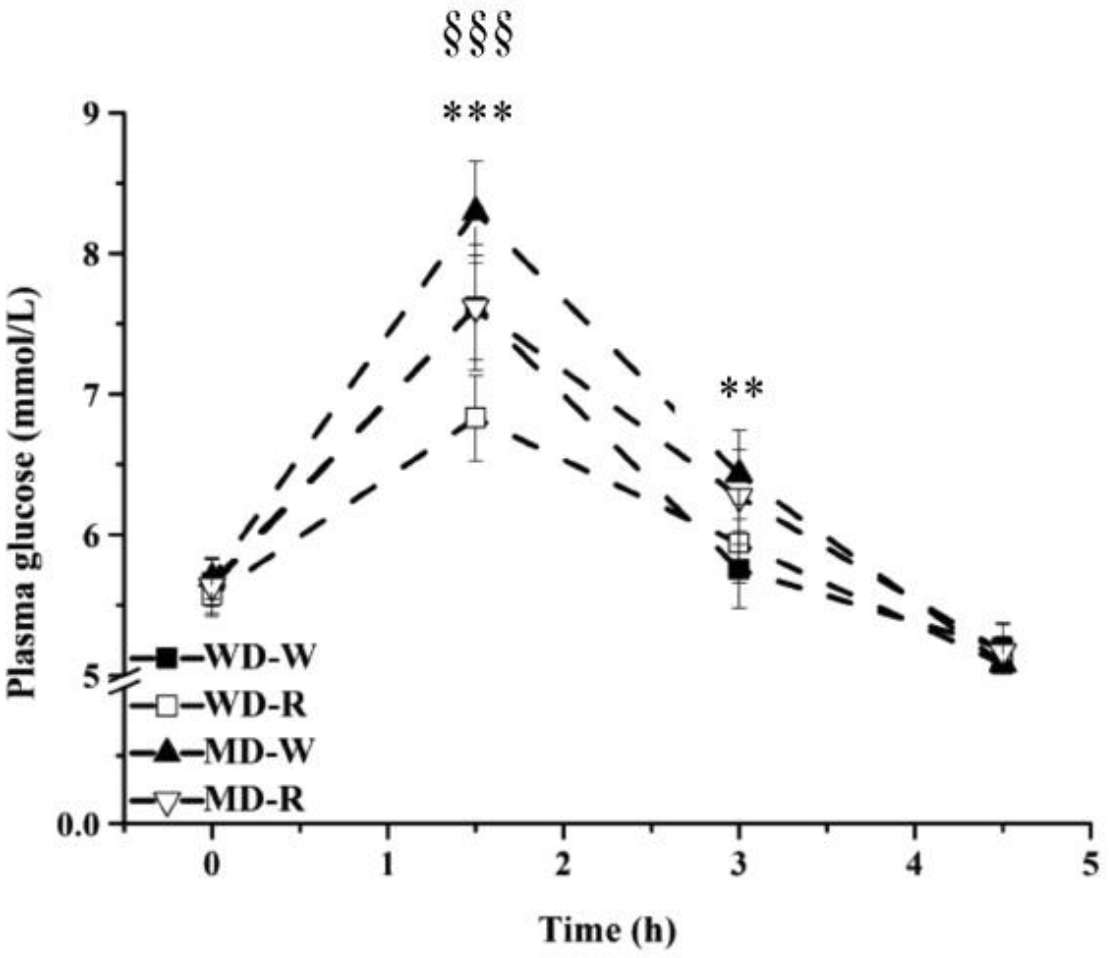

Figure 2-4 Fasting (0 h) and postprandial (1.5, 3.0, 4.5 h) plasma glucose concentrations in the four treatments in participants at high risk of cardiovascular disease. Mean ± SEM, n = 26. ***P<0.001, **P<0.01 meal effect for specific time point. §§§P<0.001 activity effect for specific time point. MD-R, Mediterranean-type diet meal plus postprandial resting; MD-W, Mediterranean-type diet meal plus postprandial walking; WD-R, Western diet high-fat meal plus postprandial resting; WD-W, Western diet high-fat meal plus postprandial walking.

Serum insulin concentrations were higher after resting compared to walking (P=0.021), and after MD compared to WD (P<0.001). As for glucose data, analysis of the insulin data revealed a significant activity x time and meal x time interaction. At 1.5 h postprandially, a meal effect only was observed, with higher concentrations after MD (P<0.001). At 3.0 h postprandially, insulin concentrations were higher after resting for both meals (P<0.001). No meal or activity effects were seen at 4.5 h postprandially (**Figure 2-5)**. Statistical analysis of AUC values showed an effect for meal type (P<0.001) (AUC in nmol/L x min: WD-W 82.0 ± 10.3; WD-R 88.6 ± 12.8; MD-W 129 ± 14.7; MD-R 138 ± 20.5).

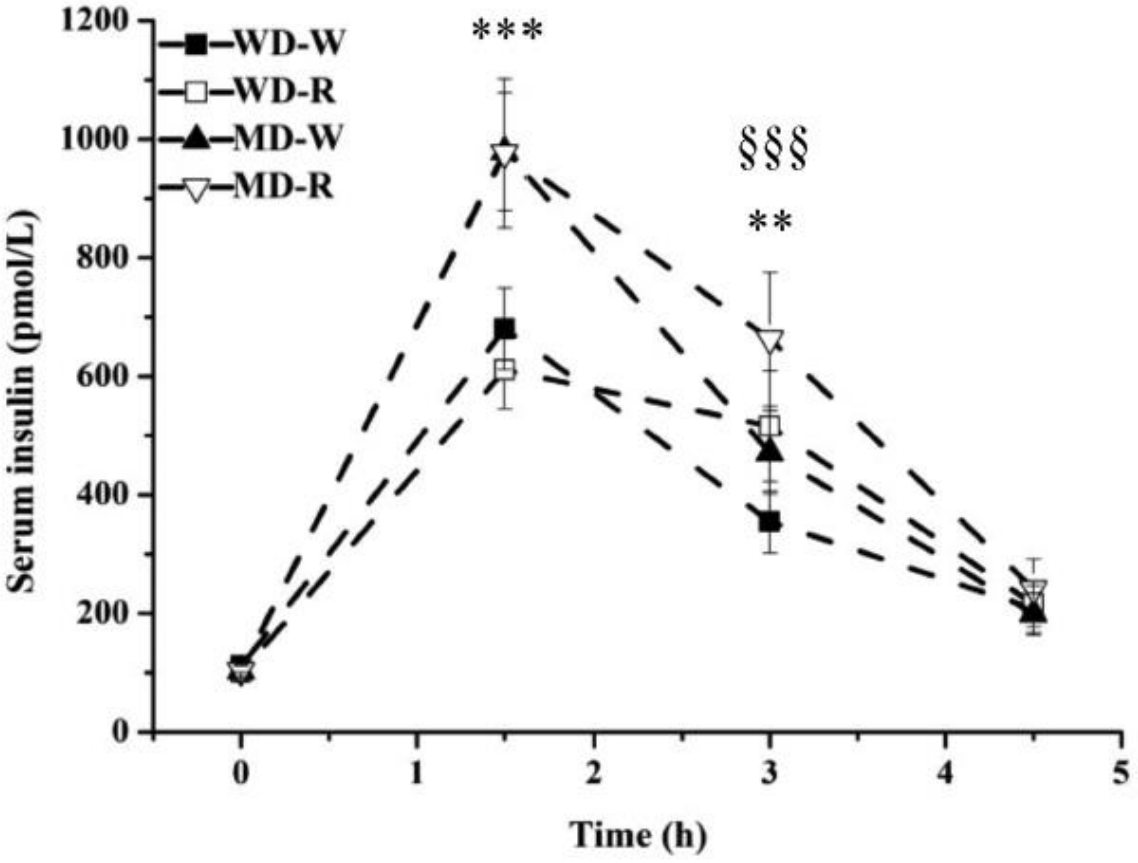

Figure 2-5 Fasting (0 h) and postprandial (1.5, 3.0, 4.5 h) serum insulin concentrations in the four treatments in participants at high risk of cardiovascular disease. Mean ± SEM, n = 26. ***P<0.001, **P<0.01 meal effect for specific time point. §§§P<0.001 activity effect for specific time point. MD-R, Mediterranean-type diet meal plus postprandial resting; MD-W, Mediterranean-type diet meal plus postprandial walking; WD-R, Western diet high-fat meal plus postprandial resting; WD-W, Western diet high-fat meal plus postprandial walking.

Heart rate, blood pressure and endothelial adhesion molecules

Heart rate was higher after walking for both meals ($P<0.001$). Meal type had no effect on heart rate values over time. No meal effect was observed for systolic and diastolic blood pressure. However, lower values were observed after walking compared to resting ($P<0.001$). Data are summarized in **Figure 2-6.** The endothelial markers sICAM-1 and sVCAM-1 significantly decreased over time, with no meal or activity effect. For sE-selectin, no effect was found for time, meal, or activity (**Table 2-8**).

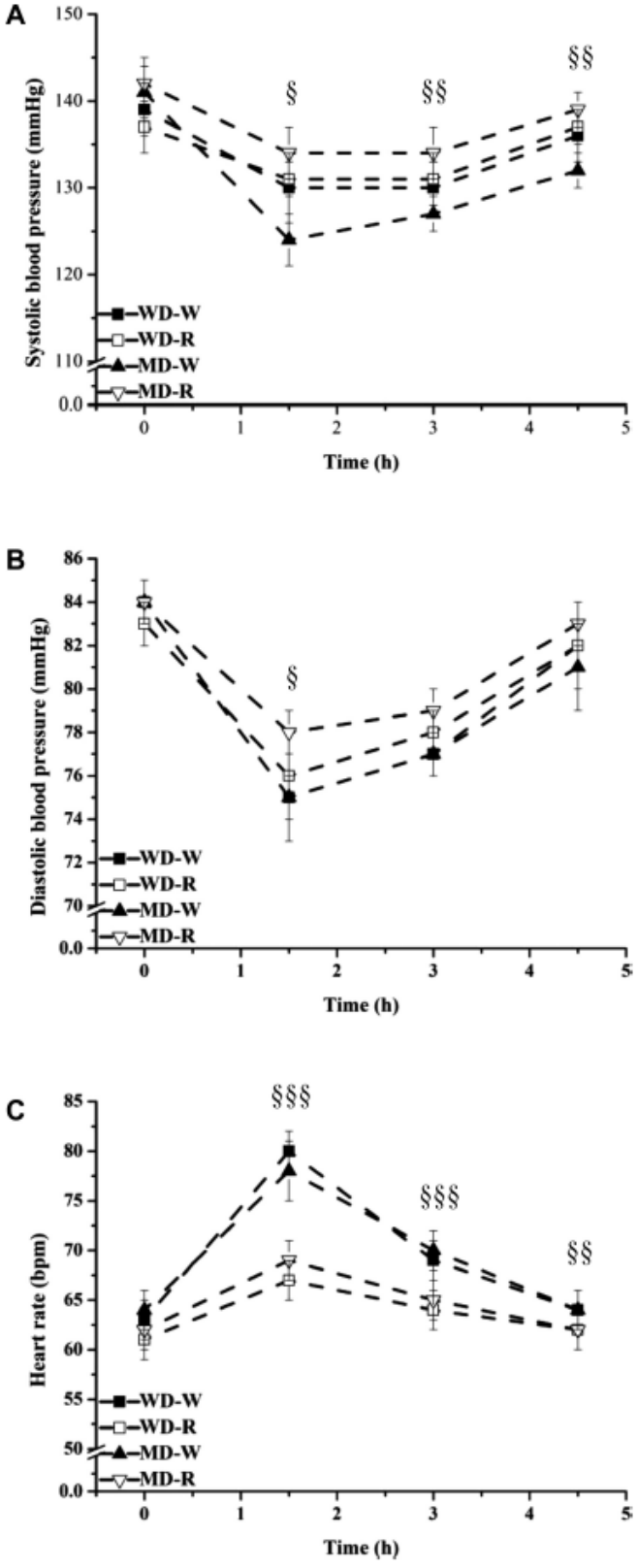

Figure 2-6 Fasting (0 h) and postprandial (1.5, 3.0, 4.5 h) blood pressure (A + B) and heart rate (C) in the four treatments in participants at high risk of cardiovascular disease. Mean ± SEM, n = 26. §§§*P*<0.001, §§*P*<0.01, §*P*<0.05 activity effect for specific time point. MD-R, Mediterranean-type diet meal plus postprandial resting; MD-W, Mediterranean-type diet meal plus postprandial walking; WD-R, Western diet high-fat meal plus postprandial resting; WD-W, Western diet high-fat meal plus postprandial walking.

Table 2-8 Fasting and postprandial soluble endothelial adhesion molecules and oxidized LDL in the four treatments in participants at high risk of cardiovascular disease[1]

	Fasting	**Postprandial**			***P*-values from linear mixed models**					
	0 h	1.5 h	3.0 h	4.5 h	time	meal	activity	meal x activity	meal x time	activity x time
Plasma sICAM-1 (ng/mL)					0.030	0.945	0.367	0.028	0.639	0.475
WD-W	158 ± 6.77	153 ± 6.17	147 ± 5.12	151 ± 6.44						
WD-R	161 ± 8.15	157 ± 9.02	153 ± 7.35	152 ± 7.64						
MD-W	165 ± 8.78	166 ± 10.7	152 ± 7.21	152 ± 7.45						
MD-R	168 ± 9.67	152 ± 6.77	160 ± 5.89	150 ± 6.11						
Plasma sVCAM-1 (ng/mL)					<0.001	0.021	0.591	0.388	0.508	0.097
WD-W	534 ± 29.0	509 ± 22.7	490 ± 25.0	483 ± 24.9						
WD-R	526 ± 20.6	512 ± 19.9	475 ± 21.9	481 ± 21.5						
MD-W	536 ± 26.0	528 ± 25.1	502 ± 23.7	496 ± 24.7						
MD-R	502 ± 22.5	511 ± 23.0	459 ± 21.9	467 ± 23.3						
Serum sE-selectin (ng/mL)					0.207	0.889	0.862	0.248	0.253	0.263
WD-W	35.8 ± 2.60	34.0 ± 2.60	34.5 ± 2.61	34.7 ± 2.83						
WD-R	36.2 ± 2.89	34.6 ± 2.88	34.3 ± 2.75	34.1 ± 2.72						
MD-W	36.4 ± 3.13	34.1 ± 2.72	33.9 ± 2.79	35.3 ± 2.91						
MD-R	35.1 ± 2.61	34.1 ± 2.53	33.3 ± 2.30	34.3 ± 2.77						

Table 2-8 continued

	Fasting	Postprandial			*P*-values from linear mixed models					
	0 h	1.5 h	3.0 h	4.5 h	time	meal	activity	meal x activity	meal x time	activity x time
Plasma oxLDL (ng/mL)					<0.001	0.068	0.473	0.415	0.820	0.323
WD-W	81.8 ± 8.32	76.7 ± 8.92	80.5 ± 8.25	89.1 ± 11.4						
WD-R	78.7 ± 7.55	77.4 ± 8.68	88.0 ± 11.5	82.2 ± 7.80						
MD-W	83.4 ± 10.3	76.0 ± 10.8	82.1 ± 10.1	85.9 ± 10.5						
MD-R	81.4 ± 9.30	71.5 ± 6.86	81.7 ± 8.40	85.0 ± 10.4						

[1]Shown as mean ± SEM, $n = 26$. *P*-value for meal x time x activity interaction not significant, data not shown.
oxLDL, oxidized Low-Density Lipoprotein; sE-Selectin, soluble endothelial-selectin; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; MD-R, Mediterranean-type diet meal plus postprandial resting; MD-W, Mediterranean-type diet meal plus postprandial walking; WD-R, Western diet high-fat meal plus postprandial resting; WD-W, Western diet high-fat meal plus postprandial walking.

Plasma markers of inflammation and oxidation

Plasma IL-6 significantly increased over time, with no effect being observed for meal or activity (**Figure 2-7)**. Statistical analysis of AUC-data revealed an effect for activity (P=0.035). Here, higher plasma IL-6 concentrations were observed after walking compared to resting (AUC in pg/mL x min: WD-W 72.0 ± 34.0; WD-R 14.3 ± 38.8; MD-W 70.8 ± 39.4; MD-R 5.60 ± 26.0). For plasma oxLDL concentrations, an effect was observed for time (P<0.001) but not for meal or activity (**Table 2-8**).

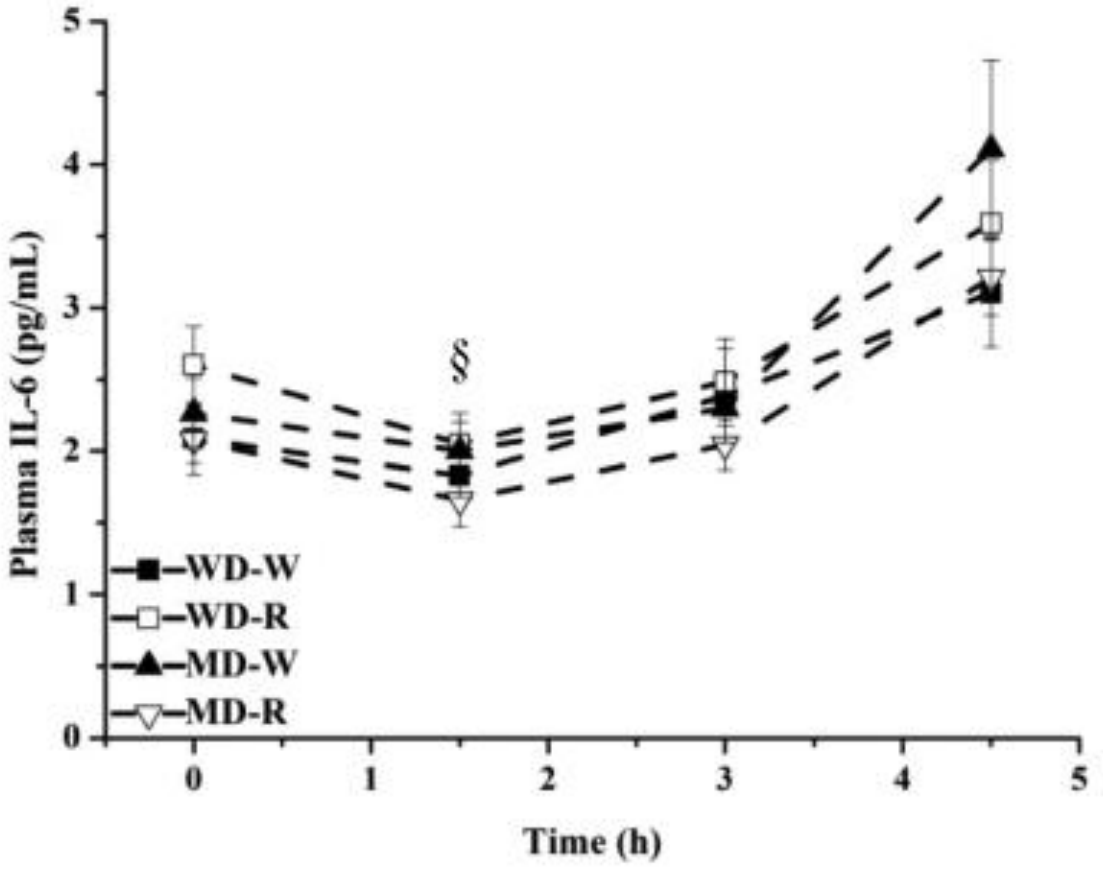

Figure 2-7 Fasting (0 h) and postprandial (1.5, 3.0, 4.5 h) plasma IL-6 concentrations in the four treatments in participants at high risk of cardiovascular disease. Mean ± SEM, n = 26. §P<0.05 activity effect for specific time point. IL, interleukin; MD-R, Mediterranean-type diet meal plus postprandial resting; MD-W, Mediterranean-type diet meal plus postprandial walking; WD-R, Western diet high-fat meal plus postprandial resting; WD-W, Western diet high-fat meal plus postprandial walking.

Plasma α-tocopherol, retinol, ß-carotene, Vitamin C and TEAC

Plasma α-tocopherol concentrations were higher after MD compared to WD (P=0.032). For plasma retinol concentrations, a significant effect was found for time (P=0.014) but not for meal or activity. Plasma ß-carotene concentrations were significantly higher after MD compared to WD (P=0.002) Activity had no effect on the postprandial concentration of retinol, α-tocopherol, or ß-carotene. Postprandial vitamin C concentrations were higher after MD compared to WD (P<0.001) and after walking compared to resting (P=0.002) (AUC in mg/L x min: WD-W -305 ± 59.6; WD-R -396 ± 84.0; MD-W 113 ± 56.4; MD-R -44.5 ± 48.1). Plasma TEAC was higher after MD compared to WD (P=0.001). Data are summarized in **Table 2-9**.

Table 2-9 Fasting and postprandial plasma α-tocopherol, retinol, ß-carotene, and TEAC in the four treatments in participants at high risk of cardiovascular disease[1]

	Fasting	**Postprandial**			***P*-values from linear mixed models**					
	0 h	1.5 h	3.0 h	4.5 h	time	meal	activity	meal x activity	meal x time	activity x time
Plasma α-tocopherol (µmol/L)					0.001	0.032	0.345	0.195	0.732	0.499
WD-W	40.7 ± 1.50	38.4 ± 1.46	38.8 ± 1.77	40.3 ± 1.49						
WD-R	40.3 ± 1.45	39.7 ± 1.49	38.7 ± 1.45	40.5 ± 1.68						
MD-W	40.1 ± 1.57	39.7 ± 1.59	38.8 ± 1.57	41.1 ± 1.96						
MD-R	41.0 ± 1.68	40.9 ± 1.74	39.6 ± 1.80	41.4 ± 1.84						
Plasma retinol (µmol/L)					0.014	0.837	0.543	0.074	0.744	0.760
WD-W	3.35 ± 0.20	3.29 ± 0.20	3.27 ± 0.21	3.35 ± 0.19						
WD-R	3.26 ± 0.19	3.31 ± 0.19	3.25 ± 0.19	3.34 ± 0.18						
MD-W	3.28 ± 0.19	3.30 ± 0.19	3.24 ± 0.18	3.38 ± 0.16						
MD-R	3.42 ± 0.19	3.43 ± 0.18	3.32 ± 0.19	3.45 ± 0.18						
Plasma ß-carotene (µmol/L)					0.291	0.002	0.571	0.224	0.725	0.267
WD-W	0.87 ± 0.08	0.84 ± 0.07	0.85 ± 0.08	0.84 ± 0.07						
WD-R	0.82 ± 0.07	0.81 ± 0.07	0.79 ± 0.07	0.81 ± 0.07						
MD-W	0.81 ± 0.07	0.81 ± 0.07	0.80 ± 0.07	0.83 ± 0.08						
MD-R	0.85 ± 0.09	0.86 ± 0.09	0.84 ± 0.09	0.84 ± 0.09						

Table 2-9 continued

	Fasting	Postprandial			*P*-values from linear mixed models					
	0 h	1.5 h	3.0 h	4.5 h	time	meal	activity	meal x activity	meal x time	activity x time
Plasma vitamin C (µmol/L)					0.307	<0.001	0.002	0.343	0.662	0.720
WD-W	61.4 ± 2.92	53.9 ± 2.51	52.9 ± 2.56	54.7 ± 3.05						
WD-R	61.8 ± 3.32	51.4 ± 2.09	51.0 ± 2.71	54.1 ± 2.34						
MD-W	60.7 ± 3.44	63.8 ± 3.57	63.2 ± 3.58	63.9 ± 3.15						
MD-R	61.7 ± 3.14	59.8 ± 2.84	60.9 ± 3.17	61.3 ± 2.47						
Plasma TEAC[2]					0.009	0.001	0.354	0.684	0.467	0.848
WD-W	1.00 ± 0.02	0.96 ± 0.02	0.95 ± 0.02	0.95 ± 0.02						
WD-R	0.97 ± 0.02	0.96 ± 0.02	0.95 ± 0.02	0.95 ± 0.02						
MD-W	0.99 ± 0.02	0.99 ± 0.01	0.96 ± 0.01	0.97 ± 0.01						
MD-R	0.98 ± 0.02	1.00 ± 0.02	0.97 ± 0.02	0.97 ± 0.02						

[1]Shown as mean ± SEM, $n = 26$. *P*-value for meal x time x activity interaction not significant, data not shown.
[2]Plasma TEAC in mmol of trolox equivalents/L.
TEAC, trolox equivalent antioxidative capacity; MD-R, Mediterranean-type diet meal plus postprandial resting; MD-W, Mediterranean-type diet meal plus postprandial walking; WD-R, Western diet high-fat meal plus postprandial resting; WD-W, Western diet high-fat meal plus postprandial walking.

DISCUSSION

The aim of the present randomized, controlled, crossover trail was to investigate the acute impact of dietary composition and moderate postprandial walking on metabolic, inflammatory, and oxidative postprandial events in adults with a CVD risk phenotype. As expected, significant alterations in parameters of lipid, glucose, and insulin metabolism were observed following the ingestion of both meal types. Previous intervention studies have shown that the ingestion of a high-fat meal induces a pronounced and sustained increase in serum triglycerides, and that the postprandial lipemic response is directly proportional to the amount of fat ingested (2, 28, 29). Available research data are equivocal in terms of whether the fatty acid composition of high-fat meals, in particular the SFA content, plays an important role in postprandial lipemia (2, 28–33). In the present study, postprandial triglycerides were significantly higher after WD, which may be attributable to the higher fat content of this meal (59.4 g vs. 40.1 g), and/or to the higher proportion of SFAs (32.0 g vs. 5.1 g) (**Table 2-4**). In contrast to previous postprandial exercise trials, activity had no effect on postprandial triglycerides over time. Research suggests that acute exercise in the 18 h pre-meal to 90 min post-meal period is effective in terms of attenuating postprandial lipemia (28). However, studies demonstrating the attenuating effects of post-meal moderate exercise on postprandial lipemia involved exercise bouts of higher duration (e.g., 90 min), compared to the 30 min walking period used in the present study (34, 35). This shorter exercise duration may explain the absence of any effect for activity in the present trial. As with postprandial triglycerides, postprandial NEFAs were significantly higher after WD compared to MD. The postprandial decrease in NEFAs observed following consumption of both meal types is probably attributable to the increase in postprandial insulin, which suppresses intracellular lipase activity (36). The observed attenuation in postprandial serum NEFA suppression after walking may reflect an increase in the lipolysis of triglycerides stored in adipose tissue in order to supply the working muscle, since research has shown that even during low-intensity exercise, adipose tissue lipolysis appears to increase 2- to 5-fold above resting levels (37). However, comparison of AUC data revealed no activity effect for postprandial NEFAs, which emphasizes the statistical significance, rather than the physiological relevance, of the described activity effect.

The ingestion of both test meals resulted in a postprandial increase in glucose and insulin. This was significantly higher after MD, due to the higher total carbohydrate content of this meal type (133 g vs. 93.7 g). The high insulin response after both meals caused a rapid decline in postprandial glucose, with lower plasma glucose concentrations being observed 4.5 h postprandially than at baseline. Previous research suggests that acute post-meal exercise is beneficial in terms of postprandial glycemic control, in particular among high risk adults (38). However, the present data

do not support this hypothesis, since significantly higher plasma glucose concentrations were found directly after walking (1.5 h postprandial) for both meal types. This may have been attributable to the timing of the present walking sessions, which commenced immediately after meal consumption, since moderate exercise in the early postprandial period (< 30 min post-meal) can lead to glucose elevation secondary to endogenous glucose production (39, 40). However, the AUC data revealed no effect for activity. A plausible hypothesis is, that the glucose-lowering effect of walking might have occurred in the earlier postprandial period (< 90 min postprandial), as shown in previous postprandial trials (41).

For both meal types, heart rates were significantly higher after walking. However, no effect of meal type was found on postprandial heart rate, indicating that the high energy content of the meals, rather than their differing nutritional content, was responsible for the increase in postprandial heart rate over time (42). Increase in heart rate following the consumption of a meal is compensated for by a decrease in blood pressure, which is even more prominent in older adults (43). As expected, a significant decrease was observed in postprandial blood pressure over time. This was independent of meal composition but significantly higher after walking. This finding is consistent with the more pronounced increase in heart rate observed after walking and is of clinical importance considering the participants high baseline blood pressure.

Previous postprandial studies have shown, that meals that are rich in fat and energy lead to a meal-induced impairment of parameters of endothelial function (31, 44, 45). In this context, the quality of the fat, rather than simply the quantity of the fat, is important, in particular the amount of SFA (33, 46). Surprisingly, the pronounced and sustained hyperlipidemia, hyperglycemia, and hyperinsulinemia induced by all four of the present treatment conditions, did not lead to increased endothelial activation. In fact, the endothelial-derived parameters (sVCAM-1 and sICAM-1) decreased over time, indicating a slight improvement in endothelial function during the 4.5 h time frame. These findings support data generated in a previous postprandial trial by our study group (47). The slight postprandial improvement in endothelial function may be attributable to diurnal fluctuations, since vascular function exhibits circadian variability, with an attenuation during the early morning (48–50).

Several postprandial studies have demonstrated an increase in postprandial IL-6 following the ingestion of high-fat, high energy meals (28, 51–53). This is consistent with the present data, which showed a significant increase in postprandial IL-6 over time following both meal types. Furthermore, comparison of the AUC data revealed higher postprandial IL-6 concentrations after walking. During exercise, IL-6 is secreted from skeletal muscle tissue in an exponential manner in

response to exercise (54), and is therefore referred to as a myokine. Myokines are generally considered to be anti-inflammatory cytokines (28, 55–57). However, the release of IL-6 from muscle mass is dependent, inter alia, on the intensity and the duration of the exercise, as well as the amount of muscle mass involved (56, 57). Since the present walking session was of low duration and moderate intensity, it is questionable whether the stimulus was sufficient to trigger a pronounced systemic IL-6 response, or if the higher postprandial IL-6 concentration observed after walking was due instead to other physiological factors (e.g., systemic stress response).

In the present study, postprandial oxLDL declined at the beginning of the postprandial period, followed by an increase that resulted in higher concentrations at 4.5 h compared to baseline. The increase in plasma oxLDL in the later postprandial period indicates that the consumption of a single high energy meal might be sufficient to trigger postprandial oxidative stress. Surprisingly, meal composition (e.g., higher amount of antioxidants in MD) had no influence in the present trial. In general, the effect of meal ingestion on postprandial oxLDL is a contentious issue (58–60). In contrast to our expectations, walking had no effect on postprandial oxLDL concentrations, despite the fact that acute aerobic exercise appears to increase oxLDL concentrations in high CVD risk adults (61). This may suggest that the stimulus of the present walking session was insufficient to cause a significant impact on postprandial oxLDL.

The observed decrease in TEAC over the postprandial period is inconsistent with the hypothesis that high-fat challenges increase postprandial oxidative stress (45). However, since the observed decrease was minimal, the physiological relevance of this finding is questionable (**Table 2-9**). The postprandial plasma concentrations of α-tocopherol, ß-carotene, and vitamin C were higher after MD, which is consistent with the higher nutrient content of this test meal (**Table 2-9**). The higher concentration of postprandial vitamin C observed after walking may have been attributable to the higher concentration of postprandial glucose detected after walking. Since vitamin C and glucose share a common transport system, acute hyperglycemia may induce the transport of vitamin C from cells, thus triggering the depletion of intracellular vitamin C (62).

The major strengths of the present study were the controlled, crossover design, the absence of study dropouts, and the high rate of treatment compliance. In addition to the strictly controlled postprandial protocol, a wide range of postprandial parameters were examined and statistically significant time- and treatment effects were observed. In contrast to previous studies of exercise and postprandial metabolism, the analysis focused on meals reflecting typical dietary patterns and not on the administration of nutrient solutions (e.g., fat tolerance tests). The 30 min postprandial session of moderate walking was designed to be both suitable for daily life and easy to implement. The

postprandial walking session was designed to be a conventional walk outdoors, in order to generate realistic conditions (transferable to everyday situations) and a high relevance for public health. The walking sessions were conducted under stable weather conditions (June and July 2017) in the morning hours, standardized for each participant. Furthermore, walking speed of the participants was measured and standardized between the sessions. The metabolic responses (plasma lactate concentrations) of participants showed no significant differences between WD-W and MD-W, which is a relevant indicator for good standardization as well (**Table 2-7**). However, despite the good standardization of the walking sessions, it cannot be ruled out, that the lack of environmental control between resting and walking might have been a potential confounding factor.

A potential limitation of the study was the time intervals used for the measurement of endpoints. Particularly in terms of parameters of glucose metabolism, it would have been relevant to include postprandial time points at 30 min and 1 h, in order to evaluate possible walking effects on the early postprandial rise in plasma glucose and serum insulin. However, due to scheduling reasons, no further time points could be included in the study design. Furthermore, the duration of the postprandial measurements (4.5 h) in the present study may not have been long enough to represent the extent and duration of the entire postprandial period. However, the fact that the majority of the outcome measures were about to reach baseline values at 4.5 h postprandially indicates otherwise.

In conclusion, in older adults with a CVD risk phenotype the MD, which is rich in unsaturated fatty acids, dietary fiber, vitamins, and minerals, was associated with superior effects on several postprandial parameters (e.g., triglycerides, antioxidants) in comparison to the WD. The present data revealed no relevant difference between postprandial walking and resting. However, postprandial walking had no obvious negative effects in this population either. On the basis of the present data, in older adults with a CVD risk phenotype none of our four treatments (WD-W, WD-R, MD-W, MD-R) can be rated as superior regarding their acute effects on the measured postprandial metabolic, oxidative, and inflammatory parameters.

ACKNOWLEDGEMENT

The authors show their gratitude to Saskia Groh for her support with the implementation of the trial; to Christine Bierschbach, Anke Carstensen, Anke Ernst, Hedwig Heuser, Christine Laurini, Adelheid Fürste and Anja Stratmann for excellent technical assistance and to Karoline Bauer, Martha Römer, Tanja Sanders and Florian Simon for performing the venipunctures.

STATEMENT OF AUTHORS` CONTRIBUTIONS TO MANUSCRIPT

The author's responsibilities were as follows – CD, MP, PP, H-GP, RF, PS, and SE: designed the study; CD, HH, MP, PP, H-GP, and SE conducted the study; BS-W analyzed blood samples; CD and RF performed statistical analysis; CD and SE wrote the manuscript and had primary responsibility for the final content. All authors have read and approved the final manuscript.

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CHAPTER 3: MANUSCRIPT 2

Acute impact of dietary pattern and walking on postprandial attention, mood, and satiety in older adults: a randomized crossover trial

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Keywords: postprandial metabolism, physical activity, walking, postprandial attention, postprandial mood, satiety, hunger, appetite, cortisol.

Published in *Nutrients* (Nutrients. 2019 Sep 26;11(10). pii: E2294. doi: 10.3390/nu11102294).

ABSTRACT

Research suggests that attention, mood, and satiety can be influenced by meal composition and postprandial activity. The present study examined whether this hypothesis applies to persons with a risk phenotype for cardiovascular/neurodegenerative diseases. A randomized crossover trial was conducted in subjects with metabolic syndrome traits (n = 26, 8 female, age 70±5, BMI 30.3 ± 2.3 kg/m^2). Each subject participated in four interventions: isoenergetic (4300 kJ) meals (Western diet high-fat, WD, and Mediterranean-type diet, MD) followed by either 30 min of moderate walking (4.6 ± 0.1 km/h) or rest. Attention, mood, satiety and plasma cortisol concentrations were measured at fasting and 1.5, 3.0, 4.5 h postprandially. Data were analyzed by linear mixed models. In all interventions, attention increased continuously in the postprandial period (time effect, P<0.001). After WD, attention was lower after walking compared to resting (meal x activity effect, P<0.05). Postprandial mood was generally "good" with no intervention effects. Postprandial satiety increased reaching maximum at 1.5 h after meal (time effect, P<0.001) and was higher after MD compared to WD (meal effect, P<0.001). In all interventions, plasma cortisol decreased similar to its diurnal variation (time effect, P<0.001). In our subjects, meal composition had no relevant impact on attention and mood. After typical WD, resting instead of walking seems to have a more beneficial effect on postprandial attention. MD leads to a strong and long-lasting feeling of satiety, possibly resulting in reduced energy intake in the further course of the day and, thus, long-term effect on weight control.

This trial was registered at http://www.germanctr.de and http://drks.de under identifier DRKS00012409.

INTRODUCTION

Research suggests that the sedentary lifestyle of today's Western societies is associated with the development of chronic systemic low-grade inflammation, which is at the root of many typically Western diseases associated with the metabolic syndrome [1]. Due to the anti-inflammatory capacities of aerobic physical activity, integration of regular activity sessions into everyday life seems to be beneficial regarding improvement of general health and, furthermore, regarding protection of the brain from metabolic stress [1,2]. In addition, especially regular aerobic activity has been consistently reported to prevent mental illness (e.g., depression) and alleviate mood problems, as well as to improve cognitive and brain function, but even acute, moderate activity sessions seem to exert similar effects [2–5]. In this context, different research studies describe modulators of effect size being the temporal sequencing of cognitive assessment in relation to exercise (e.g., following exercise session or during exercise session), the modality of aerobic training (e.g., cycling or running), and the cognitive parameters measured (e.g., memory or processing speed), as well as age and medical condition [3,4,6].

While supplementation studies suggest that single nutrients (e.g., docosahexaenoic acid) can increase cognitive performance, research on the effects of whole meals and, especially, different meal compositions on cognitive function and mood is limited [7]. Compared to a meal intake which is in accordance with the Western dietary pattern, a Mediterranean diet provides higher levels of nutrients including essential fatty acids, vitamins, minerals, and antioxidants, which seem to support brain function. Additionally, the Mediterranean dietary pattern contains fewer refined carbohydrates and saturated fatty acids, which have been associated with cognitive deficits [7,8]. Therefore, it is likely that a regular choice of food items characteristic for the Mediterranean dietary pattern is beneficial with regard to the prevention of age-related cognitive deficits [9,10]. In this context, numerous epidemiological studies suggest that an adherence to plant-based dietary patterns, especially the Mediterranean dietary pattern, is associated with improved cognitive performance, slower age-related cognitive decline and lower risk of cognitive impairment and neurodegenerative disease in older adults [11–14].

Current randomized interventions trials evaluating the acute interactive effects of meal composition and physical activity on cognitive performance and emotions are limited [15,16] and to the best of our knowledge, no previous human study has investigated the acute effects of postprandial exercise suitable for daily implementation neither on postprandial attention as a complex cognitive function, nor on mood/emotions following the consumption of meals reflecting different dietary patterns, especially in subjects with a risk phenotype for the development of cardiovascular and

neurodegenerative diseases (e.g., elevated age; characteristics of metabolic syndrome). Since current research suggests that breakfast as the first meal of the day is most important from a dietary perspective [17] and is vital for optimal cognitive function and intellectual performance by providing readily available energy to the brain [18], the test meals in the present study were provided as breakfast challenges after an overnight fast (≥ 12 h). The study tested two main hypotheses: (i) a Mediterranean-type diet meal (MD) generates higher postprandial satiety, postprandial attention and a better subjective mood than an iso-energetic Western diet high-fat meal (WD); and (ii) Moderate walking in the postprandial period as compared to remaining sedentary, results in increased postprandial attention and a better subjective mood. In addition to these main hypotheses, this study examined the impact of plasma cortisol concentration on postprandial attention, since elevated systemic cortisol concentrations have been associated with detrimental effects on cognition and a long-term contribution to Alzheimer's disease pathology [19,20]. In this context, the present study evaluated if the activity session or the intake of high-energy meals were high enough stressors to trigger cortisol release and if effects of different plasma cortisol concentrations on postprandial attention are relevant even in an acute study design. The data presented in this manuscript are ancillary examinations (secondary outcome measures) of the intervention study which has initially been designed to investigate the effects of meal composition and postmeal walking on different metabolic, inflammatory, oxidative, and endothelial events in the postprandial period, with postprandial triglycerides as primary outcome measure [21].

MATERIALS AND METHODS

Participants

Details of the study design and subject recruitment, enrollment, and randomization have been described previously [21]. In brief, interested volunteers (n = 31) aged 60 to 80 y attended a screening that included physical assessments (e.g., body height and weight, waist circumference), clinical assessments (e.g., liver and kidney function, serum lipids and lipoproteins, plasma glucose), medical history, and the documentation of dietary habits. Main inclusion criteria were: (i) overweight or obesity stage 1 (BMI 27–34.9 kg/m2), (ii) visceral fat distribution (waist circumference ≥ 94 cm for men and ≥ 80 cm for women), and (iii) prehypertension (systolic blood pressure: ≥ 120 mmHg, and ≤ 139 mmHg; diastolic blood pressure: ≥ 80 mmHg, and ≤ 89 mmHg) or stage 1 hypertension (systolic blood pressure: ≥ 140 mmHg, and ≤ 159 mmHg; diastolic blood pressure: ≥ 90 mmHg, and ≤ 99 mmHg). In addition, study eligibility required fulfillment of at least one of the following criteria: (i) dyslipidemia (fasting serum triglycerides ≥ 1.7 mmol/L and/or serum HDL-cholesterol < 1.0 mmol/L for men and < 1.3 mmol/L for women), (ii) fasting plasma glucose ≥ 5.6 mmol/L) or iii) a pro-inflammatory state (hs-CRP ≥ 2.0 mg/L). A total of 26 subjects (18 male, eight female) were included in the study. All subjects completed the entire intervention trial, and their respective data were included in the analysis. The study was conducted in accordance with the guidelines laid down in the 1964 Declaration of Helsinki and its later amendments. All study procedures were approved by the ethics committee of the Medical Faculty of the University of Bonn, Germany (ethic approval code 070/17). Written informed consent was obtained from all subjects prior to inclusion. This trial was registered at http://www.germanctr.de and http://drks.de under identifier DRKS00012409.

Study design

This postprandial study was conducted as a randomized controlled crossover trial at the Department of Nutrition and Food Sciences, Nutritional Physiology (University of Bonn, 53115 Bonn, Germany). All subjects participated in four treatment conditions, each lasting 4.5 h from morning to afternoon. Study days were separated by 2 wk wash-out periods. The order of treatments was randomized for each subject via computer-generated randomization tables (Microsoft Excel 2010, Microsoft Corp., Redmond, WA., USA). The four treatment conditions were as follows: (i) MD plus 30 min postprandial walking; (ii) MD plus 30 min postprandial resting; (iii) WD plus 30 min postprandial walking and (iv) WD plus 30 min postprandial resting. On each treatment day, venous blood sampling for cortisol analysis and questionnaires for attention, mood, and satiety were taken at fasting (0 h) and at three time points during the postprandial period (1.5, 3.0, and 4.5 h). The

outcome measures shown in the present manuscript were examined as secondary outcome measures in the context of the randomized crossover trial evaluating the impact of meal composition and postmeal walking on selected postprandial events. Further details of this trial and the study design have been previously described [21].

Test meals

WD and MD test meals (challenges) were designed specifically for the purposes of the present study. The meals were iso-energetic (4300 kJ/meal) and iso-nitrogenous. WD was rich in total fat, saturated fatty acids, and animal protein. MD was rich in unsaturated fatty acids, dietary fiber, and antioxidative compounds (**Table 3-1**). The main components of the WD were croissant, bread roll, jam, butter, cold cuts, boiled egg and cream yogurt. The MD mainly comprised ciabatta, smoked salmon, muesli, fruit, and vegetables. Details of food items and nutrient composition of MD and WD have been previously described [21]. Study personnel prepared both breakfast challenges according to a standardized protocol, which included the weighing of each food item to the nearest gram. The test meals were consumed in the morning as first meal of the day and had to be ingested within 20 min.

Table 3-1 Nutrient composition per serving of the two test meals (adapted from [21]).

Energy and Nutrients	**WD**	**MD**
Energy (kJ)	4247	4251
Protein (g)	26.1	25.9
Carbohydrates (g)	93.7	133
Dietary fiber (g)	4.2	14.5
Total fat (g)	59.4	40.1
SFAs (g)	32.0	5.1
MUFAs + PUFAs (g)	23.8	30.9
ß-carotene (mg)	0.2	5.4
Vitamin E[1] (mg)	2.3	12.1
Vitamin C (mg)	9	102

[1]α-Tocopherol equivalent. MD, Mediterranean-type diet meal; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; SFAs, saturated fatty acids; WD, Western diet high-fat meal.

Physical activity

The activity (walking or resting) was conducted directly after meal intake. The 30 min walking session was performed outdoors on the University of Bonn campus. Participants were accompanied by study personnel. The duration was selected to reflect current recommendations for the minimum level of moderate-intensity physical activity required on most days of the week to reduce the risk of cardiovascular events [22]. During the first walking session, the subjects were told to walk at a moderate pace, reflecting their individual speed of comfort. For standardization purposes, this speed was then reproduced during the following walking session. The resting (control) phase was conducted at the study location. Each participant remained in a supine position, and was told to abstain from any distraction over a period of 30 min [21].

Measurements

Assessment of cognitive abilities: attention/focus

The German version of the Frankfurt Attention Inventory 2 (FAIR-2, Test version A) was used, which is a validated paper and pencil measure of visual selective attention as one facet of cognitive function with good psychometric properties [23,24] and proven sensitivity to pharmacological interventions [25–27]. Test completion requires the accurate and quick identification and marking of target items among similar non-target items. In this context, a continuous line needs to be drawn under each row of items, with a peak clearly pointing into the target-items. Participants need to be alert and show a rapid reaction time, as well as the ability to maintain focused attention throughout the test duration. Both accuracy and speed are taken into account when evaluating test performance and are combined into an overall performance score (K score). The FAIR-2 was conducted in the fasting state (baseline) and 1.5, 3.0, and 4.5 h postprandially on each of the four study days. All subjects were familiarized with FAIR-2 prior to the commencement of the study to reduce practice effects.

Assessment of subjective mood

The German version of the Multidimensional Mood State Questionnaire (MDMQ) was used to assess subjective mood [28]. The MDMQ is a paper and pencil test, which uses selected adjectives (24 in the long form and 12 in the short form), which can be assigned to three bipolar dimensions of mood: (i) good mood vs. bad mood, (ii) alertness vs. fatigue, and (iii) ease vs. unease. For each adjective, subjects were asked to classify their current feeling on a five-point scale from 1 (“not at all”) to 5 (“very much”). An overall score was calculated for each of the three bipolar dimensions,

with higher (or lower) values associated with the respective positive (or negative) sensations. The test was conducted in the fasting state (baseline) and 1.5, 3.0, and 4.5 h postprandially on each of the four study days. The two versions of the short form (type A and B) were used alternately at the respective time points, with the order being randomized for each subject. All subjects were familiarized with the MDMQ prior to the commencement of the study to reduce practice effects.

Assessment of hunger, appetite, and satiety

The sensations 'hunger', 'appetite' and 'satiety' were assessed using 100-mm visual analogue scales (VAS). On three different VAS, the sensations 'hunger', 'appetite' and 'satiety' were paired with the correspondingly opposite sensations 'no hunger', 'no appetite' and 'no satiety'. Subjects were requested to make a vertical mark on each scale that best matched their current feeling. Each score was determined by measuring the distance from the left side of the line to the vertical mark. Since VAS values for hunger and appetite were highly correlated ($r = 0.8$), both were combined to a value describing the overall sensation of hunger / desire to eat (arithmetic mean). The test was conducted in the fasting state (baseline) and 1.5, 3.0, and 4.5 h postprandially on each of the four study days. All subjects were familiarized with the VAS scales prior to the commencement of the study to reduce practice effects.

Blood sample processing and analysis

Details of the pre-analytical procedures of fasting and postprandial blood samples have been described previously [21]. Fasting and postprandial cortisol was analyzed in duplicate using commercially available enzyme-linked immunoassay kits (IBL International GmbH, Hamburg, Germany) in accordance with the manufacturer's instructions and recommended quality control procedures.

Sample size calculation

The outcomes measured in the present manuscript were examined as secondary outcome measures as part of the randomized crossover trial evaluating the impact of meal composition and postmeal walking on selected postprandial events. Therefore, a priori sample size calculation was based on serum triglycerides as primary outcome measure of the entire postprandial intervention study [21].

Statistical analysis

All statistical analyses were performed using the IBM SPSS statistical software package (SPSS version 25, IBM Corporation, Somers, NY, USA). The linear mixed model procedure was used to test the effects of meal and activity, time points, and their interaction on postprandial cortisol and

FAIR-2, MDMQ, and VAS values. Meal type (WD, MD); activity (walking, resting); time points (1.5, 3.0, 4.5 h postprandially); and interactions (meal x activity, meal x time, activity x time, and meal x activity x time) were set as fixed factors and subject identifier as a random factor. Baseline values were included as covariates. For FAIR-2 analysis, the order of study visits was set as an additional covariate in order to control for any residual practice effects. In all tests, the residuals showed no relevant deviations from a normal distribution. In case of significant meal x activity interaction, the linear mixed model procedure was performed separately for WD and MD to examine possible activity effects for both meal types. Furthermore, incremental area under the curve (iAUC) was calculated for all parameters using the trapezoidal rule, and the linear mixed model procedure was performed to test for meal, activity, and meal x activity effects. In all analyses, significance level was set at $P < 0.05$. Descriptive data are presented as arithmetic mean x standard error of the mean (SEM), unless otherwise stated.

RESULTS

Participants

Baseline characteristics are shown in **Table 3-2**. All participants were overweight (46.2%) or obese (53.8%), had a visceral fat distribution, and were prehypertensive or displayed stage 1 hypertension [21].

Table 3-2 Baseline characteristics of participants (adapted from [21]).[1]

Parameters	**Total (*n* = 26)**
Age (y)	69.9 ± 4.7
BMI (kg/m^2)	30.3 ± 2.3
Body fat (%)	38.4 ± 8.1
Waist circumference (cm)	104 ± 5.8
Systolic blood pressure (mmHg)	149 ± 16.4
Diastolic blood pressure (mmHg)	88.3 ± 7.3
Serum triglycerides (mmol/L)	1.76 ± 0.79
Serum total cholesterol (mmol/L)	4.86 ± 1.60
Serum HDL cholesterol (mmol/L)	1.61 ± 0.37
Serum LDL cholesterol (mmol/L)	3.19 ± 0.76
Plasma glucose (mmol/L)	5.64 ± 0.66
Serum hs-CRP (mg/L)	2.5 ± 3.0
Age (y)	69.9 ± 4.7
BMI (kg/m^2)	30.3 ± 2.3
Body fat (%)	38.4 ± 8.1
Waist circumference (cm)	104 ± 5.8
Systolic blood pressure (mmHg)	149 ± 16.4

[1]Shown as mean ± SD, *n* = 26. hs-CRP, high sensitivity C-reactive protein.

FAIR-2

In all four treatment conditions, the overall test performance (K score) increased over time (P<0.001) which was due to an increase in speed (P<0.001) rather than an increase in accuracy (P=0.429) over time. A significant interaction for meal x activity (P=0.026) was observed: for WD but not MD, K scores were lower after walking compared to resting (P<0.001) (**Figure 3-1a, Table 3-3).** Comparison of iAUC data revealed an effect of meal type (P=0.045) and activity (P=0.027), with higher K scores for MD compared to WD and for resting compared to walking (**Figure 3-1b**).

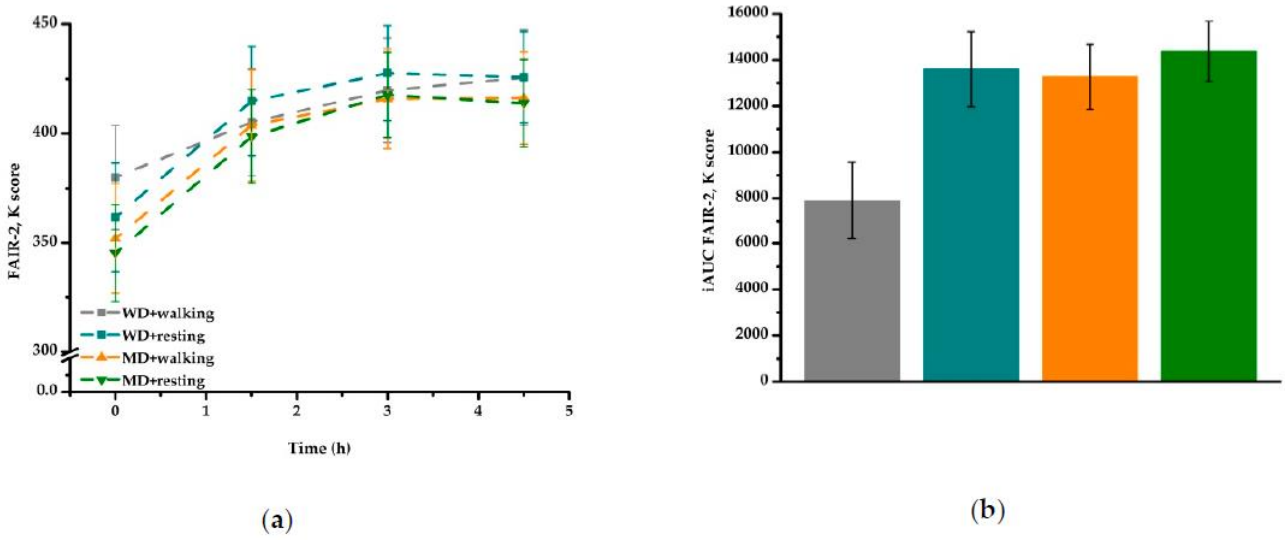

Figure 3-1 Fasting and postprandial attention (FAIR-2, K score) according to treatment condition: (**a**) K score over time: the overall test performance increased over time (P<0.001). A significant interaction for meal x activity (P=0.026) was observed: for WD but not MD, values were lower after walking compared to resting (P<0.001) (**b**) iAUC of K score: data revealed an effect of meal type (P=0.045) and activity (P=0.027). FAIR-2, Frankfurt Attention Inventory 2; iAUC, incremental area under the curve; MD, Mediterranean-type diet meal; WD, Western diet high-fat meal.

Table 3-3 Fasting and postprandial attention (FAIR-2, K score)[1,2]

	Fasting	**Postprandial**			***P*-values from linear mixed models**					
	0 h	1.5 h	3.0 h	4.5 h	time	meal	activity	meal x activity	meal x time	activity x time
K score (FAIR-2)					<0.001	0.039	0.001	0.026	0.905	0.770
WD + walking	380 ± 23.8	405 ± 24.3	420 ± 23.9	426 ± 21.8						
WD + resting	362 ± 24.9	415 ± 25.0	428 ± 21.7	426 ± 20.8						
MD + walking	352 ± 25.0	404 ± 25.4	416 ± 22.8	416 ± 21.0						
MD + resting	345 ± 22.3	399 ± 21.4	418 ± 19.4	414 ± 20.1						

[1]shown as mean ± SEM. *P*-value for meal x time x activity interaction not significant.
[2]K score describes overall test performance during FAIR-2. Scores range from 0 – 640.
FAIR-2, Frankfurt Attention Inventory 2; MD, Mediterranean-type diet meal; WD, Western diet high-fat meal.

MDMQ

For the values of the dimension good vs. bad mood, a time effect was observed (P=0.014), as well as a significant interaction for meal x activity (P=0.027). Here, an activity effect was observed for MD (P=0.004) but not for WD. The values for the dimension alertness vs. fatigue were significantly influenced by time (P=0.006) and meal (P=0.003), with lower values after WD compared to MD. The values for the dimension ease vs. unease were affected by activity (P=0.022) but neither by time nor by meal type. For all three dimensions, neither a meal x time nor an activity x time effect has been observed. Comparison of iAUC data revealed no effect for meal or activity either. Data are summarized in **Table 3-4**.

Table 3-4 Fasting and postprandial parameters of MDMQ[1,2].

	Fasting	**Postprandial**			***P*-values from linear mixed models**					
	0 h	1.5 h	3.0 h	4.5 h	time	meal	activity	meal x activity	meal x time	activity x time
Good vs. bad mood					0.014	0.047	0.171	0.027	0.580	0.804
WD + walking	17.4 ± 0.63	18.5 ± 0.41	18.0 ± 0.45	18.4 ± 0.35						
WD + resting	18.6 ± 0.37	18.7 ± 0.32	18.2 ± 0.35	18.2 ± 0.38						
MD + walking	17.9 ± 0.48	18.0 ± 0.36	17.7 ± 0.45	17.8 ± 0.34						
MD + resting	17.7 ± 0.54	18.1 ± 0.36	18.0 ± 0.40	18.6 ± 0.35						
Alertness vs. fatigue					0.006	0.003	0.089	0.404	0.600	0.573
WD + walking	15.2 ± 0.79	16.4 ± 0.68	15.2 ± 0.65	14.8 ± 0.65						
WD + resting	16.7 ± 0.57	16.3 ± 0.51	16.2 ± 0.56	15.5 ± 0.67						
MD + walking	15.2 ± 0.85	14.9 ± 0.60	14.6 ± 0.71	14.2 ± 0.77						
MD + resting	15.4 ± 0.85	15.8 ± 0.60	14.4 ± 0.75	15.4 ± 0.63						
Ease vs. unease					0.444	0.107	0.022	0.248	0.253	0.837
WD + walking	17.3 ± 0.68	17.6 ± 0.53	17.8 ± 0.53	18.1 ± 0.41						
WD + resting	18.1 ± 0.49	18.4 ± 0.39	18.2 ± 0.45	18.0 ± 0.41						
MD + walking	17.2 ± 0.51	17.8 ± 0.45	17.1 ± 0.61	17.2 ± 0.51						
MD + resting	17.5 ± 0.57	18.0 ± 0.44	17.8 ± 0.49	18.0 ± 0.51						

[1]shown as mean ± SEM. *P*-value for meal x time x activity interaction not significant.
[2]values range from 5 (lower end of the scale) until 20 (upper end of the scale).
MD, Mediterranean-type diet meal; MDMQ, Multidimensional Mood Sate Questionnaire; WD, Western diet high-fat meal.

VAS

The overall sensation of hunger (desire to eat) decreased over time (P<0.001), with no meal or activity effect (**Figure 3-2a, Table 3-5**). Comparison of iAUC data confirmed these results (**Figure 3-2b**). Satiety values increased over time (P<0.001) with higher values for MD compared to WD (P<0.001) (**Figure 3-3a, Table 3-5**). This meal effect was confirmed by the iAUC data (**Figure 3-3b**).

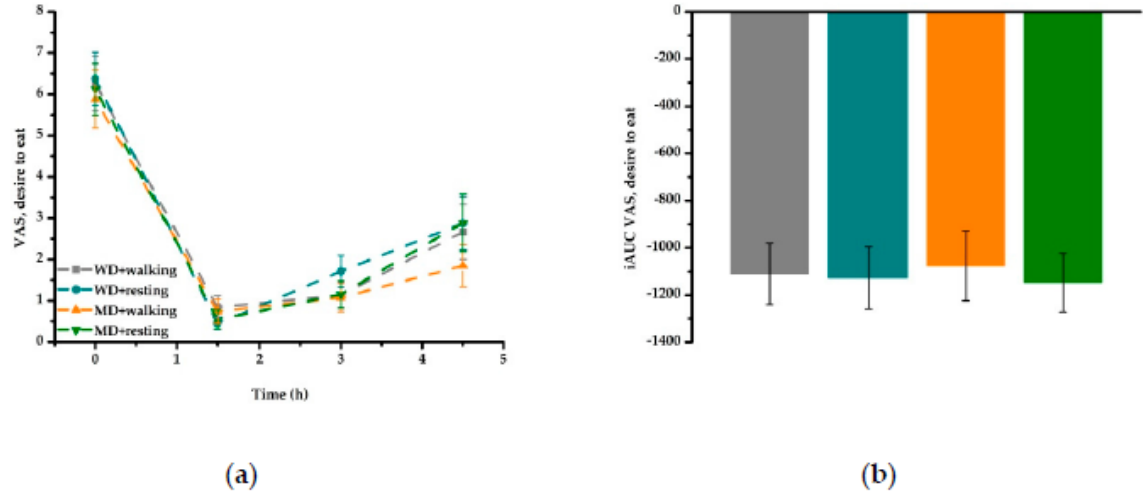

Figure 3-2 Fasting and postprandial hunger (desire to eat) according to treatment condition: (**a**) the overall sensation of hunger decreased over time (P<0.001) in all four treatment conditions. (**b**) iAUC revealed no meal or activity effect. iAUC, incremental area under the curve; MD, Mediterranean-type diet meal; VAS, visual analogue scale; WD, Western diet high-fat meal.

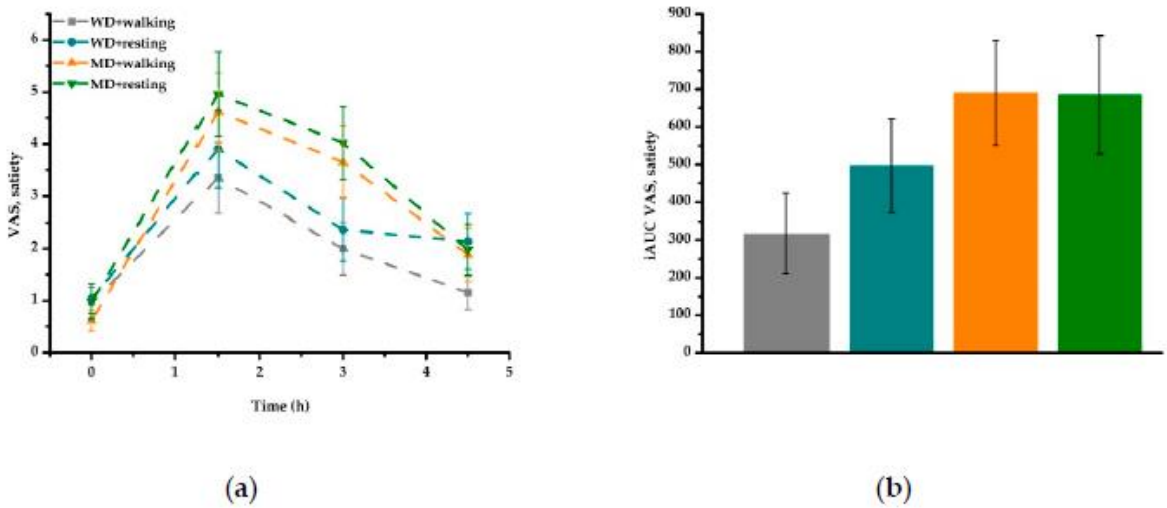

Figure 3-3 Fasting and postprandial satiety according to treatment condition: (**a**) satiety increased over time (P<0.001) with higher values for MD compared to WD (P<0.001). (**b**) iAUC data confirmed the observed meal effect (P=0.004). iAUC, incremental area under the curve; MD, Mediterranean-type diet meal; VAS, visual analogue scale; WD, Western diet high-fat meal.

Table 3-5 Fasting and postprandial hunger and satiety[1,2.]

	Fasting	Postprandial			*P*-values from linear mixed models					
	0 h	1.5 h	3.0 h	4.5 h	time	meal	activity	meal x activity	meal x time	activity x time
Desire to eat (hunger)					<0.001	0.283	0.359	0.552	0.656	0.105
WD + walking	6.26 ± 0.67	0.85 ± 0.28	1.13 ± 0.32	2.66 ± 0.67						
WD + resting	6.38 ± 0.64	0.45 ± 0.15	1.71 ± 0.38	2.88 ± 0.65						
MD + walking	5.88 ± 0.70	0.74 ± 0.29	1.08 ± 0.34	1.85 ± 0.51						
MD + resting	6.12 ± 0.62	0.55 ± 0.23	1.15 ± 0.33	2.88 ± 0.70						
Satiety					<0.001	<0.001	0.158	0.490	0.160	0.972
WD + walking	0.96 ± 0.30	3.35 ± 0.68	2.00 ± 0.51	1.15 ± 0.32						
WD + resting	1.04 ± 0.28	3.90 ± 0.74	2.37 ± 0.60	2.13 ± 0.53						
MD + walking	0.62 ± 0.20	4.62 ± 0.75	3.65 ± 0.70	1.88 ± 0.52						
MD + resting	0.98 ± 0.34	4.96 ± 0.81	4.02 ± 0.70	1.98 ± 0.49						

[1]shown as mean ± SEM. *P*-value for meal x time x activity interaction not significant.
[2]values were measured via VAS and range from 0 (lower end of the scale) until 10 (upper end of the scale).
MD, Mediterranean-type diet meal; VAS, visual analogue scale; WD, Western diet high-fat meal.

Plasma cortisol

Postprandial cortisol concentration decreased over time (P<0.001), with no effect being observed for meal or activity (**Figure 3-4a, Table 3-6**). Comparison of AUC data confirmed these results. Data are summarized in **Figure 3-4b.**

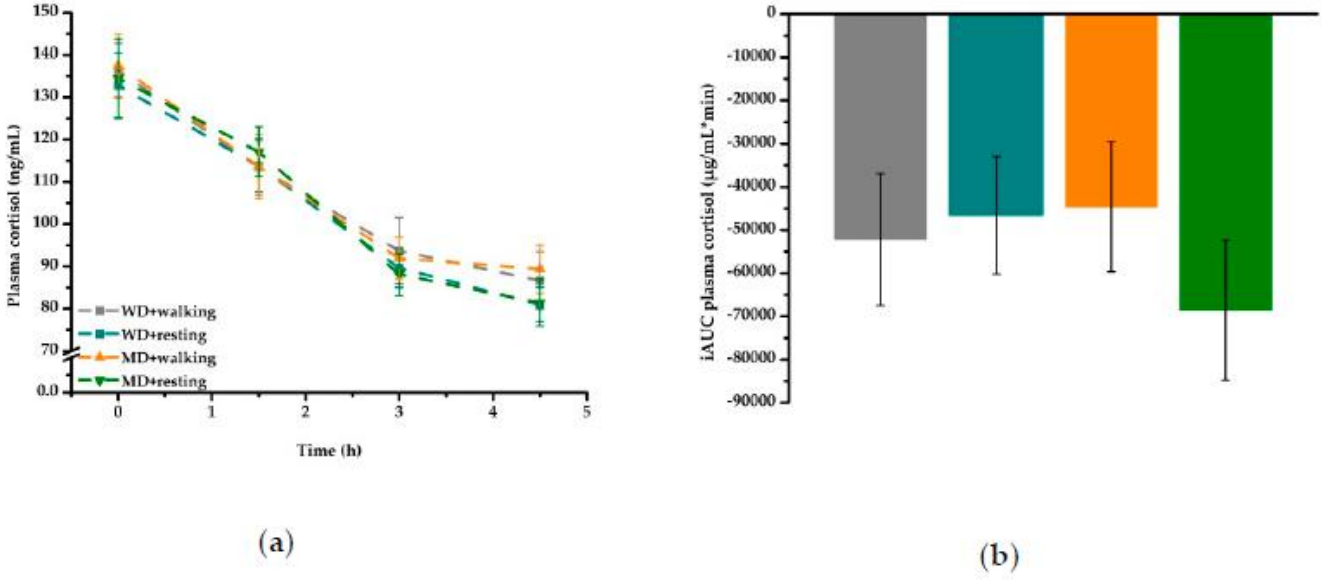

Figure 3-4 Fasting and postprandial plasma cortisol according to treatment condition: (**a**) postprandial cortisol concentration decreased over time (P<0.001) in all four treatment conditions. (**b**) iAUC data revealed no effect of meal or activity. iAUC, incremental area under the curve; MD, Mediterranean-type diet meal; WD, Western diet high-fat meal.

Table 3-6 Fasting and postprandial plasma cortisol concentration[1]

	Fasting		**Postprandial**		***P*-values from linear mixed models**					
	0 h	1.5 h	3.0 h	4.5 h	time	meal	activity	meal x activity	meal x time	activity x time
Plasma cortisol (ng/mL)					<0.001	0.810	0.160	0.863	0.659	0.569
WD + walking	136 ± 6.46	114 ± 6.76	93.7 ± 7.86	86.6 ± 6.90						
WD + resting	133 ± 7.76	114 ± 6.07	89.6 ± 4.52	81.0 ± 4.10						
MD + walking	137 ± 7.38	114 ± 7.47	91.9 ± 4.90	89.4 ± 5.71						
MD + resting	134 ± 9.34	117 ± 5.90	88.1 ± 4.96	81.4 ± 5.55						

[1]shown as mean ± SEM. *P*-value for meal x time x activity interaction not significant, data not shown.
MD, Mediterranean-type diet meal; WD, Western diet high-fat meal.

DISCUSSION

The purpose of this study was to investigate the acute impact of dietary composition and moderate postmeal walking on postprandial attention (representing one aspect of cognitive function), mood, and the sensations of hunger and satiety in older subjects with a risk phenotype for the development of cardiovascular and neurodegenerative diseases.

Prior research suggests that the consumption of breakfast is vital for optimal cognitive performance, since it provides readily available energy as first meal of the day after an overnight fast [15,18]. In the present study, the consumption of both test meals (breakfast challenges) yielded a reliable and substantial (10–20%) increase of postprandial attention over time. iAUC data revealed that the increase in postprandial attention was significantly higher after MD than after WD, which is in accordance with our hypothesis that a MD results in higher postprandial attention than a WD. Considering the fact that glucose is the main fuel for brain function and therefore plays an important role in general cognitive performance [29,30], the observed meal effect on postprandial attention in the present study might be due to the higher amount of carbohydrate in MD (133.3 g vs. 93.7 g). It remains unclear, whether the different nutrient composition of the breakfast challenges (**Table 3-1**) contributed to the observed results. Since an adherence to the Mediterranean dietary pattern is in the long run associated with improved cognitive performance and mental health, future intervention studies in this field of research might consider taking into account the habitual diet/nutritional status of their participants as a further possible influencing factor of acute nutritional effects on cognitive parameters such as postprandial attention.

Furthermore, an activity effect was observed after WD, with lower postprandial attention after walking than after resting. From the perspective of energy availability to the brain, these findings are rather unexpected, since we observed higher plasma glucose concentrations after walking than after resting for both meal types [21].

An increase in postprandial cortisol concentrations could further explain the decreased attention values observed after the WD+walking treatment, since elevated plasma cortisol is associated with altered cognitive function [31]. However, our data showed no activity effect on postprandial plasma cortisol over time for none of the four treatments. Since the walking session in the present study was of moderate intensity and short duration only, the stressor might not have been high enough to trigger an increase in plasma cortisol concentrations [32]. However, it is possible that an activity effect on postprandial cortisol would have been detectable if blood samples had been taken during and/or directly at the end of the walking session [32]. In accordance with previous postprandial

trials [33,34], in the present study, postprandial cortisol significantly decreased from morning to afternoon, similar to its diurnal variation, and the stimulus of meal intake was not strong enough to alter this distinct pattern (**Figure 3-4a, Table 3-6**). Since postprandial attention as well as cortisol showed a strong time effect, it is diffcult to separate between the extent to which time influenced postprandial attention and the extent to which postprandial cortisol had an influence on this parameter.

The fact that the increase of overall postprandial attention was due to an increase in test speed and not in test accuracy suggests, that the repetition of the same test procedure on each time point on each of the four study days led to a learning effect. This learning effect, however, cannot be quantified but should be taken in to account when evaluating the practical relevance of the statistical results.

In contrast to a previous postprandial exercise trial conducted in healthy, habitually active, middle-aged women, which showed an association between the consumption of breakfast and lower fatigue and higher overall mood and alertness post-exercise [16], in the present study, no relevant effect of meal intake or postprandial activity behavior on the measured mood dimensions (good vs. bad mood, alertness vs. fatigue, and ease vs. unease) could be observed (**Table 3-4**). Despite statistical significance, for all three dimensions, changes in mean values between all time points were minor. The obtained results showed that the subjects were alert, at ease and in rather good mood during the course of each study day (**Table 3-4**). Since meal or activity effects on subjective parameters like mood are complex to measure, it is possible that the MDMQ was not sensitive enough to determine clinically relevant treatment effects on mood over time [35].

In comparison to the present study, future intervention studies in this field of research might consider the habitual activity level/physical activity status of their participants as a modulator of effect size. It can be assumed that the intensity of an acute physical activity session is perceived differently depending on the activity status of a person (low or high metabolic stressor), possibly resulting in different effects on postprandial attention and/or postprandial emotional state.

Research suggests that the consumption of food in the early morning leads to control and moderation of total energy intake throughout the whole day, since the complex carbohydrates usually consumed during breakfast affect activity as well as release of hormones (e.g., gastric inhibitory peptide, glucagon-like peptide-1, cholecystokinin), which differently affect postprandial plasma glucose and, consequently, satiety [18]. In the present study, the higher satiety values over time that were observed after MD treatments compared to WD treatments are mainly due to the

higher volume of the MD (781 g/MD meal vs. 390 g/WD meal), as well as the higher dietary fiber content (14.5 g/MD meal vs. 4.2 g/WD meal). It is possible that this marked satiating power led to control and moderation of total energy intake throughout the remaining day.

The major strengths of the present study are the controlled, crossover design, the absence of study dropouts, and the high rate of treatment compliance. In contrast to previous studies in this flied of research, this trial followed a holistic approach and focused on regular meals reflecting different dietary patterns and not on the administration of nutrient solutions (e.g., fat tolerance tests). The 30 min session of moderate postmeal walking was designed to be easily incorporable into daily routines, even by inactive or physically more restricted individuals. One limitation of the present work is that it is an explorative analysis of secondary outcome measures. The study was originally designed to investigate the effects of meal composition and postmeal walking on different metabolic, inflammatory, oxidative, and endothelial outcome measures in the postprandial period and a priori sample size calculation was based on serum triglycerides as primary outcome measure of the postprandial intervention study [21]. Another potential limitation of the study is the time points selected for the measurement of outcome measures, which may not have been representative of the overall postprandial period. However, for scheduling reasons, further time points and shorter intervals were precluded from the study design. Furthermore, the repeated use of the FAIR-2 type A to examine attention behavior may have led to a learning effect which might have influenced time- and treatment effects. However, alternate use of both test types (A and B) could not be performed as there was a risk of possible bias due to changes in target items and test procedures. Future intervention trials focusing on the evaluation of selective attention as a primary outcome measure might consider including a variety of test procedures focusing on different aspects of cognitive performance (including vigilance) and a chronometric approach might be reasonable in order to evaluate cognitive function more specifically. This might be especially relevant in chronic rather than acute intervention trials.

CONCLUSION

In conclusion, the present study shows no relevant effect of meal composition or postprandial activity behavior regarding subjective mood and none of the four treatment conditions can be rated superior in older adults with a risk phenotype for cardiovascular diseases. Compared to a Western diet high-fat meal, a meal composition reflecting the Mediterranean dietary patter seems to be beneficial regarding postprandial attention. After the consumption of WD, postprandial resting seems to be more beneficial than postprandial walking for optimal cognitive performance. Due to its nutrient composition and food items (e.g., higher amount of low-energy/nutrient-dense foods and

higher fiber content), MD leads to a stronger and longer lasting feeling of satiety. A selection of food items in accordance with the Mediterranean dietary pattern might therefore have a positive impact on weight regulation and should be of special importance in overweight-to-obese subjects. Future randomized, controlled trials should focus on the investigation of the chronic rather than the acute impact of dietary composition and postprandial activity behavior on cognition and emotion to further understand mechanisms involved and to develop strategies to attenuate or even prevent comorbid neurological conditions in risk subjects.

ACKNOWLEDGMENTS

The authors are indebted to our volunteers for their interest and participation in our study; to Saskia Groh for her support with the implementation of the trial; to Christine Bierschbach, Anke Carstensen, Anke Ernst, Adelheid Fürste, Hedwig Heuser, Christine Laurini and Anja Stratmann for excellent technical assistance; to Karoline Bauer, Martha Römer and Florian Simon for performing the venipunctures.

AUTHOR CONTRIBUTIONS

Conceptualization, C.D., M.P., P.P., H.-G.P., P.S. and S.E.; methodology, C.D. and S.E.; software, M.W., M.P., P.P. and S.E.; validation, C.D. and S.E.; formal analysis, C.D., B.S-W., R.F..; investigation, C.D., H.H., M.P., P.P., H.-G.P., B.S-W., R.F., P.S. and S.E.; resources, M.W., M.P., P.P. and S.E..; data curation, C.D. and S.E.; writing—original draft preparation, C.D.; writing—review and editing, C.D., H.H., M.P., P.P., H.-G.P., B.S-W., R.F., P.S. and S.E.; supervision, S.E..; project administration, S.E.

FUNDING

This research received no specific external funding.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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CHAPTER 4: GENERAL DISCUSSION

The present study examined the acute effects of different meal patterns (Mediterranean-type diet meal vs. Western diet high-fat meal) combined with either 30-minutes postprandial moderate walking or 30-minutes postprandial resting, on physiological and neuropsychological outcome measures in older subjects with increased risk for cardiovascular and neurodegenerative diseases. In order to create realistic conditions, the present study, in comparison to other postprandial intervention studies in this field of research, followed a holistic approach. Therefore, focused was set on the effects of complete meals rather than single nutrients and on a physical activity session that can easily be incorporated into everyday situations, especially by rather inactive or physically restricted individuals.

Research suggests that even acute postprandial responses following the consumption of high-carbohydrate or high-fat meals seem to increase the risk of development of CVDs. In this context, postprandial hyperglycemia and hyperlipidemia are described to be major independent risk factors triggering subsequent postprandial responses of oxidation, inflammation, and endothelial dysfunction (Jiang et al. 2017; Pirillo et al. 2014). Therefore, the development of strategies to counteract an excessive increase in plasma glucose and serum triglyceride concentrations after meal intake, while considering the summative metabolic response of both carbohydrate and lipids in the context of holistic meals, is of physiological relevance. This is particularly the case for individuals already at increased risk to develop cardiovascular complications (e.g., individuals with metabolic syndrome traits) (Edinburgh et al. 2017; Emerson et al. 2016).

As expected, both test meals led to a significant increase in serum triglycerides, plasma glucose, and serum insulin in the postprandial period, similar to their characteristic nutrient composition (total amount of carbohydrate and fat; fatty acid composition). Next to the lower amount of total fat (59.4 g vs. 40.1 g) and SFAs (32.0 vs. 5.1 g) in the Mediterranean-type diet meal, its higher amount of dietary fiber (14.5 g vs. 4.2 g) might have additionally been responsible for the lower increase in postprandial triglycerides observed after this meal type. Especially soluble dietary fiber is described to be associated with moderate reductions in postprandial serum triglycerides following the consumption of mixed meals (Hannon et al. 2019; Edinburgh et al. 2017; Lopez-Miranda et al. 2007). Furthermore, soluble dietary fiber has the potential to reduce the postprandial glucose absorption rate after the consumption of a high carbohydrate load through delayed gastric emptying and altered viscosity properties (Cassidy et al. 2018; Stewart and Zimmer 2018). Therefore, despite the higher total amount of carbohydrate in the Mediterranean-type diet meal than in the Western diet high-fat meal (133 g vs. 93.7 g), attenuating effects on postprandial glucose and insulin

concentrations could have been expected after the Mediterranean-type diet meal, due to its higher amount of dietary fiber and lower mono- and disaccharides to polysaccharides ratio (0.96 vs. 0.65). However, both, plasma glucose and serum insulin, were higher after the Mediterranean-type diet meal than after the Western diet high-fat meal. Since the study protocol did not allow including further measuring points in the earlier postprandial period (< 1.5 h postprandial), it remains unclear, whether the potential attenuating effects of the complex carbohydrates on plasma glucose and serum insulin concentrations occurred during this time frame. Additionally, as observed in the present study as well (higher satiety values after the Mediterranean-type diet meal than after the Western diet high-fat meal), fiber ingestion induces increased satiety. This might lead to a decrease in further energy intake in the case of multiple meal consumption (Tucker and Thomas 2009). Therefore, the regular consumption of meals / food items characteristic for the Mediterranean dietary pattern might indirectly contribute to attenuated postprandial responses during the course of one day, due to their effects on postprandial satiety.

Glucose is an important brain substrate and neural tissue depends on an adequate glucose supply under physiological conditions. Therefore, a habitual diet in accordance with the Mediterranean dietary pattern, that induces a low but sustained blood glucose profile and avoids higher glucose peaks and, thus, secures optimal glucose delivery to the brain in the fed and fasting states, should be most advantageous for the maintenance of cognitive function (Sünram-Lea and Owen 2017; Nilsson et al. 2012). It remains unclear, if the higher amount of carbohydrates in the Mediterranean-type diet meal was decisive for the significant meal effect (higher overall attention scores in the Mediterranean-type diet meal than in the Western diet high-fat meal) in the present trial, or to what extent the interaction of different nutrients contributed to the observed effects.

Impaired insulin sensitivity / insulin resistance as a major characteristic of the metabolic syndrome is associated with an exaggerated postprandial glycemic response after meal intake (Ormazabal et al. 2018; Edinburgh et al. 2017; Beilby 2004). To evaluate the effect of insulin resistance on postprandial glucose and insulin concentrations in the present trial, the homeostasis model assessment for insulin resistance (HOMA-IR) was calculated according to Matthews et al., 1985 (calculation of mean HOMA-IR for the four treatment days for each participant). Postprandial glucose and insulin concentrations were compared in dependence on this factor (Matthews et al. 1985). In the present study, 73% of participants (n = 19) had an HOMA-IR > 2.5, which indicates possible insulin resistance. For the remaining 27% of participants (n = 7) the calculations resulted in HOMA-IR < 2.5. **Figure 4-1** compares the iAUC for plasma glucose and serum insulin concentrations for the four treatment groups in dependence on HOMA-IR and shows exaggerated

plasma glucose and especially serum insulin concentrations in participants with HOMA-IR > 2.5. This confirms the association between insulin resistance and an exaggerated postprandial glycemic response, which might have influenced the observed intervention effects on mean glucose and insulin concentrations in the postprandial period.

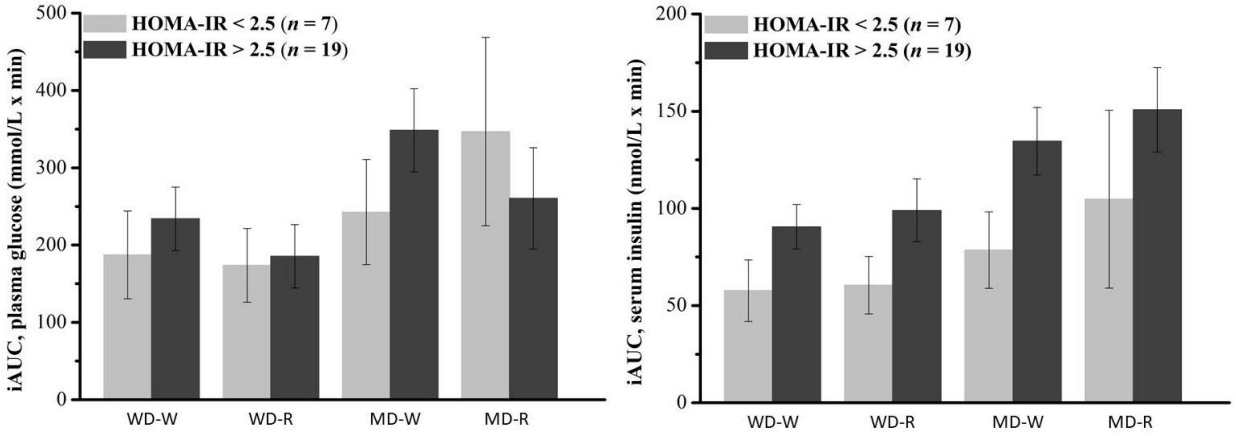

Figure 4-1 Comparison of iAUC for plasma glucose and serum insulin concentrations in all four treatment groups in dependence of HOMA-IR. Data show exaggerated plasma glucose and especially serum insulin concentrations in participants with HOMA-IR > 2.5. HOMA-IR, Homeostasis model assessment for insulin resistance; iAUC, Incremental area under the curve; MD-R, Mediterranean-type diet meal plus postprandial resting; MD-W, Mediterranean-type diet meal plus postprandial walking; WD-R, Western diet high-fat meal plus postprandial resting; WD-W, Western diet high-fat meal plus postprandial walking.

Robertson et al., 2002 demonstrated that the extent to which postprandial glucose concentration increases during an oral glucose tolerance test seems to be dependent on the amount of dietary fat consumed the night before the treatment day. Similarly, postprandial triglyceride concentrations after an oral fat tolerance test seem to be higher after a high-carbohydrate, than after a high-fat evening meal (Robertson et al. 2002). The impact of previous macronutrient consumption on the subsequent metabolism of meal carbohydrate and fat is described as “second meal effect”, which has to be taken into consideration while planning postprandial intervention studies (Lambert and Parks 2012). To account for this phenomenon in the present trial, participants were asked to consume the same evening meal prior to each treatment day, which had to be specifically documented as part of the 1-day food diary participants completed on the four pre-treatment days. The comparison of mean energy, macronutrient, and dietary fiber intake using one-way ANOVA showed no significant differences between the four prior-treatment evening meals (**Table 4-1**). However, especially due to the high intra-individual variance in intake of energy and macronutrients (intra-individual coefficient of variation: energy, 23%; fat, 35%; carbohydrate, 28%; dietary fiber, 29%; protein, 30%), it cannot be ruled out that the different carbohydrate and fat intake during prior evening meals may have influenced postprandial glycemic and lipemic

responses on the individual treatment days differently. However, since the fasting concentrations of all outcome measures did not differ significantly between the four treatment days (similar starting point) it can be assumed that the "second meal effect" was not predominant in the present trial. Particularly for studies with the aim to examine the effect of multiple meal intakes (e.g., three meals per treatment day) on postprandial metabolism, considering "second meal effect", as well as the consideration of summative metabolic responses of both carbohydrate and lipids, might be of particular importance.

Table 4-1 Energy, macronutrient and dietary fiber intake of participants during prior-treatment evening meals[1]

	V 1	V 2	V 3	V 4	*P*-value[2]
Energy (kcal)	590 ± 217	672 ± 263	634 ± 249	634 ± 241	0.691
Fat (g)	29.2 ± 17.5	32.6 ± 17.7	30.4 ± 18.0	28.3 ± 16.4	0.824
Carbohydrate (g)	52.3 ± 25.8	57.2 ± 23.6	58.6 ± 25.8	60.1 ± 28.8	0.722
Dietary fiber (g)	6.4 ± 3.6	7.7 ± 5.1	7.1 ± 3.2	6.9 ± 3.7	0.448
Protein (g)	26.1 ± 11.3	32.2 ± 18.4	26.0 ± 16.0	28.1 ± 15.6	0.658

[1]Data from 1-d food diaries; Shown as mean ± SD, $n = 26$.
[2]Compared using one-way ANOVA.

Research suggests that glucose and lipid metabolism is influenced by central (brain) and peripheral (skeletal muscle, liver, adipose tissue) circadian rhythms (Heden and Kanaley 2019). In this context, in metabolically healthy individuals, optimal liver and peripheral insulin sensitivity and glycemic control seems to be measurable in the morning hours and worsens through the remainder of the day. In individuals with manifested type 2 diabetes, circadian rhythms for these parameters seem to be inverted (Heden and Kanaley 2019; Poggiogalle et al. 2018). Therefore, circadian rhythms of metabolic parameters might be another important factor which has to be taken into consideration while planning dietary intervention trials and evaluating postprandial plasma glucose, serum insulin, and serum triglyceride concentrations (Wallis and Gonzalez 2019). In the present trial each participant received individual time schedules which provided that all interventions (meal intake and walking / resting session), measurements, and blood analyses on each of the four study days were carried out at the same time of day. Since each participant served as its own control (crossover design), this procedure was the best possible standardization to account for circadian rhythm.

In contrast to previous postprandial interventions trials examining the effect of postmeal exercise on postprandial lipidemia, physical activity in the present trial did not result in mitigating effects on serum triglycerides in the postprandial period. On the one hand, the rather short duration and low intensity of the walking session might have been responsible for the observed results. On the other hand, it is possible that the missing effect of walking on postprandial triglyceride concentrations was related to the timing of the exercise session. Research suggests that exercise-induced reductions in postprandial triglycerides are more profound in premeal, rather than in postmeal exercise (Plaisance and Fisher 2014; Malkova and Gill 2006). Exercise timing might be the reason for the observed effects on postprandial glucose and insulin concentrations (exaggerated glycemic response after walking compared to resting) as well: Exercise performed in the early postprandial period (0 – 29 min post-meal intake), seems to result in elevated plasma glucose concentrations due to stimulated hepatic glucose output, which rises up to 8-fold, especially when exercise intensity is high (> 80% VO_{2max}) (glucose becomes the main fuel). Exercise sessions of low-to-moderate intensity (< 80% VO_{2max}) performed during the mid-postprandial period (30 – 120 min post-meal intake) preferentially use meal-derived glucose without precipitating counter-regulation (Chacko 2016). Future postprandial intervention trials might consider planning the exercise session with respect to food intake (e.g., postmeal vs. premeal walking), especially for individuals with increased CVD risk, in order to optimize the health and therapeutic benefits of exercise (Wallis and Gonzalez 2019).

Solomon et al., 2018 indicate that the beneficial effect of physical exercise in glycemic control shows inter-individual variability, resulting in some individuals experiencing no plasma glucose lowering effects of exercise at all. This hypothesis emphasizes the importance of personalized exercise recommendations taking into account different modifiable factors (e.g., exercise-meal timing, exercise type, exercise dose), as well as, if feasible, non-controllable factors such as genetic disposition and individual practicability (Solomon et al. 2018). Regarding genetic disposition, the apolipoprotein E (apoE) genotype might be an important factor predicting the extent of postprandial lipidemia, especially in patients with the metabolic syndrome (Cardona et al. 2005). The apoE gene is central to the metabolism of LDL and triglycerides and has been associated with increased risk of cardiovascular (e.g., coronary heart disease), and neurodegenerative (e.g., AD and dementia) diseases (Plourde 2018; Phillips 2017; Haan and Mayeda 2010). The polymorphic protein apoE codifies three different alleles (E2, E3, and E4) which account for apoE polymorphism and determine six different genotypes (APOE ε2/ε2, APOE ε2/ε3, APOE ε2/ε4, APOE ε3/ε3, APOE ε4/ε3, and APOE ε4/ε4) (Marrzoq et al. 2011; Mahley and Rall 2000; Paik et al. 1985). The apoE3 allele is regarded as the neutral parent isoform and is the most prevalent especially in people of

Northern European ancestry. It accounts for no increased risk for cardiovascular or neurodegenerative diseases (Haan and Mayeda 2010). In comparison to the apoE3 allele, the apoE4 allele is associated with higher serum concentrations of total and LDL cholesterol. This seems to be the main reason why individuals with apoE4 genotype, even carriers of one apoE4 allele, are at increased risk for atherosclerosis and concomitant cardiovascular outcomes; homozygosity seems to increase risk even further (Marrzoq et al. 2011). Research suggests that there might be a continuous decrease in apoE4 allele prevalence after 60 years of age, especially for homozygotes. This, however, might by confounded by the combined mortality from cardiovascular and neurodegenerative diseases with increasing age (Heffernan et al. 2016; McKay et al. 2011). The apoE2 allele is associated with lower serum concentrations of total and LDL cholesterol compared to the apoE3 allele. In a meta-analysis from Zhang et al., 2015, the apoE2 allele is even associated with decreased CVD risk (Zhang et al. 2015; Marrzoq et al. 2011). On the other hand, individuals with apoE2 genotype show higher serum triglyceride concentrations. Homozygosity (APOE ε2/ε2) seems to be a necessary genetic influence that, together with additional genetic or environmental risk factors, may lead to the development of type III hyperlipoproteinemia (Utermann et al. 1979). The distribution of the apoE genotypes in the present study was APOE ε3/ε3, 85% (n = 22); APOE ε4/ε3, 8% (n = 2); APOE ε2/ε3, 4% (n = 1); APOE ε2/ε4; 4% (n = 1). Thus, despite their increased CVD risk (compare Table 2-1 Baseline characteristics of participants at high risk of cardiovascular disease, in CHAPTER 2: MANUSCRIPT 1), none of the participants had a homozygote APOE ε4/ε4 genotype. Only three participants were heterozygote for the apoE4 allele. Due to uneven distribution of data, the apoE genotype was not included as covariate / influencing factor in the statistical analysis of the present study. However, the observed data put the impact of genetic susceptibility on the development of cardiovascular / neurodegenerative outcomes in perspective, and emphasize the importance of lifestyle factors in this context. Future intervention trials in this field of research might consider prospective apoE-genotyping during screening analysis in order to be able to recruit an equal number of APOE ε3/ε3, APOE ε4/ε3, and APOE ε4/ε4 participants. This would allow determining the effects of meal composition and physical activity on postprandial events in dependence on apoE genotype.

In the present study, the postprandial rise in serum triglycerides, plasma glucose, and serum insulin concentrations did not trigger a postprandial oxidative stress response and concomitant endothelial dysfunction, which would have been expected due to current model ideas (Wallace et al. 2010). Next to oxLDL, additional biomarkers would have been warranted to further elucidate the postprandial oxidative stress response. Since oxidative stress is difficult to measure, evaluation based on more than one criterion might be reasonable, whereby giving an overall index of redox

status should be focused in future intervention trials (Marrocco et al. 2017). Due to scheduling reasons, additional measurements which would have evaluated endothelial function more specifically (e.g., flow mediated dilatation of the brachial artery), could not be included in the present study. However, this might be necessary to consider in future similar intervention trials, to be able to fully evaluate the matters of endothelial dysfunction in the postprandial period (Al-Qaisi et al. 2008).

Independent of nutrient composition, both high-energy, high-fat meal types triggered a transient rise in postprandial IL-6 concentrations over time. Since IL-6 did not reach baseline concentration at 4.5 h postprandially, it can be hypothesized, that the stimulus of meal consumption was high enough to trigger a postprandial low-grade inflammatory response. Additional time points in the later postprandial period (4 – 8 h postprandially) would have been necessary to further examine the impact of the test meals on this parameter. Current research suggests that chronic low-grade inflammation is associated with altered brain signaling patterns affecting cognition. Furthermore, it seems to interact with neurotransmitters and neurocircuits to influence the risk for depression. This might be one reason why different chronic diseases (e.g., diabetes, CVD) are characterized by increased risk for depressive disorders (Felger 2019; Amodeo et al. 2017). Interactions between immune and metabolic processes are known to be evolutionarily conserved. Furthermore, scientific evidence regarding the complex immunometabolic signaling networks and cellular and molecular events involved is constantly emerging (Hotamisligil 2017a, 2017b). Therefore, future intervention trials might shift the focus from analysis of proinflammatory cytokines in the blood stream and the analysis of gene-expression of these parameters; additionally measuring the activation of macrophages or other innate immune cells, which are known to participate in the process, might be reasonable (Hotamisligil 2017a, 2017b). In the present study, higher IL-6 concentrations could be observed after walking compared to resting, which might have been due to the skeletal muscle release of IL-6 as an anti-inflammatory myokine. Even though acute activity sessions already seem to exert anti-inflammatory effects, the regular engagement in physical activity needs to be recommended to optimally benefit regarding the prevention and treatment of cardiovascular and neurodegenerative diseases (Phillips and Fahimi 2018; Gleeson et al. 2011; Dinas et al. 2011).

Conclusion

The present trial examined the effects of meal composition and physical activity on physiological and neuropsychological outcome measures in the postprandial period. In this context, the study followed a holistic approach (effects of meals rather than single nutrients) and included a physical activity session that can easily be incorporated into everyday situations. Regarding the effect of meal composition alone, the Mediterranean-type diet meal resulted in reduced postprandial triglyceride and NEFA concentrations compared to the Western diet high-fat meal. Furthermore, the Mediterranean-type diet meal led to better overall attention scores in the postprandial period as well as increased satiety. Contrary to our hypotheses, moderate walking in the postprandial period, as compared to remaining sedentary, did neither result in attenuated postprandial events nor in increased postprandial attention or a better subjective mood. Overall, in older adults at increased risk for cardiovascular and neurodegenerative diseases, none of the four treatment conditions (Western diet high-fat meal plus postprandial walking; Western diet high-fat meal plus postprandial resting; Mediterranean-type diet meal plus postprandial walking; Mediterranean-type diet meal plus postprandial resting) can be particularly recommended to optimally reduce postprandial metabolic, inflammatory, endothelial and oxidative events, and to improve postprandial attention and mood. However, due to the steady rise in obesity and metabolic syndrome in recent years, the need for targeted dietary and lifestyle strategies for primary and secondary prevention of concomitant cardiovascular and neurodegenerative complications is constantly increasing. Therefore, further hypothesis-driven postprandial intervention trials reflecting realistic lifestyle conditions are warranted in order to be able to further develop scientifically based prevention recommendations in the long term.

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SUMMARY

The postprandial state is a dynamic period of metabolic processes that occur following the digestion and absorption of a meal. Current research suggests that a chronic oversupply of macronutrients and total energy and the resulting prolonged and exaggerated postprandial metabolic events (glycemia, insulinemia, and lipidemia) that repeat multiple times each day, lead to a short-term oxidative imbalance, a status referred to as postprandial oxidative stress. This status is further associated with low-grade inflammation and low-grade endothelial dysfunction. Altogether, these processes may increase the susceptibility to the development of cardiovascular diseases (CVD) in the long term. Therefore, attenuating the postprandial stress response and its associated events through specific nutritional and lifestyle interventions seems to be a promising and important approach, which is particularly relevant in individuals already at increased risk to develop cardiovascular or neurodegenerative complications (e.g., individuals with metabolic syndrome).

The present study followed a holistic approach and examined the effects of meal composition and moderate physical activity on postprandial events in 26 older subjects with increased risk for the development of cardiovascular and neurodegenerative diseases (age 70 ± 5 y; BMI 30.3 ± 2.3 kg/m^2). In a randomized crossover design, two high-energy meals reflecting different dietary patterns (Mediterranean-type diet meal, MD; Western diet high-fat meal, WD) were combined with either 30-minutes of postprandial moderate walking or 30-minutes of postprandial resting. Next to metabolic outcomes (serum triglycerides, serum non-esterified fatty acids, plasma glucose, serum insulin) the present study included selected oxidative (plasma oxidized low density lipoprotein), endothelial (plasma soluble intercellular adhesion molecule-1, plasma soluble vascular cell adhesion molecule-1, serum soluble endothelial selectin), and inflammatory (plasma interleukin-6) parameters, as well as blood pressure and heart rate. Additional focus was set on neuropsychological parameters (attention, mood, and the feeling of hunger and satiety) and plasma cortisol concentration. All outcome measures were analyzed at fasting and 1.5 h, 3.0 h, and 4.5 h postprandially.

The study tested the following hypotheses: i) a MD generates a lower postprandial response than a WD; ii) moderate walking in the postprandial period as compared to remaining sedentary, results in attenuated postprandial events; iii) a MD generates higher postprandial satiety, postprandial attention, and a better subjective mood than a WD; and iv) moderate walking in the postprandial period as compared to remaining sedentary, results in increased postprandial attention and a better subjective mood.

In comparison to the WD, the MD was associated with superior effects on several postprandial parameters (e.g., lower serum triglyceride concentration). Contrary to our hypothesis, data revealed no beneficial effects of walking over resting. Furthermore, meal composition had no relevant impact on attention and mood. However, after the WD, resting instead of walking resulted in increased postprandial attention. Additionally, the MD led to a stronger and longer-lasting feeling of satiety, compared to the WD.

Overall, none of the four treatment conditions could be particularly recommended to optimally reduce postprandial metabolic, oxidative, inflammatory, and endothelial events, and to improve postprandial attention and mood. However, due to the steady rise in obesity and metabolic syndrome in recent years, the need for targeted dietary and lifestyle strategies for primary and secondary prevention of concomitant cardiovascular and neurodegenerative complications is constantly increasing. Therefore, further hypothesis-driven postprandial intervention trials reflecting realistic lifestyle conditions are warranted in order to be able to further develop scientifically based prevention recommendations in the long term.

ZUSAMMENFASSUNG

Der postprandiale Stoffwechsel beschreibt die Gesamtheit aller dynamischen Stoffwechselprozesse, welche im Anschluss an den Mahlzeitenverzehr im Organismus zu verzeichnen sind. Aktuelle Forschungsergebnisse deuten darauf hin, dass ein chronisches Überangebot and Makronährstoffen, bedingt durch den regelmäßigen Verzehr energiereicher Mahlzeiten, zu verstärkten metabolischen Reaktionen (längere Dauer, höheres Ausmaß) führt (Hyperglykämie, Hyperinsulinämie, Hyperlipidämie), welche in einer geringgradigen oxidativen Stressreaktion resultieren. Dieser Zustand wird als postprandialer oxidativer Stress bezeichnet. Der postprandiale oxidative Stress wird weiterhin mit einer geringgradigen postprandialen Inflammation und einer geringgradigen postprandialen endothelialen Dysfunktion assoziiert. In ihrer Gesamtheit scheinen diese Prozesse langfristig mit einem erhöhten Risiko für die Entwicklung kardiovaskulärer Erkrankungen (CVD) einher zu gehen. Die Abschwächung der postprandialen Stoffwechselreaktionen über spezifische Ernährungs- und Lebensstilmaßnahmen stellt einen vielversprechenden und wichtigen Forschungsansatz dar, welcher insbesondere für Personen mit erhöhtem Risiko für kardiovaskuläre und neurodegenerativer Erkrankungen (z.B. Personen mit Metabolischem Syndrom) eine hohe Relevanz hat.

Die vorliegende Studie verfolgte einen ganzheitlichen Ansatz und untersuchte die Effekte von Mahlzeitenzusammensetzung und moderater Bewegung auf den postprandialen Stoffwechsel, bei 26 älteren Personen mit erhöhtem Risiko für kardiovaskuläre und neurodegenerative Erkrankungen (70 ± 5 Jahre; BMI 30,3 ± 2,3 kg/m^2). Im Rahmen eines randomisierten crossover Designs wurden zwei energiereiche Mahlzeiten, welche in ihrer Zusammensetzung an das Mediterrane- bzw. das Westliche Ernährungsmuster angelehnt waren (*Mediterranean-type diet meal*, MD; *Western-diet high fat meal*, WD), mit einer 30-minütigen postprandialen Walking-Einheit, oder einer 30-minütigen postprandialen Ruhephase kombiniert. Die Zielgrößen der Studie umfassten metabolische (Serum-Triglyceride, Serum-Freie Fettsäuren und Serum-Insulin, Plasma-Glucose), oxidative (oxidiertes *low density lipoprotein* im Plasma), inflammatorische (Interleukin-6 im Plasma) und endotheliale (*soluble intercellular adhesion molecule-1* und *soluble vascular cell adhesion molecule-1* im Plasma, *soluble endothelial selectin* im Serum) Parameter, sowie Blutdruck und Herzfrequenz. Zudem wurden neuropsychologische Parameter (Aufmerksamkeit, Befindlichkeit, Sättigungsempfinden) und die Plasma Cortisol Konzentration erfasst. Die folgenden Hypothesen wurden der Studie zugrunde gelegt: i) eine MD resultiert in einer abgeschwächten postprandialen Stoffwechselantwort im Vergleich zu einer WD; ii) eine postprandiale Walking-Einheit resultiert in einer abgeschwächten postprandialen Stoffwechselantwort im Vergleich zu

einer postprandialen Ruhephase; iii) eine MD resultiert in einem erhöhten Sättigungsempfinden und einer verbesserten Aufmerksamkeit und Stimmung im Vergleich zu einer WD; und iv) eine postprandiale Walking-Einheit resultiert in einer verbesserten postprandialen Aufmerksamkeit und Stimmung im Vergleich zu einer postprandialen Ruhephase. Alle Zielgrößen wurden nüchtern erfasst, sowie 1,5 h, 3,0 h und 4,5 h postprandial.

Im Vergleich zur WD zeigte die MD einen günstigeren Einfluss auf den postprandialen Verlauf einzelner Parameter (z.B. niedrigere Triglycerid-Konzentration im Serum). Entgegen unserer Erwartungen zeigte das moderate Walking keine vorteilhafteren Effekte im Vergleich zur Ruhephase. Weiterhin nahm die Mahlzeitenzusammensetzung keinen relevanten Einfluss auf Aufmerksamkeit und Stimmung in der postprandialen Phase. Nach dem Verzehr der WD wirkte sich die Ruhephase im Vergleich zur Walking-Einheit verbessernd auf die postprandiale Aufmerksamkeit aus. Darüber hinaus führte der Verzehr der MD zu einem stärkeren und länger anhaltenden Sättigungsempfinden.

Zusammenfassend ist festzuhalten, dass keine der vier Interventionsgruppen besonders empfohlen werden kann, um postprandiale metabolische, oxidative, inflammatorische und endotheliale Ereignisse optimal zu reduzieren und um Aufmerksamkeit und Stimmung in der postprandialen Phase zu verbessern. Aufgrund des stetigen Anstiegs von Adipositas und dem Metabolischen Syndrom in der heutigen Gesellschaft steigt jedoch der Bedarf an gezielten Ernährungs- und Lebensstilmaßnahmen zur Primär- und Sekundärprävention kardiovaskulärer und neurodegenerativer Ereignisse weiterhin an. Nicht zuletzt deshalb sind weitere realitätsnahe postprandiale Interventionsstudien unabdingbar, um langfristig Präventionsempfehlungen wissenschaftlich fundiert weiterentwickeln zu können.