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Health benefits of oat (Avena sativa) bioactives. Acute and second-meal effects of oat polar lipids and beta-glucans.

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2024

Document Version:
Publisher's PDF, also known as Version of record

Link to publication

Citation for published version (APA):
Hossain, M. M. (2024). *Health benefits of oat (Avena sativa) bioactives. Acute and second-meal effects of oat polar lipids and beta-glucans.* Department of Process and Life Science Engineering, Lund University.

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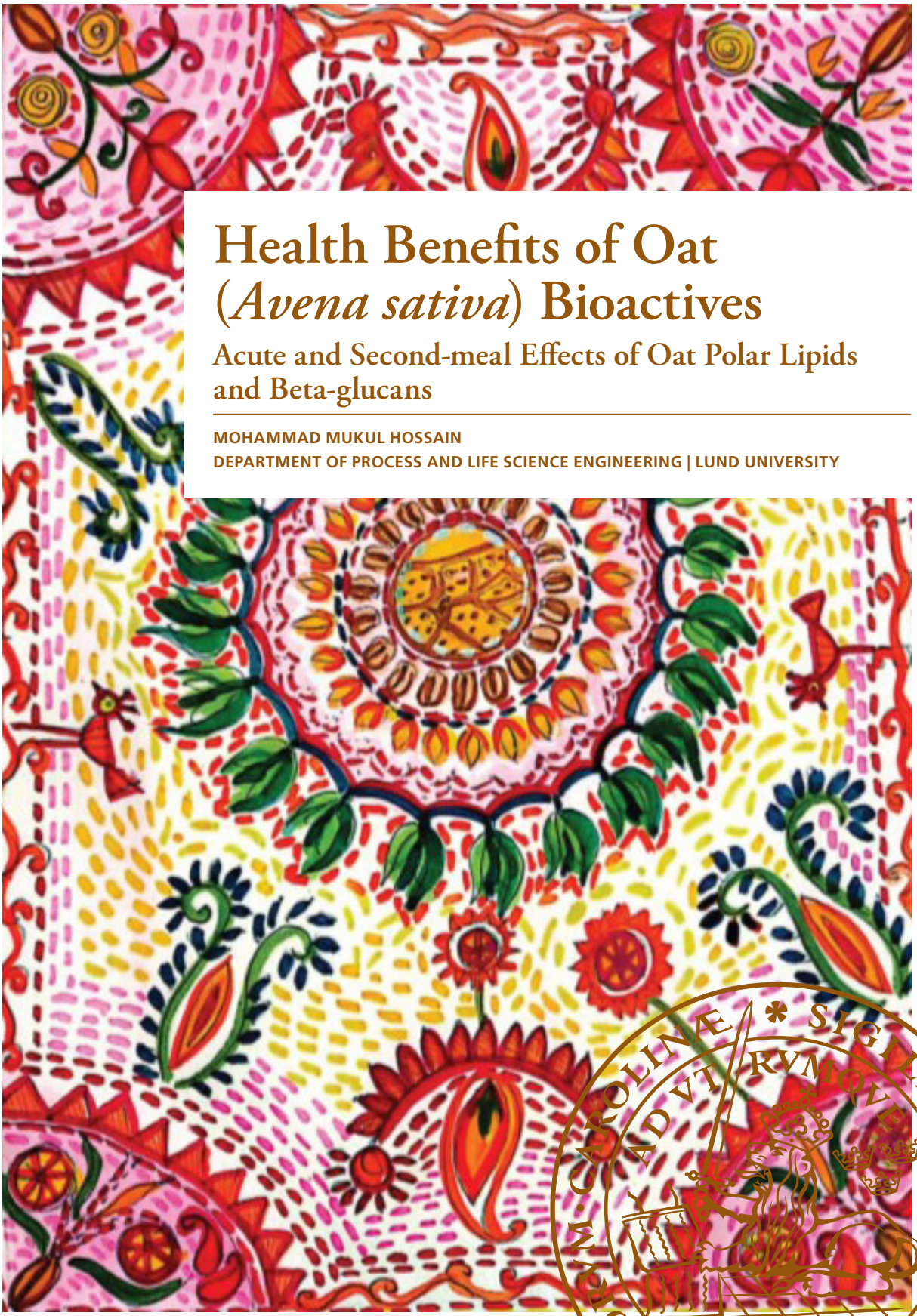

Health Benefits of Oat (*Avena sativa*) Bioactives

Acute and Second-meal Effects of Oat Polar Lipids and Beta-glucans

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Acute and Second-meal Effects of Oat Polar Lipids and Beta-glucans

Mohammad Mukul Hossain

LUND
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DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Engineering at Lund University to be publicly defended on Thursday, 13 June 2024 at 09.00 in Lecture Hall A, Kemicentrum, Naturvetarvägen 14, Lund.

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Organization: LUND UNIVERSITY

Document name: Doctoral thesis **Date of issue: 2024-06-13**

Author: Mohammad Mukul Hossain **Sponsoring organization: ScanOats, The Swedish Foundation for Strategic Research**

Title and subtitle: Health benefits of oat (*Avena sativa*) bioactives. Acute and second-meal effects of oat polar lipids and beta-glucans.

Abstract: The global prevalence of lifestyle-related diseases, including obesity, type 2 diabetes and cardiovascular diseases, continues to increase. Dietary habits are the most significant contributing modifiable factor in this context. A healthy diet must thus form part of successful preventive strategies to combat cardiometabolic diseases.

Oats are a sustainable cereal, rich in potential health-promoting bioactive compounds, such as polar lipids, soluble dietary fibres like beta-glucans and arabinoxylans, antioxidants and avenanthramides.

The present thesis explores the health potential of oat-derived bioactives, focusing on polar lipids and beta-glucans. Four intervention studies in healthy young adults were conducted to investigate postprandial metabolic effects of test foods enriched with oat polar lipids (OPL) or beta-glucans. Postprandial metabolic regulation, e.g. control of glycemia and triglyceridemia, is an important determinant of the development of cardiometabolic disorders. In this thesis work, the test products were consumed at breakfast and cardiometabolic disease-related biomarkers were measured in blood repeatedly, both after breakfast and after a standardised lunch without the bioactive compounds.

The results indicate that OPL (12–15g) included in a breakfast (liquid or solid meal) beneficially impact blood glucose regulation and circulating triglyceride (TG) concentrations acutely after the breakfast, but also after the standardised lunch meal. Furthermore, OPL increase the release of satiety-promoting gut hormones such as GLP-1 and PYY, and reduce the release of the hunger-inducing hormone ghrelin. Since GLP-1 analogues are effective drugs against type 2 diabetes and obesity, the effects of OPL on the release of gut hormones become interesting. It was also shown that a commercially available polar lipid preparation (sunflower lecithin) exerts similar effects to those of OPL.

This work also demonstrates that consumption of beta-glucans from oats improves postprandial glycaemic responses and subjective appetite sensations acutely after breakfast and after the subsequent lunch. Also noteworthy was that 2g oat beta-glucans lower the blood glucose peak after a meal, which is an appreciably lower dose than the 4g dosage stated in the health claim of the European Food Safety Authority (EFSA). This finding may facilitate the commercial application of beta-glucans in products for the dietary management of postprandial glycemia.

In conclusion, the thesis shows that consumption of OPL and beta-glucans included in a meal improves acute and second-meal postprandial glucose tolerance, reduces circulating TG and enhances secretion of appetite-regulating hormones in healthy young adults. Another remarkable observation is that relatively low amounts of beta-glucans may reduce blood glucose peaks, in doses below the EFSA's recommended ones. The new knowledge generated in this doctoral thesis can contribute to the development of innovative food products with preventive potential against cardiometabolic diseases.

Key words: Oats, polar lipids, beta-glucans, DGDG, dietary prevention, obesity, MetS, type 2-diabetes, glucose tolerance, second-meal effects, GLP-1, PYY, ghrelin, appetite regulation

Language: English **ISSN and key title**:

ISBN: 978-91-8096-042-7 (print), 978-91-8096-043-4 (digital)

Recipient's notes **Number of pages**: 97

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Acute and Second-meal Effects of Oat Polar Lipids and Beta-glucans

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Lund Univesity, Faculty of Engineering
Department of Process and Life Science Engineering
Division of Food and Pharma
ISBN 978-91-8096-042-7 (print)
ISBN 978-91-8096-043-4 (digital)

Printed in Sweden by Media-Tryck, Lund University
Lund 2024

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MADE IN SWEDEN

To Anne Nilsson and Juscelino Tovar, for their advice, patience and faith in my abilities. Because they always understood, even when I did not.

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Abstract

The global prevalence of lifestyle-related diseases, including obesity, type 2 diabetes and cardiovascular diseases, continues to increase. Dietary habits are the most significant contributing modifiable factor in this context. A healthy diet must thus form part of successful preventive strategies to combat cardiometabolic diseases.

Oats are a sustainable cereal, rich in potential health-promoting bioactive compounds, such as polar lipids, soluble dietary fibres like beta-glucans and arabinoxylans, antioxidants and avenanthramides.

The present thesis explores the health potential of oat-derived bioactives, focusing on polar lipids and beta-glucans. Four intervention studies in healthy young adults were conducted to investigate postprandial metabolic effects of test foods enriched with oat polar lipids (OPL) or beta-glucans. Postprandial metabolic regulation, e.g. control of glycemia and triglyceridemia, is an important determinant of the development of cardiometabolic disorders. In this thesis work, the test products were consumed at breakfast and cardiometabolic disease-related biomarkers were measured in blood repeatedly, both after breakfast and after a standardised lunch without the bioactive compounds.

The results indicate that OPL (12–15g) included in a breakfast (liquid or solid meal) beneficially impact blood glucose regulation and circulating triglyceride (TG) concentrations acutely after the breakfast, but also after the standardised lunch meal. Furthermore, OPL increase the release of satiety-promoting gut hormones such as GLP-1 and PYY, and reduce the release of the hunger-inducing hormone ghrelin. Since GLP-1 analogues are effective drugs against type 2 diabetes and obesity, the effects of OPL on the release of gut hormones become interesting. It was also shown that a commercially available polar lipid preparation (sunflower lecithin) exerts similar effects to those of OPL.

This work also demonstrates that consumption of beta-glucans from oats improves postprandial glycaemic responses and subjective appetite sensations acutely after breakfast and after the subsequent lunch. Also noteworthy was that 2g oat beta-glucans lower the blood glucose peak after a meal, which is an appreciably lower dose than the 4g dosage stated in the health claim of the European Food Safety Authority (EFSA). This finding may facilitate the commercial application of beta-glucans in products for the dietary management of postprandial glycemia.

In conclusion, the thesis shows that consumption of OPL and beta-glucans included in a meal improves acute and second-meal postprandial glucose tolerance, reduces circulating TG and enhances secretion of appetite-regulating hormones in healthy young adults. Another remarkable observation is that relatively low amounts of beta-glucans may reduce blood glucose peaks, in doses below the EFSA's

recommended ones. The new knowledge generated in this doctoral thesis can contribute to the development of innovative oat-based food products with preventive potential against cardiometabolic diseases.

Popular scientific summary

In recent decades, there has been a significant increase in lifestyle-related diseases, including obesity, type 2 diabetes and cardiovascular diseases. According to the International Diabetes Federation, there were 536 million individuals diagnosed with diabetes in 2022, and this number is projected to increase to 780 million by 2045. Healthcare systems are under pressure and call for urgent solutions, in which prevention, as a sustainable approach, must complement the current paradigm of treatment. Dietary habits are the most significant contributing modifiable factors in this context. A healthy diet must thus form part of successful preventive strategies against cardiometabolic diseases.

Oats (Avena sativa) have been cultivated for thousands of years. Initially, however, they were found as a weed among other cereals such as wheat and barley. Oats are now recognised as a sustainable cereal grain, occupying the sixth position in global grain production rankings. Oats have been grown in Nordic countries since the Middle Ages, and cultivation of the cereal substantially increased due to weather conditions favourable for its growth. The gradual unveiling of its nutritional value has resulted in a consistent rise in popularity of oats for human consumption. They contain a wealth of potential health-promoting bioactive compounds, such as polar lipids, dietary fibres like beta-glucans and arabinoxylans, α-tocopherol, as well as polyphenols such as avenanthramides. Furthermore, oats are an excellent source of high-quality plant-based proteins, vitamins and minerals. In terms of sustainability, the global 2030 goals and health aspects, the recent Nordic Nutrition Recommendations 2023 (NNR2023) introduced a new guideline emphasising consumption of plant-based diets and a reduction of animal-based dietary choices. In this regard, oats are a versatile candidate in resolving sustainable dietary choices and can contribute to combating global lifestyle-related diseases.

The present doctoral thesis aims to explore the health potential of oat-derived bioactive compounds, with a focus on polar lipids and beta-glucans. For this purpose, four intervention studies in healthy participants were conducted. The studies focused on postprandial metabolic effects of formulated test foods enriched with polar lipids or beta-glucans. The test products were consumed at breakfast and cardiometabolic disease-related test markers were measured in blood repeatedly, both after breakfast and after a standardised lunch without the bioactive compounds, to investigate so called “second-meal” effects of the bioactives.

The present work demonstrates that intake of oat polar lipids (12–15g) included in a breakfast (liquid or solid meal) has a beneficial impact on blood glucose regulation and circulating triglyceride (TG) concentrations acutely after the breakfast, but also after the standardised lunch meal. Furthermore, oat polar lipids have the potential to increase the release of satiety-promoting gut hormones such as GLP-1 and PYY, and reduce the release of the hunger-inducing hormone ghrelin. In one of the studies,

metabolic effects of oat polar lipids were compared to those of a commercially available plant polar lipid preparation (sunflower lecithin). The results indicated sunflower lecithin exerts effects similar to those of oat polar lipids. Additionally, the results demonstrate that consumption of beta-glucans from oats improves postprandial glycaemic responses and subjective appetite sensations acutely after breakfast and after a subsequent lunch. Another notable observation was that a dose of 2g of oat beta-glucans might effectively lower the blood glucose peak after a meal, which is appreciably lower than the 4g dosage as stated by the health claim of the European Food Safety Authority (EFSA). This finding may facilitate the development of innovative products for the dietary management of postprandial blood glucose regulation.

In summary, the thesis shows that the consumption of oat polar lipids included in a meal may enhance acute and second-meal postprandial glucose tolerance, reduce circulating TG and enhance the secretion of appetite-regulating hormones in healthy young adults. Similar effects are observed after consumption of sunflower lecithin. Furthermore, it confirms that oat beta-glucans improve the acute glycaemic response, but in addition exert beneficial effects following a second meal. A remarkable observation is that relatively low amounts of oat beta-glucans may reduce blood glucose peaks, in doses below the EFSA's recommended levels. The findings in this doctoral thesis are new knowledge, which can contribute to the development of innovative oat-based food products with preventive potential against cardiometabolic diseases.

List of Papers

Paper I

Oat Polar Lipids Improve Cardiometabolic-Related Markers after Breakfast and a Subsequent Standardized Lunch: A Randomized Crossover Study in Healthy Young Adults.

Hossain, M.M.; Tovar, J.; Cloetens, L.; Florido, M.T.S.; Petersson, K.; Prothon, F.; Nilsson, A.

Nutrients 2021, 13, 988. https://doi.org/10.3390/nu13030988

Paper II

Inclusion of Oat Polar Lipids in a Solid Breakfast Improves Glucose Tolerance, Triglyceridemia, and Gut Hormone Responses Postprandially and after a Standardized Second Meal: A Randomized Crossover Study in Healthy Subjects.

Hossain, M.M.; Tovar, J.; Cloetens, L.; Nilsson, A.

Nutrients 2023, 15, 4389. https://doi.org/10.3390/nu15204389

Paper III

Oat Polar Lipids and Sunflower Lecithin similarly Improve Cardiometabolic Risk Markers and Appetite Controlling Hormone Responses after Breakfast and a Subsequent Lunch. A Randomized Crossover Study in Healthy Adults.

Hossain, M.M.; Tovar, J.; Cloetens, L.; de Kam, S. S.; Nilsson, A.; Manuscript.

Paper IV

Oat Beta-glucans Consumed at Breakfast Improves Glucose Tolerance Acutely and after a Subsequent Lunch. – A Randomized Dose Response Study in Healthy Young Adults.

Hossain, M.M.; Tovar, J.; Cloetens, L.; Geraldi1, M. V.; Venuti, C.; Nilsson, A.; Manuscript

Other Publications

Synergistic Effect of Oat Polar Lipids and Oat Beta-Glucans on Postprandial Blood Glucose: A Randomized Controlled Crossover Study in Healthy Subjects. Cloetens, L.; Hossain, M.M.; Deenissai, W.; Tovar, J.; Nilsson, A. Proceedings 2023, 91, 153. https://doi.org/10.3390/proceedings2023091153

Author's contribution to the papers

Paper I

Hossain, M.M, was involved in the study design. Coordinated the study, including participant recruitment, experimental and analytical work. Involved in statistical evaluation of results, wrote the first draft of the manuscript and was the corresponding author.

Paper II

Hossain, M.M, was involved in the study design. Coordinated the study, including participant recruitment, test and reference meals formulation, experimental and analytical work. Performed the statistical evaluation of results, wrote the first draft of the manuscript and was the corresponding author.

Paper III

Hossain, M.M, was responsible for the study design together with the co-authors. Coordinated the study, including participant recruitment, test and reference meals formulation, experimental and analytical work. Performed the statistical evaluation of results, drafted the manuscript and is responsible for its final contents.

Paper IV

Hossain, M.M, was responsible for the study design together with the co-authors. Coordinated the study, including participant recruitment, test and reference meals formulation, experimental and analytical work. Performed the statistical evaluation of results, drafted the manuscript and is responsible for its final contents.

Abbreviations

AVAs	Avenanthramides
AUC	Area under the curve
avCHO	Available carbohydrates
BMI	Body mass index
BG	Beta-glucan
CMD	Cardiometabolic disease
CVD	Cardiovascular disease
DF	Dietary fibre
DGDG	Digalactosyldiacylglycerol
EFSA	European Food Safety Authority
FFA	Free fatty acids
GLP-1	Glucagon- like peptide 1
GIP	Glucose-dependent insulinotropic polypeptide
GI	Glycaemic Index
HDL	High-density lipoprotein
IDF	International Diabetes Federation
iAUC	Incremental area under the curve
kDa	Kilodalton
LDL	Low-density lipoprotein
LPL	Sunflower lecithin
MetS	Metabolic syndrome
NNR2023	Nordic Nutrition Recommendations 2023
NL	No added lipids
OPL	Oat polar lipids
OBG	Oat beta-glucans
PL	Polar lipid
PLL	Polar lipids low dose
PLH	Polar lipids high dose

PYY	Peptide tyrosine tyrosine
RSO	Rapeseed oil
SDG	Sustainable Development Goal
SEM	Standard error of the mean
TG	Triglyceride
T2D	Type 2 diabetes
TriGDG	Trigalactosyldiacylglycerol
TetraGDG	Tetragalactosyldiacylglycerol
VLDL	Very low-density lipoprotein
WWB	White wheat bread

Introduction

Over the last several decades, there has been a concerning increase in global prevalence of lifestyle-related disorders, such as obesity, metabolic syndrome, cardiometabolic diseases (CMD, e.g. type 2 diabetes (T2D) and cardiovascular diseases (CVD)), which are considered to be a major global health and economic burden. The International Diabetes Federation (IDF) reported in 2022 that around 536 million people aged between 20 and 79 years were living with diabetes, and by 2045, prevalence is predicted to rise to 780 million [1,2]. T2D accounts for over 90% of diabetes cases and, despite being largely preventable, successful preventive measures are still lacking [3]. Readily available calorie-dense and nutritionally poor foods, refined foods, foods high in sugar, salt and saturated fats are significant contributors to the surge in lifestyle-related disorders. Immediate implementation of preventive measures is crucial in order to mitigate the global health impact.

In this regard, choice of diet is probably the most significant lifestyle-related factor that can be implemented for successful prevention of CMD. A large body of evidence indicates that consumption of bioactive components found, for instance, in whole grain foods is linked to moderate body mass index (BMI) as well as to a lesser likelihood of developing T2D and CVD. Oats are a wealth of potential health-promoting bioactive compounds, such as polar lipids, soluble dietary fibres like beta-glucans and arabinoxylans, antioxidants (i.e. α-tocopherol) and polyphenols such as avenanthramides [4,5]. Furthermore, oats are an excellent source of high-quality plant proteins [6], vitamins and minerals. In terms of sustainability, the global 2030 goals and health aspects, the recent Nordic Nutrition Recommendations 2023 (NNR2023) introduced a new guideline emphasising consumption of plant-based diets and a reduction of animal-based dietary choices [7]. In this regard, oats are versatile candidates as sustainable dietary choices that can contribute to combating global lifestyle-related diseases.

Additionally, oats contain 2–5-fold higher contents of lipids compared with other cereals [5,8,9]. Moreover, oats are rich in polar lipids (approximately 15 wt% of the lipids) [10,11]. Oat polar lipids (OPL) include phospholipids, glycolipids and sphingolipids. The most abundant polar lipid in oats is glycolipid digalactosyldiacylglycerol (DGDG and its derivatives such as TriGDG, TetraGDG and several forms of galactolipid estolides) [10,11].

Studies investigating the effects of dietary OPL on metabolic biomarkers are scarce. However, it has been suggested that OPL may exert beneficial health effects. It has been reported that a breakfast containing liposomes made from a polar lipid-rich oat oil results in increased postprandial release of the appetite hormones Glucagon-like peptide 1 (GLP-1) and Peptide tyrosine tyrosine (PYY) [12]. Furthermore, the subjective appetite sensation was improved, which led to a reduction of voluntary energy intake throughout the rest of the day [12].

Besides polar lipids, another abundant bioactive compound in oats is beta-glucans (BG). Several studies have demonstrated that consumption of oat products rich in beta-glucans (OBG) are linked to a lower postprandial glycaemic response acutely after intake, and to reduction of low-density lipoprotein (LDL) cholesterol levels in blood when ≥3g OBG is included in daily diet [13-15]. The European Food Safety Authority (EFSA) has approved a health claim stating that intake of 4g OBG per 30g available carbohydrates (avCHO) in a meal can reduce postprandial glycaemic response [16]. Nowadays, the exact dose required in a meal to lower the glycaemic response is debated because it has been demonstrated that the molecular weight of OBG plays a crucial role in this effect [17]. Additionally, studies conducted on postprandial effects of OBG on metabolic test markers have only investigated acute postprandial effects, without looking at possible effects that OBG may exert in the postprandial period after a subsequent meal ("second-meal effects").

The present PhD thesis aimed to elucidate the effects of oat polar lipids on cardiometabolic risk-related biomarkers, such as postprandial glycaemic and blood lipids responses, as well as effects on the release of appetite-regulating gut hormones, acutely after intake and following a standardised second meal. Furthermore, the thesis aimed to investigate the effect of a commercially available OBG preparation on acute and second-meal postprandial glycemia. An additional objective was to investigate whether a dose lower than 4g of OBG per 30g avCHO has the potential to improve postprandial glycaemic regulation.

The PhD thesis is based on four intervention studies in healthy young adults. All studies were conducted using an acute and second-meal study design, in which test meals were served as breakfast, and a standardised lunch without the bioactive compounds was provided three and a half hours later. The test biomarkers were determined at fasting (baseline) and repeatedly after breakfast and lunch.

Background

Oats

Oats, scientifically known as Avena sativa L. and Avena byzantiana L., are an important annual crop in the Gramineae family, commonly known as grasses. Initially, they were found as a weed among other cereals such as wheat and barley. They have ample adaptability and may grow in many countries, but thrive in temperate areas with chilly and damp conditions. Oats have been grown in Nordic countries since the Middle Ages, and their cultivation has substantially increased, partly due to the region's climate being particularly favourable for their growth. Oats are the sixth most widely cultivated grain worldwide and the third most important crop in Sweden. In 2022, global oat production was 25.13 million metric tonnes, with European Union production ranking at the top [18]. The top oat-producing countries globally in 2022 are presented in Figure 1. Oat production in Sweden has reached 0.743 million metric tonnes, with an annual export of roughly 200,000 tonnes [19]. The majority of Swedish oats are used as animal feed. However, it is worth noting that 15% of the total oats produced in Sweden are used in food production. This percentage is expected to increase in the future owing to advancements in product development and the acknowledged health benefits of this grain. Oat-based dairy alternatives have become very popular in recent years, and the market is steadily growing [20]. An oat-based dairy alternative was first introduced by Swedish scientists, who established the world's first brand, Oatly, in the 1990s [21]. They are widely recognised in plant-based meat analogues to replicate the taste, texture and appearance of traditional meat products [22]. They are used in plant-based meat alternatives due to their nutritional benefits, unique texture and capacity to effectively combine with other components, and can be used in several forms, such as oat flour, or isolates such as oat proteins, fibres, to enhance texture and mouthfeel [23,24]. Meat alternatives may be found in the form of burgers, sausages and other forms resembling typical meat products.

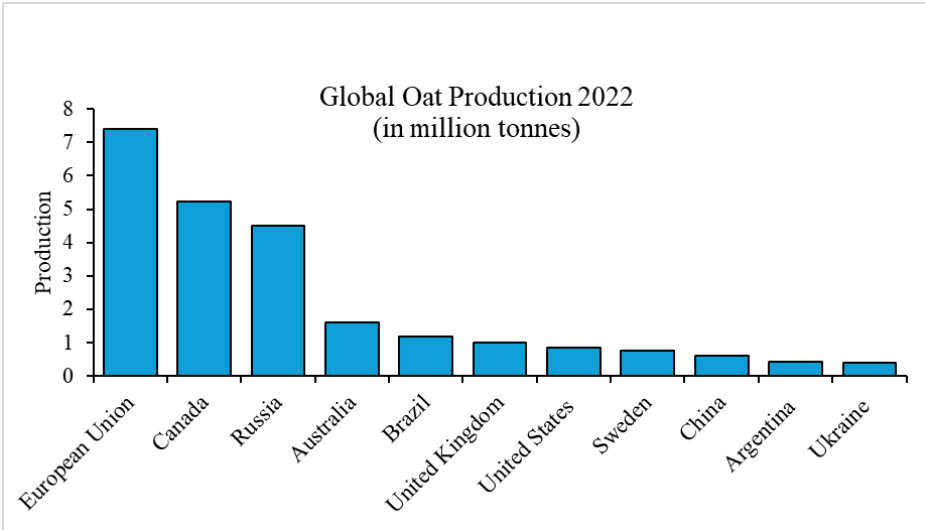


Figure 1: Global oat production in 2022. Data compiled from various sources, USDA database [18].

The oat kernel, known as the groat, constitutes the edible portion of the plant. The oat groat consists of three main components – the bran, the endosperm and the germ. The bran, which is the outermost layer, consists of the pericarp, seed coat, nucellus, aleurone layer and sub-aleurone layer (Figure 2). The endosperm, which makes up 55–80% of the grain, is mainly composed of larger cells with thinner walls [25,26]. The endosperm is rich in starch and lipids and surrounds the embryonic germ. The main constituent of oats is starch, which makes up approximately 44–64% of the groat composition [25]. Additionally, oats exhibit high lipid and protein content compared to other cereals, ranging from 5% to 20% and 10% to 20%, respectively. The lipids are mostly deposited in the endosperm, especially close to the aleurone layer and germ. The germ comprises 30–35% of the protein and 10% of the lipid content [4,27].

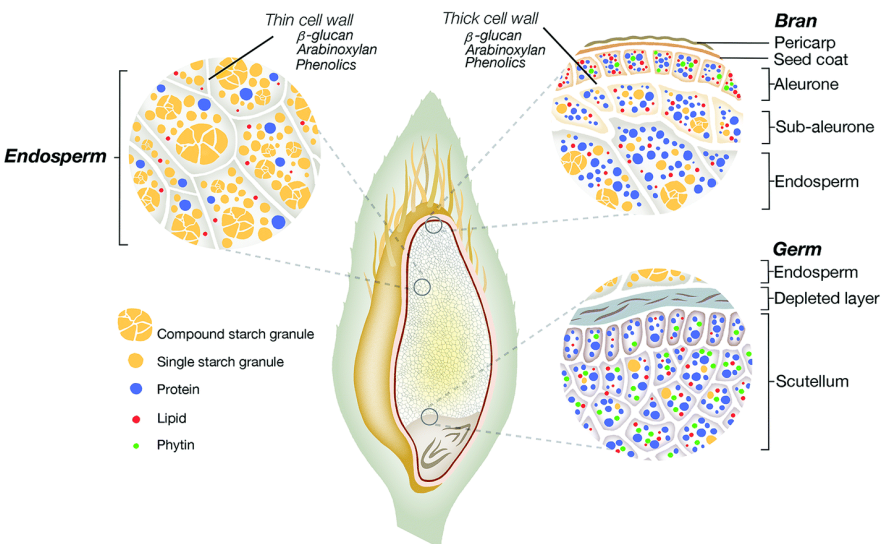
Furthermore, oats are a good source of dietary fibre (DF). One of the DF fractions is the soluble and highly viscous beta-glucans. Beta-glucans are mainly found in the bran portion, especially enriched in the sub-aleurone layers compared to the aleurone layer. The distribution of beta-glucans in oats differs from that found in barley and rye, where beta-glucans instead are spread more evenly in the groats. The general oat groats composition is presented in Table 1. The composition may vary significantly depending on the variety.

Table 1: Typical composition of oat groats[1]

Component	Range (%)
Starch	44–64
Fat	5–20
Protein	10–20
Total dietary fibre Beta-glucans Arabinaxlylan	6–11 2.1–6.8 1.5–4
Free sugars	0.8–1.5
Moisture	10–14

[1]Data are based on values obtained from various sources [5,27,28].

A



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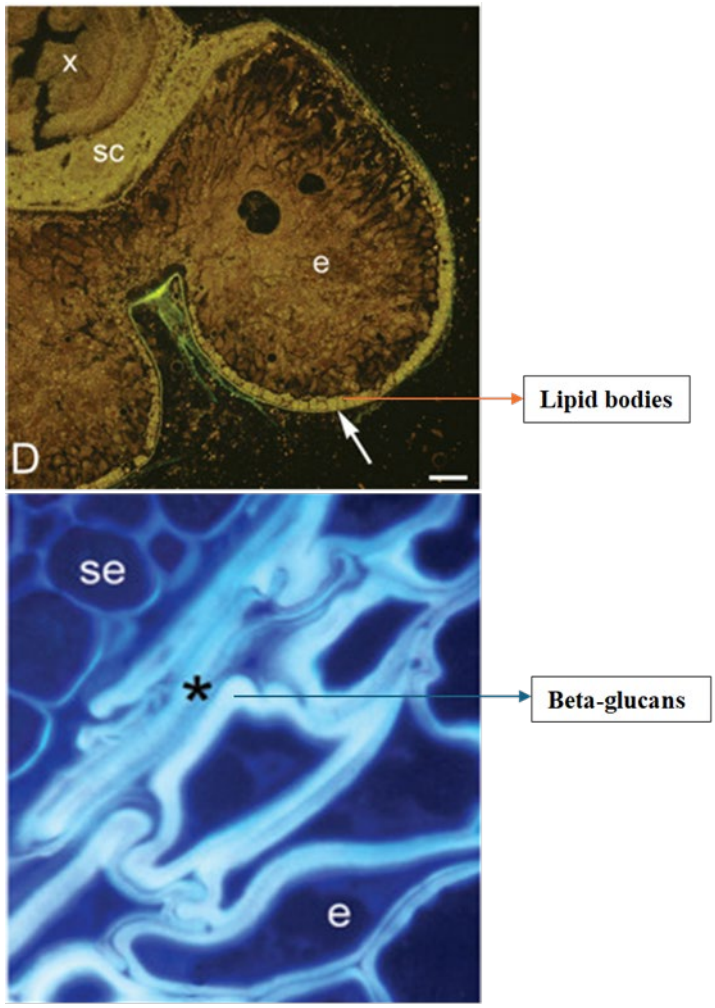

Figure 2: The composition of oat grain (**A**) and microstructure of the oat (**B**) adapted from [26,29] with permission.

Oats in relation to the global Sustainable Development Goals (SDGs)

Global food production should be conducted in a manner that supports the SDGs, adopted by all United Nations member states in 2015. The specific properties of oats make their potential relevant to a number of the 17 global SDGs.

SDG 2: Zero hunger; end hunger, achieve food security and improved nutrition, and promote sustainable agriculture. Oats are rich in energy-providing macronutrients, i.e. starch, protein and fat. Oats are thus a nutritious grain and may

help in eradicating hunger. Cultivating oats as part of sustainable agricultural methods may enhance productivity and contribute to widespread access to ample and nourishing food. Oats can be cultivated in numerous locations, with less of an environmental impact than other crops, thus promoting sustainable consumption and production practices. Oats need little water and may be cultivated without excessive use of inputs such as fertilisers and pesticides, which may have detrimental effects on the environment [30]. Consumers may promote sustainable food systems by selecting oats and other plant-based foods.

SDG 3: Good health and well-being. In addition to its energy-providing macronutrients, oats are rich in DF, vitamins, minerals and antioxidants, which are crucial for maintaining good health. The nutritional composition promotes a well-balanced diet and may aid in the prevention of food-induced lifestyle-related illnesses. Thus, incorporating oats into diets has the potential to contribute to promoting good health and well-being.

SDG 13: Climate Action. Growing oats, along with other plant-based crops, often leads to reduced greenhouse gas emissions in comparison to animal-based food production [31]. By including oats in diet, consumers may help to reduce the carbon footprint of food intake, supporting initiatives to address climate change.

SDG 15: Life on land. Oats may contribute to sustainable land use and help combat desertification, land degradation and biodiversity loss, supporting life on land. Oats may be used in crop rotation systems to enhance soil health and curb the need for chemical inputs. This sustainable technique helps to preserve environmental equilibrium and promote biodiversity [30].

SDG 17: Partnerships for the goals. Advocating for oats and plant-based diets requires cooperation between numerous sectors, such as farmers, entrepreneurs, legislators and consumers. Collaboration among these stakeholders may promote sustainable agriculture, enhance nutrition and safeguard the environment. Today, oats are mainly grown for providing feed for livestock, as summarised in Figure 3.

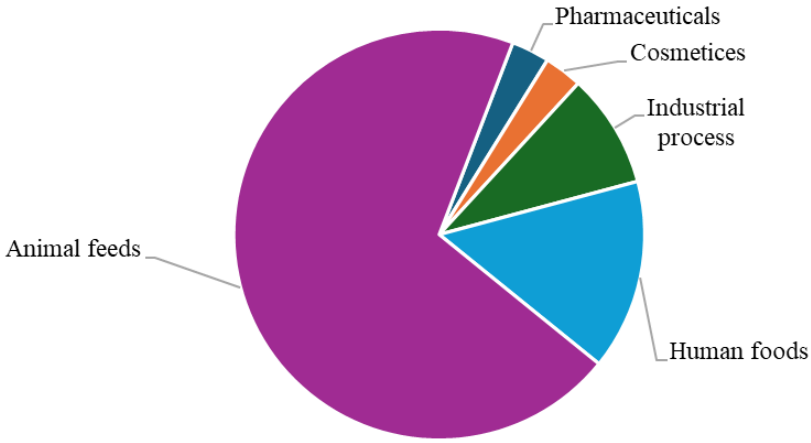

Figure 3: Commercial use and market share of oats by industry [32].

Bioactive Compounds in Oats

The term 'bioactive compound' is not yet defined in European regulations; rather, several definitions are at hand [33]. According to the different definitions, bioactive compounds can be essential or non-essential components naturally present in foods, such as fruits, vegetables, nuts, oils and wholegrains, and which have the potential to exert significant effects on health [34]. These compounds preserve their health effects even after being extracted from their source. Bioactive compounds are often referred to as functional ingredients. There has been growing interest in the effects of bioactive compounds on health and overall wellbeing in recent years [35]. Some examples of bioactive compounds in foods are polyphenols, antioxidants, carotenoids, phytosterols, polyunsaturated fatty acids and dietary fibre [36].

Oats contain a wealth of potential health-promoting bioactive compounds, such as polar lipids, dietary fibres like beta-glucans and arabinoxylans, α-tocopherol and polyphenols such as avenanthramides. Furthermore, oats are an excellent source of vitamins and minerals. This thesis focuses mainly on two specific oat bioactives – polar lipids and beta-glucans.

Oats are unique among the cereal grains due to their high content of lipids. They contain around 2–5-fold more lipids than other cereals, but may vary significantly depending on the oat variety. Oat lipids can be divided into polar and non-polar lipids. The majority of oat lipids are triglycerides (non-polar lipids), which are composed of palmitic acid 20%, oleic acid 35% and linoleic acid 40%. Lipid content

and fatty acid composition in oats are greatly influenced by the heredity, soil and climate conditions. Unlike other cereals, oat lipids are naturally rich in polar lipids (approximately 15 wt% of the lipids) such as glycolipids and phospholipids. Major fractions of oat glycolipids are DGDG (Figure 4 i) and its derivatives such as TriGDG, TetraGDG and several forms of galactolipid estolides [37]. Estolides are fatty acid esters that contain secondary ester linkages on the alkyl backbone of the molecule with a branched chain structure (Figure 4 ii), giving them special characteristics, e.g. good lubricant properties. Oat phospholipids include phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol and phosphatidylserine.

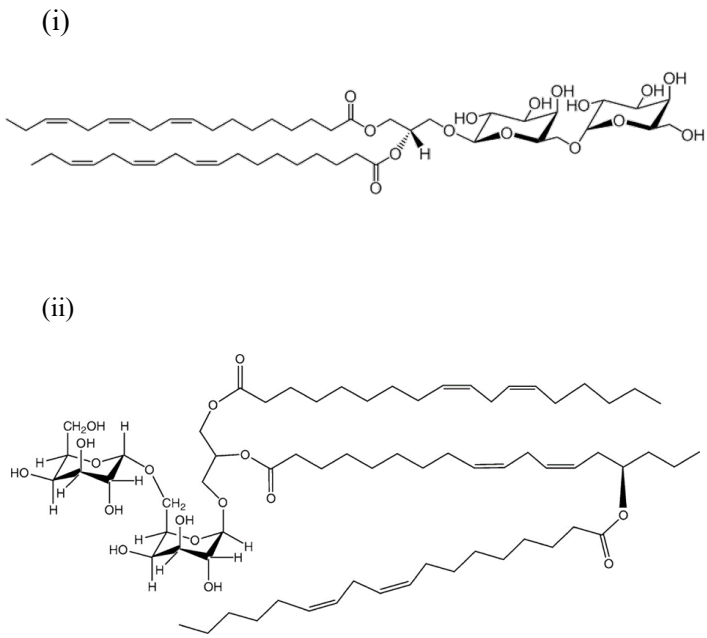

Figure 4: Examples of a digalactosyldiacylglycerol (i) and a derivative estolide (ii). Reprinted with permission [37]

Dietary fibres are widely recognised as health-promoting bioactive compounds [36,38]. Dietary fibre exerts numerous benefits for human health, e.g. improve glucose response, insulin sensitivity, lipid regulation and gut health, thereby contributing to preventing lifestyle-related diseases [39]. Oats are high in both soluble dietary fibre such beta-glucans and insoluble dietary fibre arabinoxylan. Oat beta-glucan is a linear polysaccharide composed of 1–3 and 1–4 linked beta -D glucopyranosyl units (Figure 5). Beta-glucan is the main fractions of the soluble

dietary fibre in oats. The health-promoting effects of OBG depend largely on their viscoelastic properties [40,41].

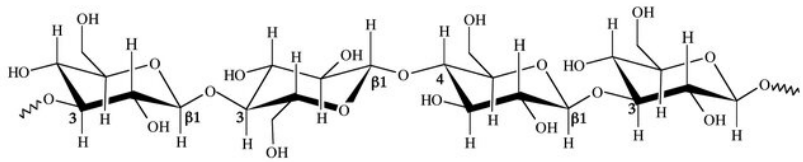

Figure 5: Chemical structure of oat beta-glucans [42].

Among the cereals, avenanthramides (AVAs) are phenolic bioactive compounds exclusively found in oats [43]. Oat avenanthramides are associated with a range of health benefits such as anti-inflammatory, antioxidant, anti-itching and possibly anti-cancer effects [43,44]. Oat AVAs demonstrate potent antioxidant effects by neutralising free radicals and shielding cells from oxidative stress-related harm [45]. The antioxidant properties may help lower the risk of chronic conditions including CVD, diabetes and cancer, which are often associated with oxidative stress [46].

Oat AVAs have been shown to potentially improve exercise performance and recovery by reducing inflammation and oxidative stress caused by strenuous physical activity [47]. This has the potential to be advantageous for athletes and individuals who participate regularly in physical activity.

Diet-related Cardiometabolic Diseases

Metabolic syndrome (MetS), also known as insulin resistance syndrome or syndrome X, is a significant global health concern that is increasingly prevalent. Metabolic syndrome is a cluster of metabolic conditions such as insulin resistance and dyslipidaemia, and is closely associated with obesity. MetS increases the risk of severe health conditions, such as T2D and CVD [48]. The metabolic disorder also increase the risk of cognitive decline and dementia, including Alzheimer's disease [48]. There is variation in the definition of MetS across various guidelines. While some place emphasis on insulin resistance, other focus on obesity – particularly waist circumference – as a pivotal component. The International Diabetes Federation (IDF) recognises chronic inflammation as an extra metabolic indication for diagnosing MetS. All definitions of MetS include the following key components: disrupted blood glucose regulation; obesity as measured by waist circumference;

elevated blood pressure and triglyceride concentration; and reduced HDL cholesterol (Table 2).

People's choice of foods and diet plays a crucial role in developing lifestyle-related disorders such as MetS and CMD. Ashkan et al. (2019) reported a comprehensive picture of food habits and their relationship with lifestyle-related diseases and premature deaths [49].

Table 2: Risk factors of MetS[1]

Risk factors	Cut points
Elevated waist circumference* (Peoples of European origin)	Males ≥ 94 cm and females ≥ 80 cm
Elevated triglycerides	≥ 150 mg/dL
Reduced HDL-C	Males < 40 mg/dL and females < 50 mg/dL
Elevated blood pressure	Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg
Elevated fasting glucose	≥ 5.6 mmol/L (≥ 100 mg/dL)

[1]Adapted from Alberti et al. 2009 [50], *ethnicity-specific according to IDF [51].

Postprandial Metabolic Regulation

The postprandial state, which refers to the metabolic processes that occur after ingesting a meal, is crucial for maintaining overall metabolic health. An imbalance in the regulation of metabolism after eating, identified by elevated blood glucose, lipids and inflammatory markers, has been recognised as a crucial element in the onset of cardiometabolic disorders such as T2D, CMD and CVD [52,53].

Type of diet significantly affects the postprandial metabolic state. The typical Western diet, which is abundant in refined carbohydrates, saturated fats and processed foods, poses a challenge to the postprandial metabolic balance. Typically, an intricate interaction of hormonal, neurological and metabolic signals ensures that the rise in blood nutrients after a meal is effectively used for energy and storage. Nevertheless, persistent overconsumption of nutritionally unhealthy food may result in postprandial dysmetabolism, which is characterised by impaired processing of glucose and lipids, and elevated inflammatory responses.

When carbohydrates have been consumed, there is an increase in blood glucose concentration, which leads to the release of insulin by the pancreatic beta-cells. Insulin promotes the absorption of glucose into tissues, mainly muscle and adipose tissue, by activating the GLUT4 transporter. Insulin also suppresses the production of endogenous glucose by the liver. Thus, insulin acts to counteract the postprandial

hyperglycaemia caused by a carbohydrate-rich meal. In response to a meal, also incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), are released to enhance secretion of insulin and inhibit release of glucagon (described in more detail below). If the target cells fail to respond to the signals of these hormones, which is prevalent in insulin resistance – a primary characteristic of MetS – the risk of CMD will significantly increase. Insulin resistance is a common complication in obesity and one of the major risk factors that connects obesity to CMD risk [54].

Dietary lipids cause a rise in plasma triglycerides [55]. After ingestion, digestion and absorption of lipids, triglycerides are re-synthetised in enterocytes of the small intestine, packed and transported together with cholesterol in the circulation in large lipoprotein assemblies, the chylomicrons. In addition, endogenous-derived triglycerides from peripheral body tissues or that are synthetised in the liver are packed and released into the circulation, assembled in very low-density lipoproteins (VLDL) particles. Lipids circulating in chylomicrons and VLDL are then delivered to body tissues, e.g. adipose tissue, whereafter the VLDL is converted into circulating LDL particles, which are later absorbed by the liver or other tissues. High concentrations of LDL-associated cholesterol – the so-called "bad" cholesterol – correlates with atherosclerosis progression [56]. High-density lipoproteins (HDL) have an opposite role, and instead collect lipids from the body's tissues and deliver them back to the liver. High HDLs are therefore sometimes referred to as "good" cholesterol because higher concentrations correlate with low rates of atherosclerosis progression [56]. In addition to regulating postprandial glycaemia, insulin has several metabolic regulatory functions. One of these is to regulate the deposition of triglycerides in adipose tissue and enhance the activity of lipoprotein lipase, an enzyme essential for the hydrolysis of triglycerides, making fatty acids available for absorption and use by tissues [57].

Food quality in postprandial metabolic regulation and CMD risk

Consuming meals, especially those high in fat, may trigger a sudden inflammatory reaction in the body, leading to elevated levels of inflammatory cytokines in the bloodstream. Postprandial inflammation is believed to serve as a protective response to the metabolic strain caused by excessive nutrient intake [58]. However, when this inflammation is consistently increased leading to so-called low-grade inflammation, it might lead to metabolic dysfunction [59,60].

Postprandial dysmetabolism is a condition in which there are excessive and extended rises in blood glucose levels, altered lipid profiles and increased inflammatory markers after meals. Postprandial dysmetabolism is influenced by

factors such as insulin resistance, beta-cell dysfunction, and changes in the incretin response. These factors are generally caused by chronic overnutrition, unhealthy food choices e.g. diet high in sugar and saturated fat, high glycaemic index (GI) foods, lack of physical exercise and genetic susceptibility [60]. Postprandial dysmetabolism is a major contributor to the likelihood of developing cardiometabolic disorders. Increased levels of glucose after a meal lead to the development of advanced glycation end products, oxidative stress, increased inflammation [61] and malfunction of the cells lining the blood vessels, which are significant factors in the development of T2D and CVD [52,62,63]. Postprandial lipid abnormalities, such as elevated LDL levels and reduced HDL cholesterol, are linked to the development of atherosclerosis [64]. In addition, persistent inflammation after meals might potentially lead to insulin resistance, failure of beta-cells and the onset of atherosclerosis [65].

Improvements in food and diet quality have favourable effects on postprandial dysmetabolism. For example, consuming diets that are high in fibre, wholegrains and unsaturated fats might beneficially affect the circulating levels of glucose and lipids in the body after a meal [66]. Relevant to mention in this respect is the GI concept, which is an important measure for evaluating how carbohydrate-rich foods affect postprandial blood glucose concentrations. It compares the increase in glucose concentrations after consuming a particular food item to a standard reference, usually a glucose solution or white wheat bread. The GI, first introduced by Jenkins et al. in 1981 [67], is calculated after quantifying the area under the glucose response curves within a two-hour timeframe after ingestion. The effect of meals on blood glucose concentration depends on a number of variables, including physiological processes (such as the availability of the substrates to digestive enzymes and the rate at which the stomach empties) and the inherent features of the food (such as its botanical, physical and chemical structure). Low-GI foods include dietary fibre rich foods, for example oats, barley kernels, beans, pasta, vegetables and fruits.

Second Meal Effects on Metabolic Variables

The second-meal effect on metabolic variables is a term used to indicate that a meal or food item consumed at one meal beneficially affects metabolic variables after the next meal, i.e. the “second meal”. A second-meal effect on postprandial glucose regulation has been seen e.g. after breakfast when barley-kernel based foods were consumed the previous evening [68], and at lunch when specific fermentable carbohydrates were consumed at breakfast [69]. A large quantity of research has acknowledged that low glycaemic index (low-GI) foods are beneficial to health and linked to a reduced susceptibility to obesity, T2D, and CVD [70,71]. In addition,

some low-GI foods have shown beneficial impacts on the management of blood glucose at a second meal [72,73].

The beneficial effect on second-meal glucose regulation after a low-GI meal was suggested to be due to supressed concentrations of circulating free fatty acids (FFA) at the second meal as a result of a favourable acute postprandial glucose excursion after the previous test meal. Considering the importance of a tight regulation of postprandial metabolism for a preventive strategy against CMD, foods that have the potential to improve risk-associated variables – not only acutely after intake, but also after a following meal – are highly desirable.

Gastrointestinal Hormones

Gastrointestinal hormones play a crucial role in regulating metabolic pathways, enabling complex communication between the digestive system, central nervous system and metabolic activities. These hormones play an important role in regulating the digestion and absorption of nutrients, as well as maintaining concentrations and distributing energy throughout the body. GLP-1, PYY, GIP and ghrelin are gastrointestinal hormones that have a wide range of effects on metabolic health. Only these four hormones will be further discussed as they are studied in the present thesis work.

GLP-1 is an important hormone and plays a significant role in regulating appetite, gastrointestinal motility and glucose metabolism. GLP-1 is produced by the enteroendocrine L-cells in the small intestine and colon after food is consumed [74]. Among the macronutrients, oral administration of glucose is the best-known stimulant of GLP-1 secretion [75]. Furthermore, GLP-1 is stimulated by the ingestion of fat, protein and complex meal [75,76]. Galactose has also been reported as a GLP-1 stimulant [77]. GLP-1 has a central function as incretin along with GIP to regulate glucose concentrations after a meal by enhancing the release of insulin from pancreatic β-cells in response to glucose [78]. The insulinotropic effects of GLP-1 are glucose-dependent, which means the concentration of GLP-1 increases with the increase of glucose, and vice versa [79]. In addition, GLP-1 inhibits the release of glucagon from pancreatic α-cells, hence reducing the synthesis of glucose in the liver. With respect to effects on glucagon, GIP exerts the opposite effect, i.e. it promotes an enhanced response [78]. In addition, GLP-1 is a main mediator of the ileal brake – a mechanism that slows the transit time through the gastrointestinal tract, resulting in slower digestion and absorption of glucose, thereby reducing postprandial blood glucose increments [80].

Furthermore, GLP-1 has notable impacts on the regulation of hunger and body weight by activating GLP-1 receptors in the brain [81]. This activation leads to a decline in desire to eat and food consumption. GLP-1 receptor agonists have been

shown in clinical studies to cause significant reductions in body weight, which may be linked to a drop in calorie consumption and an increase in feelings of satiety. GLP-1 has garnered much attention due to its metabolic effects, and GLP-1 agonists are used as pharmaceutical agents to treat both T2D and obesity [82].

PYY is another gastrointestinal hormone studied in this thesis work. PYY is released as a preprohormone from the L-cells of the ileum and colon and is subsequently cleaved to its active form, PYY (3–36), upon secretion. The release of PYY is stimulated by the ingestion of food, particularly meals high in fat and protein.

PYY exerts its effects primarily by reducing appetite and inhibiting gastric emptying, thereby contributing to energy homeostasis. PYY, together with GLP-1, takes part in the gut-brain axis, communicating nutritional status to the brain to regulate appetite and satiety [83]. Beyond these effects, several research papers suggest that PYY is involved in modulating glucose homeostasis [84,85].

Nevertheless, ghrelin – the so-called hunger response hormone – also has an important effect on controlling appetite and energy consumption. Ghrelin is primarily produced by gastric enteroendocrine cells found in the stomach [86]. Ghrelin levels often peak before meals and subsequently decline after eating, exhibiting a correlation with the quantity of energy ingested [87]. Ghrelin has been shown to stimulate appetite and food intake in both healthy individuals of normal weight, and obese individuals [87].

Objective

The main objective of this thesis was to investigate the postprandial effects of oat polar lipids and beta-glucans on cardiometabolic risk-related biomarkers in healthy adults. In particular, the thesis explored the link between the incorporation of oat polar lipids and beta-glucans in different meal settings, and the acute and second-meal metabolic responses they induce in terms of blood glucose regulation, triglycerides and FFA profiles, and appetite-controlling gut hormones such as GLP-1, PYY, GIP and ghrelin.

The specific objectives of the studies included in the thesis were:

- Investigation of the effects of two oat oils containing different concentrations of polar lipids (high and low amounts) on cardiometabolic risk variables, where the oils were incorporated into liquid oat-based beverages (*Paper I*).
- Investigation of dose-response effects of OPL and whether changing the meal physical form to solid meals affects the postprandial metabolic impact of oat polar lipids observed in *Paper I* (*Paper II*).
- Comparison of the postprandial metabolic effects of OPL with that of a commercially available polar lipid preparation, sunflower lecithin (*Paper III*).
- Investigation i) of the postprandial metabolic effects of OBG and whether a dose lower than 4g OBG per 30g carbohydrate has the potential to improve glycaemic response; and ii) whether OBG have the potential to elicit second-meal effects on blood glucose tolerance (*Paper IV*).

Materials and Methods

The Test and Reference Products

Meals with polar lipids

Paper I (Oat-based beverage)

The test products were formulated as liquid breakfasts and consisted of an oat-based preparation specially designed for this study, to which were added different types and amounts of lipids (developed and manufactured by Oatly AB, Sweden). A glucose solution was included as a reference product. The following were added to the oat base preparation: i. oat oil containing low concentrations of polar lipids (PLL), ii. oat oil containing high concentrations of polar lipids (PLH), or iii. rapeseed oil (RSO) as a reference oil. Their metabolic effects were compared to those of the oat base preparation with no added lipids (NL). The oat oils were provided by Swedish Oat Fiber AB and rapeseed oil was purchased from AAK. All the breakfast beverages containing added lipids supplied an equivalent amount of total fat (33g). All breakfast beverages contained 42g available carbohydrates. The nutritional composition of the breakfast meals is displayed in Table 3.

Table 3: Nutritional composition of the breakfast meals per serving (500 ml)[1].

	PLL	PLH	RSO	NL	Glucose
Available carbohydrates (g)	42	42	42	42	42
Free glucose (g)	1.75	1.75	1.75	1.75	42
Total fat (g)	33	33	33	3	0
Polar lipids (g)	1	12	0.6*	0	0
Protein (g)	6.5	6.5	6.5	6.5	0
Fibres (g)	5	5	5	5	0
beta-glucans (g)	2.5	2.5	2.5	2.5	0
Energy (Kcal)	491	491	491	221	168

[1]PLL, oat preparation with low concentration of oat polar lipids; PLH, oat preparation with high concentration of oat polar lipids; RSO, oat preparation with added rapeseed oil; NL, oat preparation without added oat polar lipids. * Polar lipids in RSO estimated based on reference [88].

Paper II (Solid meals)

A polar lipid-enriched oat oil was specially prepared for the study (*Papers II and III*) and kindly provided by Swedish Oat Fiber AB (Bua, Sweden). The oat oil contains 90% polar lipids. A white wheat bread (WWB, Jättefranska, Pågen AB, Sweden) was included as a source of available carbohydrates to be consumed with the oat oil, and as a reference product without added lipids. The test meals (Table 4) consisted of WWB with either 1) 15g oat polar lipids (PLH) 2) 7.5g oat polar lipids and rapeseed oil at a ratio of 50/50 (PLL), or 3) 16.6g rapeseed oil (RSO). The three test meals contained equivalent amounts of fat (16.6g). 10ml water was added to make oil spreads in the PLL and PLH breakfast meal preparations. Rapeseed oil was added on top of oat polar lipids (PLL) to make equivalent amounts of fat. All breakfast meals contained 50g available carbohydrates.

Table 4: Formulation of the test meals and reference.

Reference meal[1]	**WWB**	**120g white wheat bread, no oil, 260ml water**
Test meals[1]	PLH	120g WWB, 16.6g 90% enriched oat polar lipid, 260ml water.
	PLL	120g WWB, 8.3g of 90% enriched oat polar lipid, 8.3g rapeseed oil and 260ml water.
	RSO	120g WWB, 16.6g rapeseed oil, 260ml water.
Standardised lunch	120g WWB, 100g meatballs, 250ml water	

[1] WWB, white wheat bread; PLH, WWB plus 15g oat polar lipids; PLL, WWB plus 7.5g oat polar lipids and 8.3g rapeseed oil; RSO, WWB plus 16.6g rapeseed oil.

Paper III (OPL and Lecithin)

A polar lipid-enriched oat oil (90% polar lipids) was provided by Swedish Oat Fiber AB (Bua, Sweden). Polar lipid-enriched (83% polar lipids) sunflower lecithin was purchased from Helhetshalsa AB (Borghamnsvägen 8, 59293, Borghamn, Sweden). These two polar lipids (PL) preparations were then used to prepare test meals. A white wheat bread (Jättefranska, Pågen AB, Sweden) was included in the breakfasts, as a source of available carbohydrates, both to be consumed with the lipids investigated, and as a reference product without added lipids. There were four meals tested in the study: The reference meal, the two different PL meals with an equivalent amount of PL (15 g), and one oil with very low polar lipids meal (rapeseed oil (RSO)). Prior to serving the test meals, polar lipids spreads were prepared by gently mixing oat oil or lecithin with 10ml water. The spreads were then spread onto the WWB. Rapeseed oil was instead poured directly onto the WWB. The four test meals were noted as followed i) 15g oat polar lipids: OPL, ii) 15g lecithin: LPL, iii) 18g rapeseed oil: RSO, and iv) reference white wheat bread: WWB. Lipid-enriched test meals contained equivalent amounts of total fat (18g). The RSO meal was used as a common oil reference. All breakfast meals contained 50g available carbohydrates and were consumed together with one glass of water (260ml). Formulation and composition of the test meals are shown in Table 5 and Table 6.

Table 5: Formulation of the test and reference meals.

Reference meal[1]	WWB	120g white wheat bread, no added oil, 260ml water
Test meals[1]	OPL	120g WWB, 16.6g polar lipids-rich (90%) oat oil, 1.4g rapeseed oil, 260[2]ml water.
	LPL	120g WWB, 18.0g sunflower lecithin (83% polar lipid) and 260[2]ml water.
	RSO	120g WWB, 18g rapeseed oil, 260ml water.
Standardised lunch	120g WWB, 100g meatballs, 250ml water	

[1] WWB, white wheat bread containing 50 g available carbohydrates; OPL, 15 g oat polar lipids; LPL, 15 g lecithin; RSO, 18 g rapeseed oil. [2] Including 10 ml water used for spread preparation.

Table 6: Macronutrient composition of breakfast.

	WWB	RSO	LPL	OPL
Carbohydrates (g)	50	50	50	50
Total fat (g)	< 1	18	18	18
Polar lipids (g)*	< 1	0.6*	15	15
Non-polar lipids (g)	< 1	17.4	1.4	3

Polar lipid contents in LPL and OPL according to the supplier and in *RSO estimated according to reference [88].

Paper IV (OBG)

The test meals contained three different doses of OBG and 30g avCHO in the form of glucose. The OBG was kindly provided by Lantmännen Functional Foods AB. Test meals containing:1. A glucose solution supplemented with 2g BG (PromOat® Instant, Lantmännen Functional Foods AB, Box 30192, 104 25 Stockholm, Sweden) (BG2), 2. A glucose solution supplemented with 3g BG (BG3), 3. A glucose solution supplemented with 4g BG (BG4), 4. A glucose solution without BG was included as a reference meal (Ref.). All meals contained 30g avCHO. The test meals were prepared by adding OBG to 150ml hot water (100°C) supplemented with strawberry flavour (Wild strawberry, Aarke AB, Östgötagatan 100, Stockholm, Sweden) and pink food colours (Dr. Oetker Sverige AB, Åvägen 40, 412 51 Göteborg, Sweden). The composition of PromOat® Instant and breakfast meals is shown in Table 7 and Table 8. The average molecular weight of the PromOat® Instant was 800kDa.

Table 7: Composition of PromOat® Instant[1]

Nutritional information	Nutrients per 100 (g)
Carbohydrates	47.0
Sugars	2.0
Total fat	6.5
Protein	3.5
Total fibre	40
Beta-glucans	32.2
Other fibre	7.8

[1]In accordance with the manufacturer's provided information

Table 8: Breakfast meals formulation[1].

	Beta-glucans (g)	PromOat (g)	Glucose (g)	avCHO[2] (g)	Hot water (100°C) (ml)
Test meal 1 (BG4)	4	13.15	24.81	30	150
Test meal 2 (BG3)	3	9.86	26.5	30	150
Test meal 3 (BG2)	2	6.5	28.5	30	150
Reference (Ref)	0	0	30.42	30	150

[1]Based on one serving. [2]avCHO; available carbohydrates.

Standardised Lunch

Paper I

The standardised lunch consisted of 122g white wheat bread (Pågen AB, Malmö, Sweden) corresponding to 42g available starch, 100g meatballs (Scan AB, Stockholm, Sweden) and 250ml water. Based on the nutritional facts declared by the producers, the total energy content of the lunch meal was 537kcal. Table 9 shows the macronutrient composition of the lunch meal.

Table 9: Nutritional composition of standardised lunch meal per 100g[1].

	Meatballs	Bread
Carbohydrate (g)	8	47.0
Fat (g)	15	3.5
Protein (g)	13	8.5

[1]Based on the nutritional facts declared by the producers.

Papers II, III and IV

The standardised lunch consisted of a meatball sandwich containing WWB corresponding to 50g available starch and 100 g meatballs (Scan AB, Sweden). Water (250ml) was consumed in parallel. Based on the information provided by the manufacturer, the total energy content of the lunch meal was 485kcal (Table 10).

Table 10: Macronutrient composition of lunch meals[1]. Study (II, III and IV)

	Standardised lunch
Carbohydrate (g)	58
Fat (g)	18.5
Protein (g)	21.5
Calories (kcal)	485

[1]Based on the nutritional facts declared by the producers.

Chemical Analyses of Test and Reference Meals

Available starch

Available starch of the test meals, reference meal OB (*Paper I*) and WWB (*Papers II–III*) were determined according to Holm et. al (1986) [89].

Fat

Fat content of the meals in *Paper I* was determined using the Schmid-Bondzynski-Ratzlaff (SBR) gravimetric measurement technique.

Protein

The protein content of the test meals in *Paper I* was determined using dumas combustion method.

Meal studies

Study participants

In *Paper I* (5 males and 15 females) and *Paper II* (7 males and 13 females) twenty young healthy subjects, with age 24.8 ± 0.9 and 24 ± 0.24 years, respectively, and with BMI 22.2 ± 0.4 and 23 ± 0.49 kg/m^2, respectively (age and BMI expressed as mean ± SEM) participated in the study. *Paper III* (11 males and 7 females) and *Paper IV* (7 males and 12 females) included healthy young adults with age 25.6 ± 4.6 and 23.51 ± 0.21 years, respectively, with BMI 23.6 ± 2.9 and 23.39± 0.46 kg/m^2, respectively. The main inclusion criteria were age between 20 and 40 years and BMI between 19 and 25 (*Paper I*) and 19 and 28 kg/m^2 (*Papers II–IV*). Exclusion criteria were fasting blood glucose concentration ≥ 6.1 mmol/L, any documented metabolic diseases or food allergies. Additionally, participants were required to be non-smokers. The administration of antibiotics or probiotics was prohibited for a period of two weeks before and during the trial. Prior to inclusion, each participant received a full explanation (written and oral) of the purpose and procedure of the study, and his/her written informed consent was obtained. All test subjects were aware of the possibility of withdrawing from the study at any time they desired.

Experimental Design

An overview of the study (*Papers I–IV*) can be found in Figure 6. A single-blind randomised crossover design was followed in all studies. All the study participants consumed each test meal in a random order. The day before each experiment, the participants were told to avoid strenuous exercise, alcoholic drinks, oat-based products and food with high fibre content (e.g. beans, wholegrain bread, fibre-enriched pasta, whole cereal kernels, etc.). The participants were told to standardise their meal pattern prior to each experimental day. To keep track of standardisation, the participants were requested to provide a meal record from the day before each experiment day. Furthermore, the participants were instructed to consume individually standardised dinner meals at 18:00 the day before each experiment, and to consume a standardised evening meal at 21:00, consisting of commercial white wheat bread with a topping of their choice (same topping before each experimental day).

The test products were provided as breakfast meals in all studies. The different products were tested, approximately one week apart. The subject arrived at the trial facility at 07:30 after an overnight fast. Capillary blood samples were taken prior to breakfast (time = 0 min). Then, a test breakfast was served and consumed within 10–12 minutes. Additional capillary blood samples were drawn at 15, 30, 45, 60,

90, 120, 150 and 210 minutes after the start of the breakfast meal. After the blood test at 210 min, a standardised lunch was served, and blood samples were then drawn at 225, 240, 255, 270, 300 and 330 minutes after commencing the breakfast. During the experiment, the participants remained at the trial facility and were not allowed to eat or drink anything except for the breakfast and lunch meals provided, and they were told to limit their physical activity as much as possible.

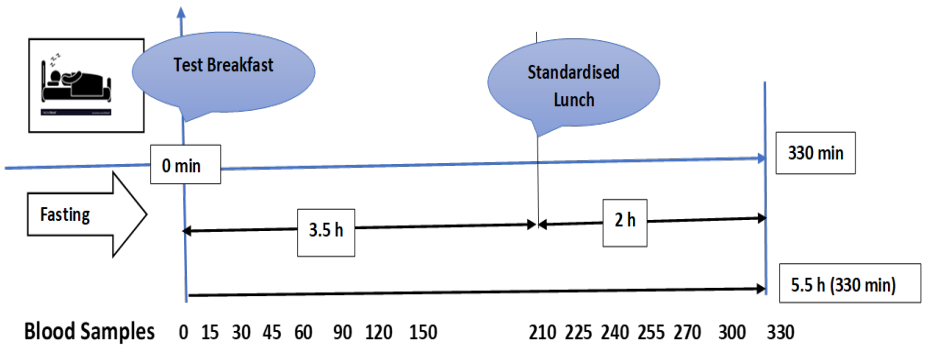

Figure 6: Schematic overview of the experimental design of meal studies included in this thesis.

Physiological Test Variables

Blood Sample and Analyses

All analyses were performed on capillary blood. Samples for serum insulin *(Papers I–IV*), free fatty acids (*Papers I–II*) and triglycerides (*Papers I–III*) analyses were collected in BD Microtainer SST tubes. The tubes were left at room temperature for approximately 30 minutes before being centrifuged for 5 minutes (5,000 rpm, 25°C, Eppendorf centrifuge 5425). The serum was then kept frozen at -40°C until analysis. Additional blood plasma samples (*Papers I–III*) for GLP-1, GIP, PYY and ghrelin analyses were collected in BD Microtainer K2E tubes. An inhibition cocktail consisting of DPP-4 inhibitor (10µl/ml blood) (Millipore, St. Charles, USA) and aprotinin (50µl/ml blood) (Sigma-Aldrich, St. Louis, USA) was added to the tube. The tubes were kept on ice before and after sampling and were centrifuged for 10 min (4,200 rpm, 4°C) within 20 minutes after collecting the blood. Plasma samples were then frozen at -40°C until analysis.

Blood Glucose

The concentrations of capillary plasma glucose were measured immediately at bleeding using a HemoCue Glucose 201^{+} analyser (HemoCue AB, Ängelholm, Sweden).

Insulin

Determination of insulin concentrations was performed using a solid phase two-site enzyme immunoassay kit (Insulin ELISA 10-1113-01, Mercordia AB, Uppsala, Sweden).

Triglycerides and FFA

Serum Triglyceride concentrations were determined using a multi-sample enzymatic assay (LabAssay™ Triglyceride 290-63701, GPO.DAOS method, FUJIFILM Wako Chemicals Europe GmbH, Germany).

Free fatty acids concentrations were analysed with an enzymatic colorimetric method with a 96 microplate (NEFA-HR (2) ACS-ACOD method, FUJIFILM Wako Chemicals Europe GmbH, Germany).

GLP-1, PYY, GIP and Ghrelin

The quantitative determination of total plasma GLP-1, PYY, GIP, and ghrelin concentrations were performed using a 10-spot U-plex assay kit (Meso Scale Diagnostics LLC, Rockville, Maryland, USA).

Subjective appetite rating

In *Papers I and IV*, the study participants ranked their feeling of satiety, hunger and desire to eat using a 100mm visual analogue scale graded from 0–100 [90].

Calculation and Statistical Methods

In all papers, data are expressed as means ± SEM. The significance level was set at P-value < 0.05. A trapezoid model was used to calculate the incremental areas and total areas under the curves (iAUC and AUC, respectively) for each subject and test meal in all studies. The iAUC were used for statistical evaluations of blood glucose and insulin concentrations. AUC were used for TG, GLP-1, PYY, GIP and ghrelin. The plotting of graphs and calculations of areas were performed in GraphPad Prism (version 10.2.1, GraphPad Software, CA, USA).

Randomisation of the consumption order of the test products was performed by using random tools of Microsoft excel (Washington, USA). Differences in the results of the test variables between the products (‘Meal’) at different time points

during the experimental day ('Time') were evaluated using a mixed model (PROC MIXED in SAS release 9.4; SAS Institute Inc, Cary, NC) with repeated measures and an autoregressive covariance structure for the test variables. Subjects were modelled as a random variable, and the corresponding baseline (fasting values) was modelled as a covariate. The effects of the test products on physiological responses were evaluated using ANOVA (general linear model) followed by Tukey's pairwise multiple comparison in MINITAB Statistical Software (version 20.1, Minitab, Minitab Inc, State College, PA, USA). Box Cox transformation was performed on the data prior to ANOVA analysis if the residuals were distributed unevenly (tested with Anderson-Darling, where $p < 0.05$ was considered unevenly distributed). If the value from a test subject was missing for one of the products, the test subject was excluded from calculations of the specific test variable.

Results and Discussion

In the following sections, I will present the main findings of this thesis, led by a series of four intervention studies.

Firstly, I will provide the results of three consecutive studies (*Paper I, Paper II and Paper III*) which, together, provide a coherent narrative. The purpose of this section is to provide an overview of the results of each paper. Following that, I will address *Paper IV* separately.

The purpose of *Paper I* was to investigate the effects of oat polar lipids on the cardiometabolic test variables after breakfast and a subsequent standardised lunch. The oat polar lipids were incorporated into the oat-based liquid beverages. *Paper II* was dedicated to exploring the consequences of changing the physical setting of the meal for the metabolic effects of oat polar lipids, adding them to a solid breakfast meal. Finally, in *Paper III*, the metabolic effects of oat polar lipids were compared with those of a commercially available plant polar lipid (sunflower lecithin). In all three papers, commercial rapeseed oil was included as a conventional oil reference. The test variables investigated in the studies were glucose and insulin responses, blood lipid profiles (FFA and TG), gut hormones (GLP-1, PYY, GIP and ghrelin) and perceived appetite sensations.

Results, Papers I–III

Baseline Characteristics

In all the three *papers (I–III)*, no statistically significant differences between experimental days were seen in fasting concentrations of any of the test variables examined ($P > 0.05$). Data can be found in the *Papers*.

Glucose and Insulin Responses

Papers I–III

The results in the studies described in *Papers I– III* revealed significant main effects of test meals on blood glucose and insulin responses along the whole experimental period (0–330 min).

In *Paper I*, lower postprandial blood glucose concentrations were observed after the test meals PLL and PLH compared to NL ($P < 0.05$) (iAUC 0–120 min, Figure 7). Interestingly, the glucose iAUC (0–120 min) after the breakfast meal with PLH was also lower compared to RSO ($P < 0.01$). Regarding the glycemic response to the standardised lunch (iAUC 210–330 min), the PLH breakfast continued to result in significantly lower glycemic response compared with the breakfasts containing NL ($P < 0.001$) or RSO ($P < 0.001$), and also compared with PLL ($P < 0.01$).

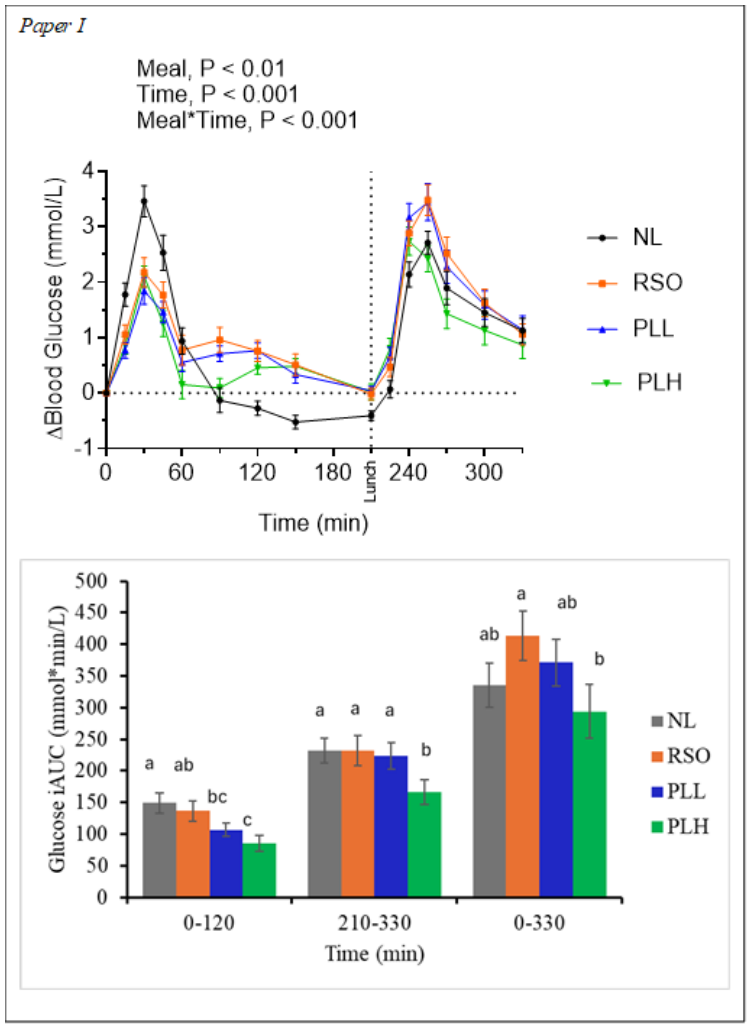

Figure 7: Incremental changes in blood glucose concentrations after test breakfasts and standardised lunch meals. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. NL, oat preparation without added lipids; RSO, oat preparation added with rapeseed oil; PLL, oat preparation with low concentration of polar lipids; PLH, oat preparation with high concentration of polar lipids. iAUC, incremental area under curve.

The post-breakfast insulin response (iAUC 0–120 min, Figure 8) was significantly lower after PLH compared to NL ($P < 0.001$) and RSO ($P < 0.01$). The insulin responses to the standardised lunch (iAUC 210–330 min) were similar regardless of the test meal consumed at breakfast ($P > 0.05$).

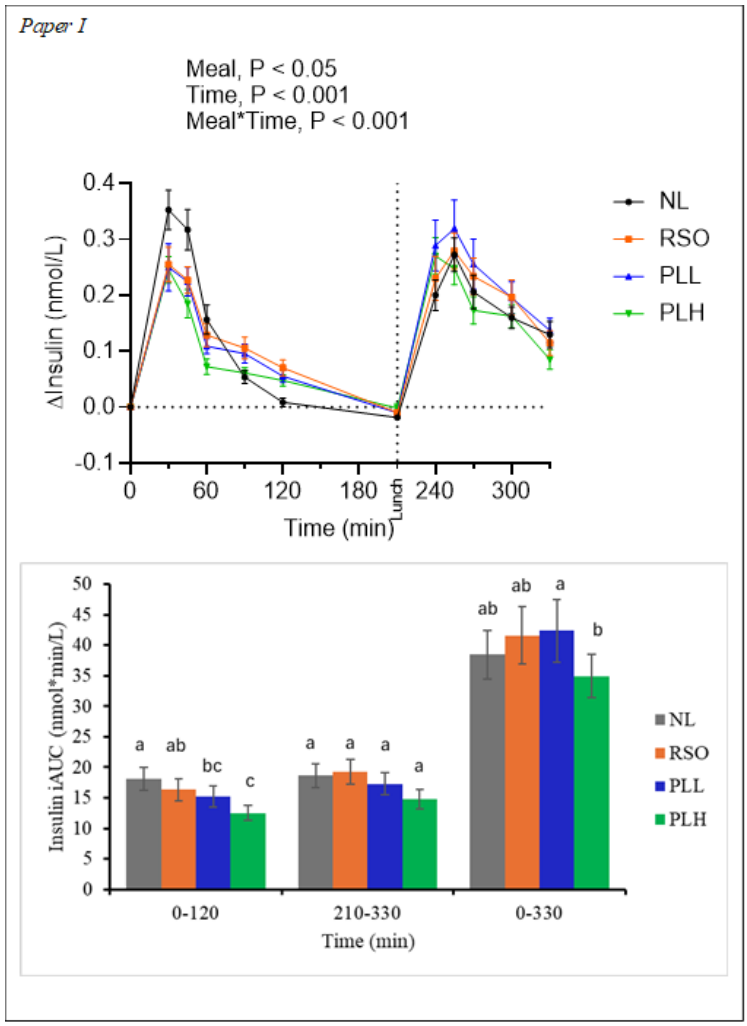

Figure 8: Incremental changes in insulin concentrations after test breakfasts and standardised lunch meals. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. NL, oat preparation without added lipids; RSO, oat preparation added with rapeseed oil; PLL, oat preparation with low concentration of polar lipids; PLH, oat preparation with high concentration of polar lipids. iAUC, incremental area under curve.

Paper II: Results in *Paper II* regarding effects of oat polar lipids on blood glucose responses were similar to those observed in *Paper I*. Consequently, the glucose iAUC (0–120 min) following the breakfast meal with PLH was reduced compared to WWB ($P < 0.001$) and RSO ($P < 0.01$). Furthermore, postprandial glucose concentrations (iAUC 0–120 min, Figure 9) were reduced also following PLL

compared to WWB. After the standardised lunch (iAUC 210–330 min), blood glucose responses were reduced after the PLH breakfast compared to those recorded after the WWB ($P < 0.001$), PLL ($P < 0.01$) and RSO ($P < 0.01$) breakfasts.

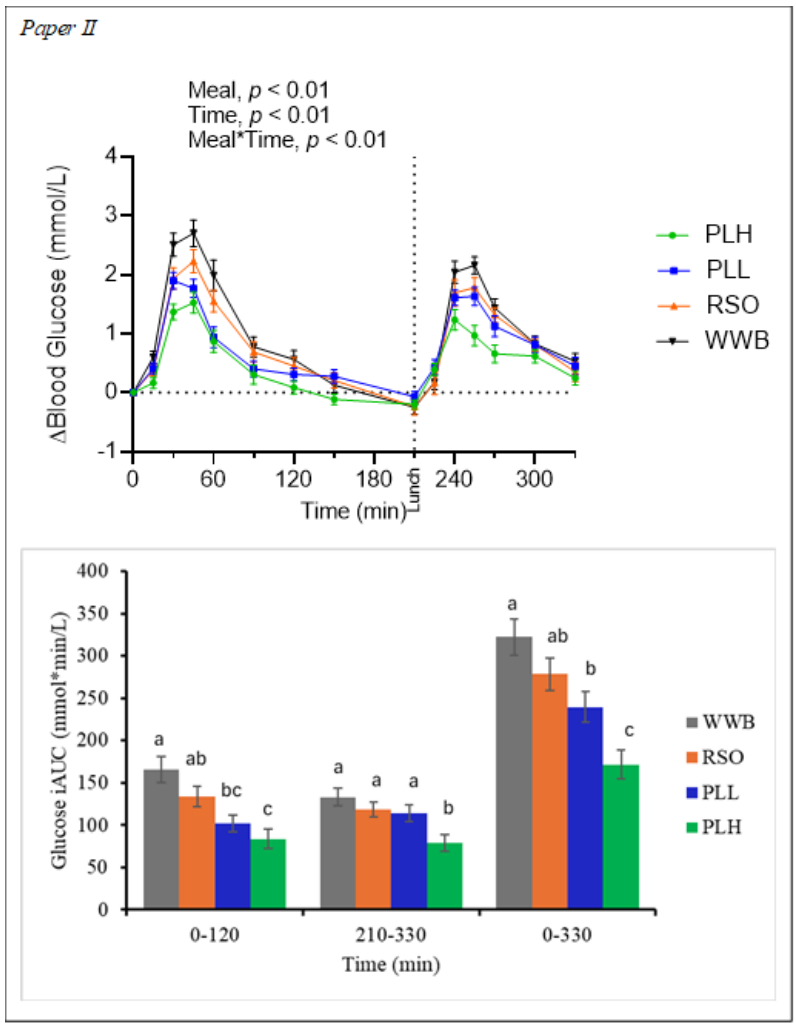

Figure 9: Incremental changes in blood glucose concentrations after test breakfasts and standardised lunch meals. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. WWB, white wheat bread; PLH, 15 g oat polar lipids; PLL, 7.5 g oat polar lipids and 8.3g rapeseed oil; RSO, 16.6 g rapeseed oil. iAUC, incremental area under curve.

The results revealed lower postprandial insulin responses (iAUC 0–120 min, Figure 10) after the breakfast following PLH compared to the breakfast with WWB ($P <$

0.001) and RSO ($P < 0.01$), and the insulin responses to the standardised lunch (iAUC, 210– 330 min) were lower after consuming the PLH breakfast compared to RSO ($P < 0.05$).

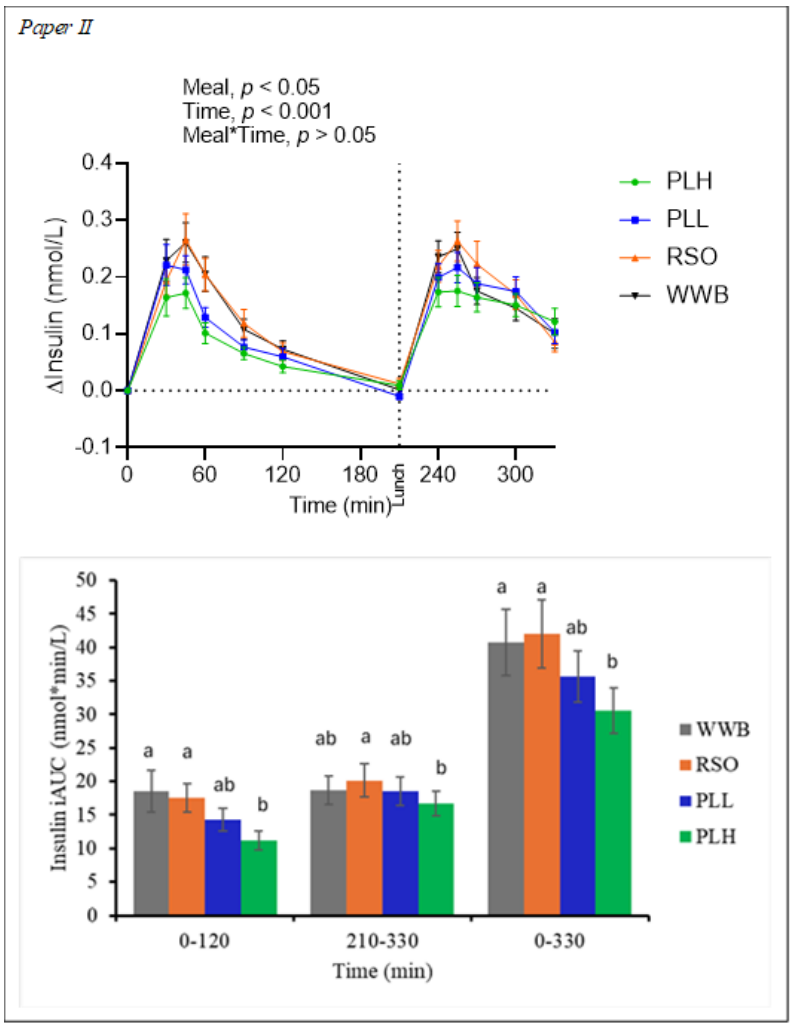

Figure 10: Incremental changes in insulin concentrations after test breakfasts and standardised lunch meals. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. WWB, white wheat bread; PLH, 15 g oat polar lipids; PLL, 7.5 g oat polar lipids and 8.3g rapeseed oil; RSO, 16.6 g rapeseed oil. iAUC, incremental area under curve.

Paper III. Blood glucose iAUC (0–120 min) following the breakfast meal with OPL and LPL was significantly reduced compared to WWB ($P < 0.001$) and RSO ($P < 0.01$). In terms of glycaemic response to the standardised lunch (iAUC 210–330 min, Figure 11), the OPL and LPL were lower compared to WWB ($P < 0.01$). No significant differences in blood glucose concentrations (iAUC 210–330min) were observed with LPL compared to RSO. However, blood glucose concentration (iAUC 210–330 min) was significantly lowered after consumption of OPL at breakfast compared to RSO ($P < 0.01$). In addition, postprandial glucose concentrations along the entire experiment (iAUC 0–330 min) were lower following OPL and LPL compared to WWB ($P < 0.05$).

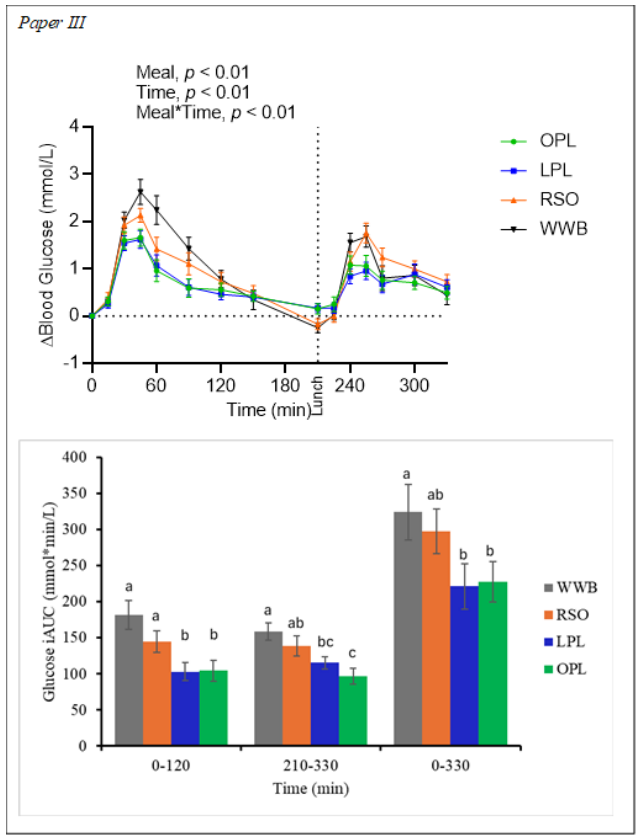

Figure 11: Incremental changes in blood glucose concentrations after test breakfasts and standardised lunch meals. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. WWB, white wheat bread; OPL, 15 g oat polar lipids; LPL, 15 g lecithin (polar lipids); RSO, 18 g rapeseed oil. iAUC, incremental area under curve.

Significantly lower postprandial insulin responses (iAUC 0–120 min, Figure 12) were observed after breakfast following OPL and LPL compared to those with WWB ($P < 0.001$) and RSO ($P < 0.01$). Furthermore, insulin responses to the standardised lunch (iAUC, 210–330 min) were significantly lower after consuming OPL and LPL breakfasts compared to WWB and RSO ($P < 0.05$). Thus, the postprandial insulin concentrations along the entire experimental session (0–330 min) were significantly lower after OPL and LPL compared to WWB and RSO ($P < 0.01$).

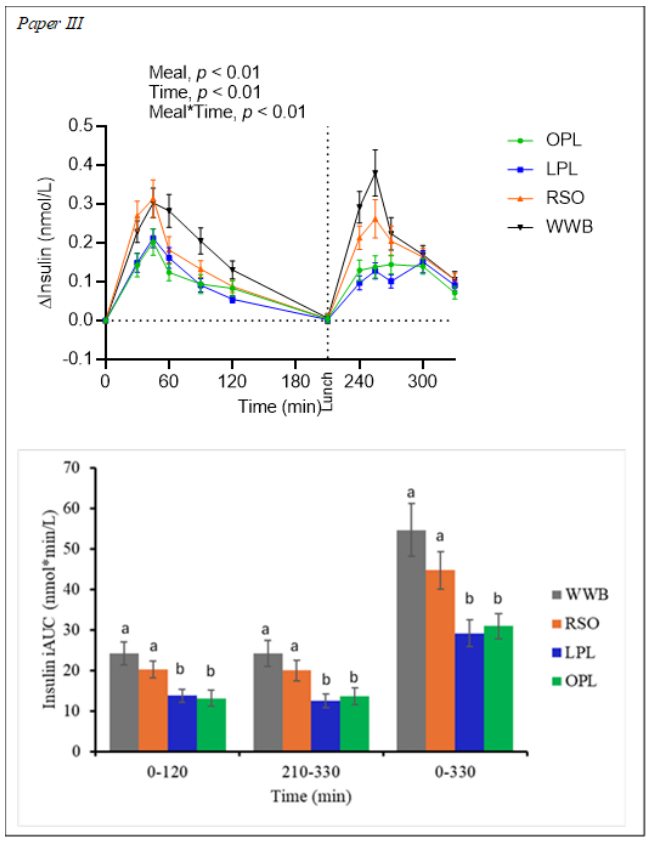

Figure 12: Incremental changes in insulin concentrations after test breakfasts and standardised lunch meals. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. WWB, white wheat bread; OPL, 15 g oat polar lipids; LPL, 15 g lecithin (polar lipids); RSO, 18 g rapeseed oil. iAUC, incremental area under curve.

Gastrointestinal Hormones

A significant main effect of test meals was detected along the entire test period (0–330 min, $P < 0.05$) on the concentrations of gut hormones GLP-1 and PYY in any of the three studies, *Papers I–III*.

GLP-1

Paper I revealed increased GLP-1 concentrations postprandial (AUC 0–210 min, Figure 13) after the breakfast composed of PLH compared to NL ($P < 0.001$) and RSO ($P < 0.001$). In addition, the PLH breakfast resulted in increased GLP-1 concentration at the end of the experimental period, time = 330 min (the only test point for gastrointestinal hormone determinations after the standardised lunch), compared to NL ($P < 0.01$), PLL ($P < 0.05$) and RSO ($P < 0.01$) breakfasts.

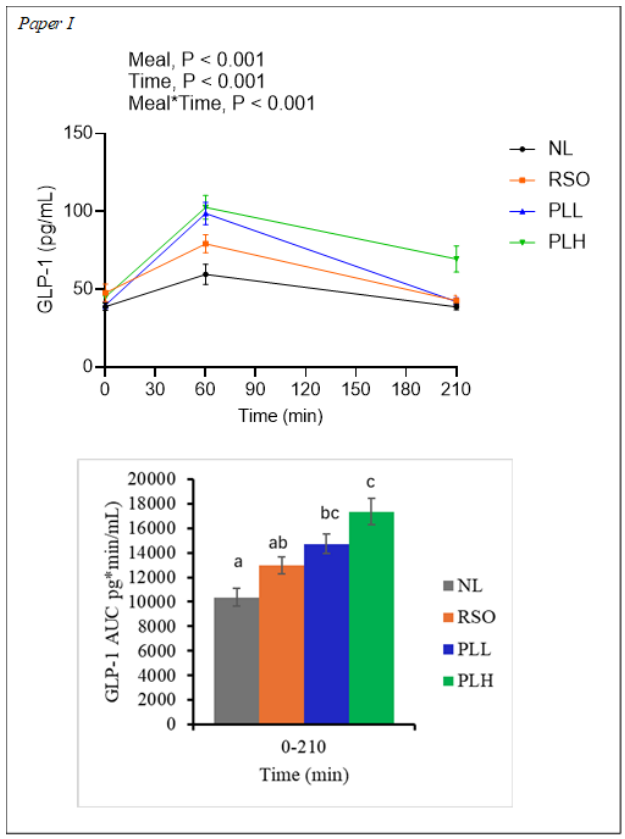

Figure 13: GLP-1 responses after breakfast and lunch. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. NL, oat preparation without added

lipids; RSO, oat preparation added with rapeseed oil; PLL, oat preparation with low concentration of polar lipids; PLH, oat preparation with high concentration of polar lipids. AUC, area under curve.

In *Paper II*, GLP-1 concentrations (AUC) in the time period 0–210 min were significantly increased after breakfasts containing PLH and PLL compared to WWB and RSO ($P < 0.05$, Figure 14). GLP-1 concentration at 330 min was significantly higher after the PLH breakfast compared to after RSO and WWB breakfasts ($P < 0.05$).

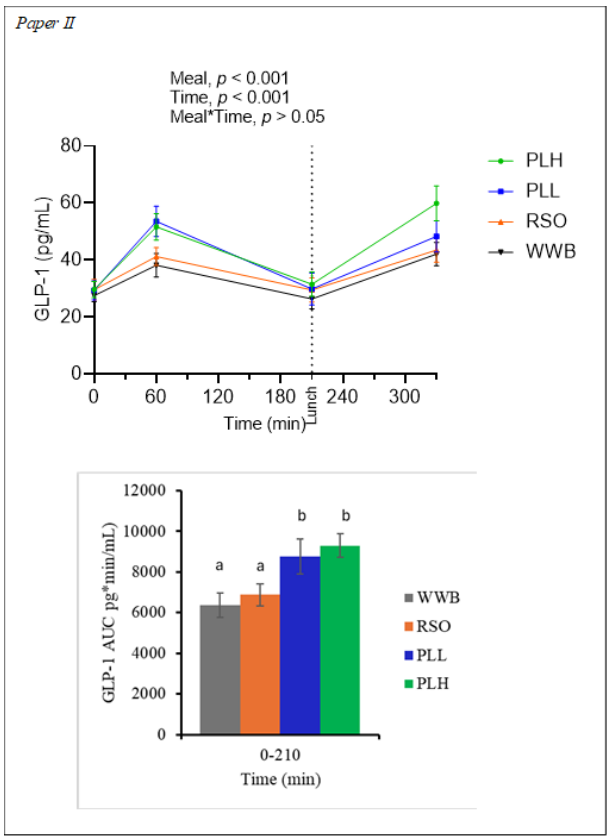

Figure 14: GLP-1 responses after breakfast and lunch. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. WWB, white wheat bread; PLH, 15 g oat polar lipids; PLL, 7.5 g oat polar lipids and 8.3g rapeseed oil; RSO, 16.6 g rapeseed oil. AUC, area under curve.

A significant increase in GLP-1 was also found after the breakfasts containing OPL and LPL in *Paper III*. GLP-1 concentrations (AUC) during the time period 0–210 min were higher after breakfasts containing OPL and LPL compared to WWB and

RSO ($P < 0.05$). Additionally, GLP-1 concentrations during the whole experimental period (0–330 min) were significantly increased after OPL and LPL breakfasts compared to WWB and RSO breakfasts ($P < 0.05$, Figure 15).

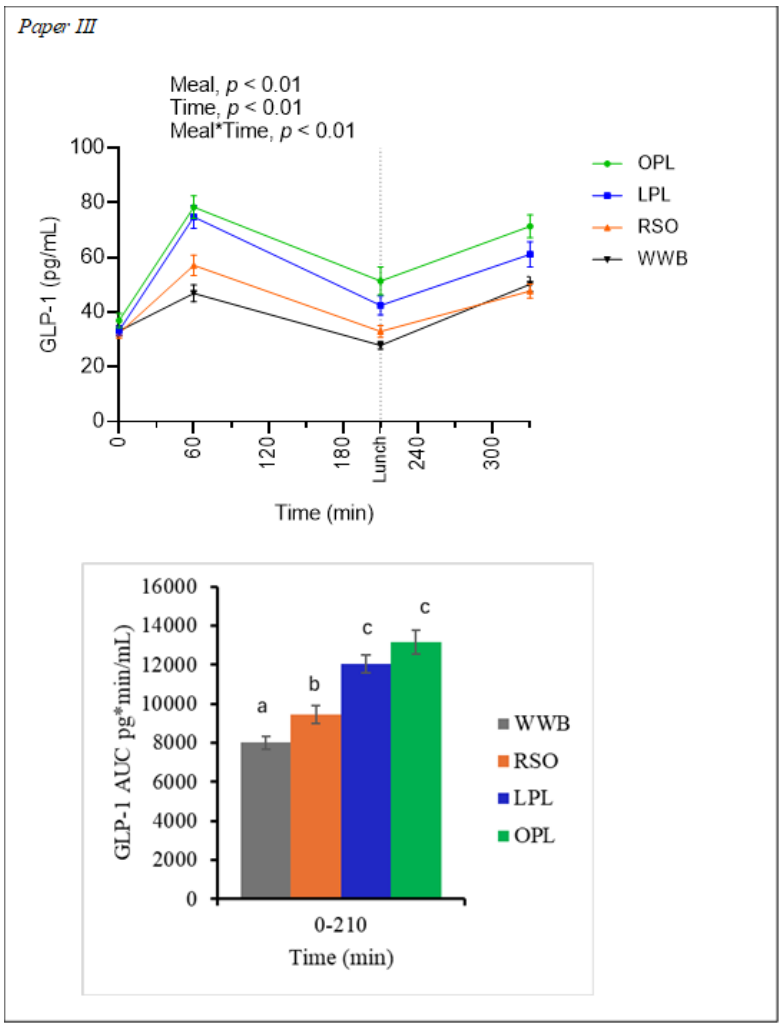

Figure 15: GLP-1 responses after breakfast and lunch. Different letters (a, b and c) in the bar diagram indicate significant differences, $P < 0.05$ (ANOVA, followed by Tukey's test). WWB, white wheat bread; OPL, 15 g oat polar lipids; LPL, 15 g lecithin (polar lipids); RSO, 18 g rapeseed oil. AUC, area under curve.

PYY

In *Paper I,* the PYY concentrations after the PLH breakfast (AUC 0–210 min, Figure 16), were significantly higher compared to after the NL ($P < 0.001$) and RSO breakfasts ($P < 0.01$). Furthermore, at the end of the experimental period (330 min), the PLH breakfast resulted in significantly higher concentrations of PYY compared to NL ($P < 0.001$), PLL ($P < 0.01$) and RSO breakfasts ($P < 0.001$).

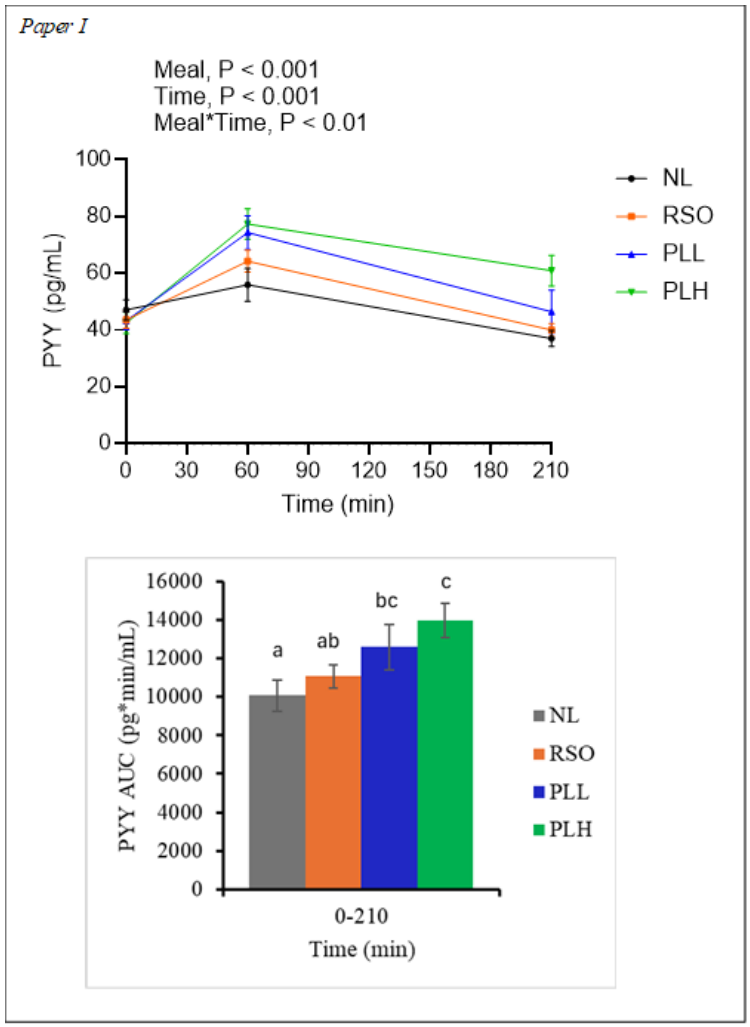

Figure 16: PYY responses after breakfast and lunch. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. NL, oat preparation without added lipids; RSO, oat preparation added with rapeseed oil; PLL, oat preparation with low concentration of polar lipids; PLH, oat preparation with high concentration of polar lipids. AUC, area under curve.

In *Paper II*, PYY concentrations after the PLH breakfast (AUC 0–210 min, Figure 17) exhibited a significant increase in comparison to both the WWB ($P < 0.001$) and RSO breakfasts ($P < 0.05$). The increase in PYY concentrations after consuming a PLH breakfast persisted after consuming a standardised lunch. As a consequence, PYY concentrations were considerably higher after a PLH breakfast meal compared to WWB and RSO breakfasts at the end of the test period (at 330 min, $P < 0.01$).

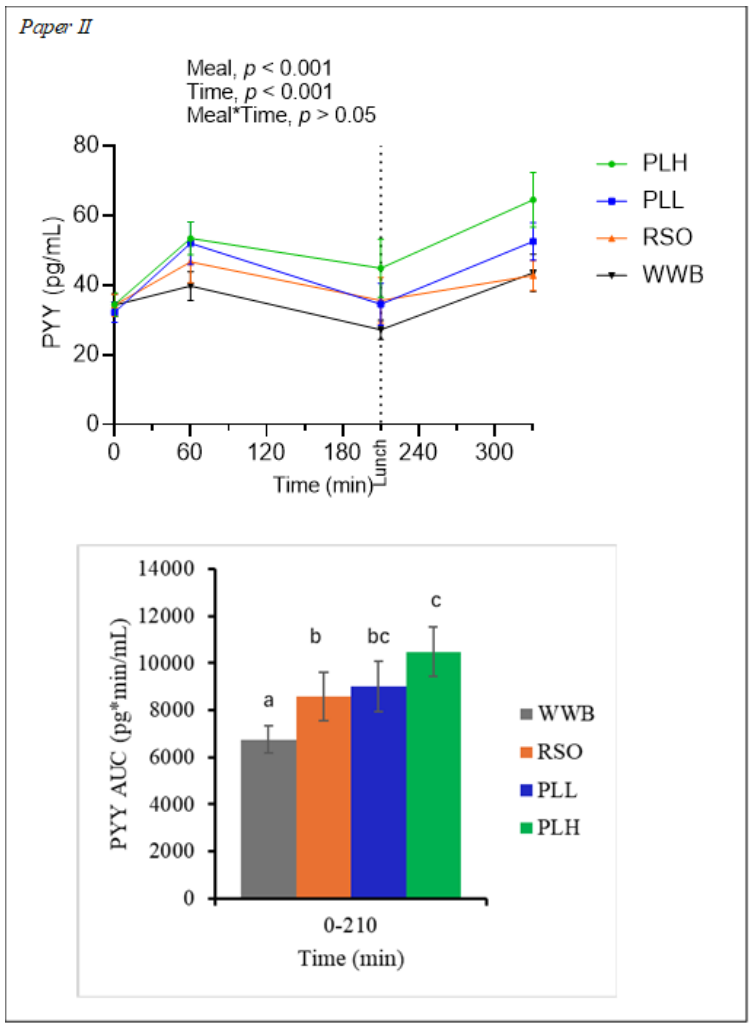

Figure 17: PYY responses after breakfast and lunch. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. WWB, white wheat bread; PLH, 15 g oat polar lipids; PLL, 7.5 g oat polar lipids and 8.3g rapeseed oil; RSO, 16.6 g rapeseed oil. AUC, area under curve.

The PYY concentrations in *Paper III* (Figure 18) were significantly higher after both OPL and LPL breakfast compared to WWB ($P < 0.05$) and RSO ($P < 0.05$) during the whole period investigated (AUC 0–210 min and at 0–330 min).

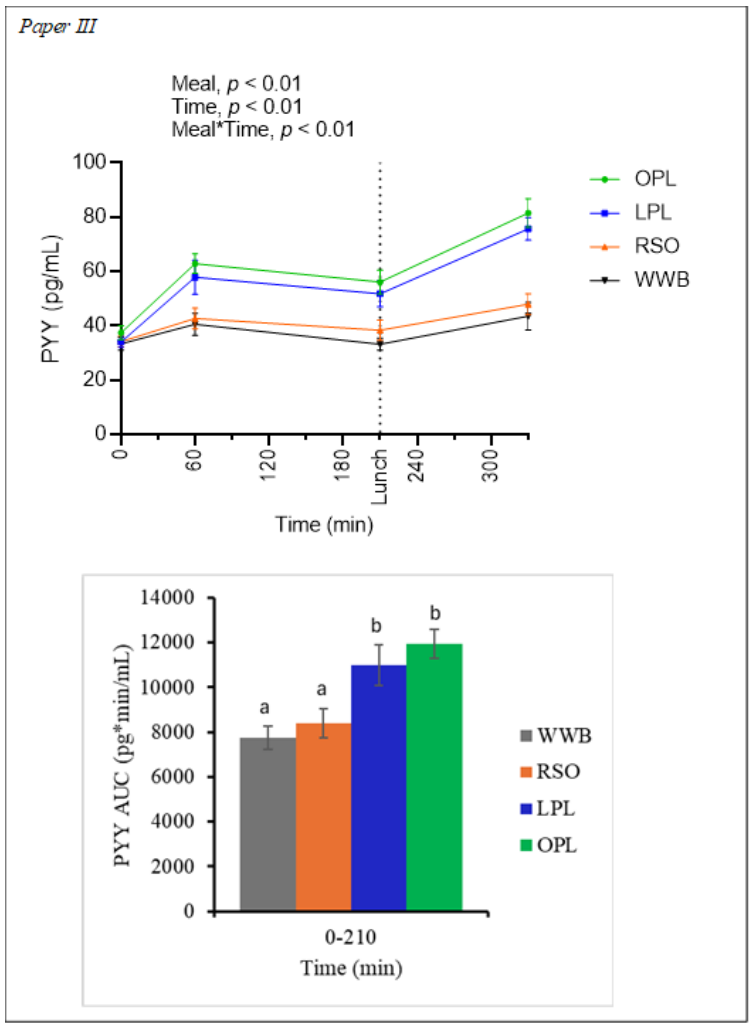

Figure 18: PYY responses after breakfast and lunch. Different letters (a, b and c) in the bar diagram indicate significant differences. WWB, white wheat bread; OPL, 15 g oat polar lipids; LPL, 15 g lecithin (polar lipids); RSO, 18 g rapeseed oil. AUC, area under curve.

GIP

In *Paper I*, a significant main effect of test meals was observed in the postprandial period after breakfast (0–210 min, Figure 19), revealing higher GIP concentrations after PLL compared to after PLH ($P < 0.01$) and NL ($P < 0.001$) breakfasts.

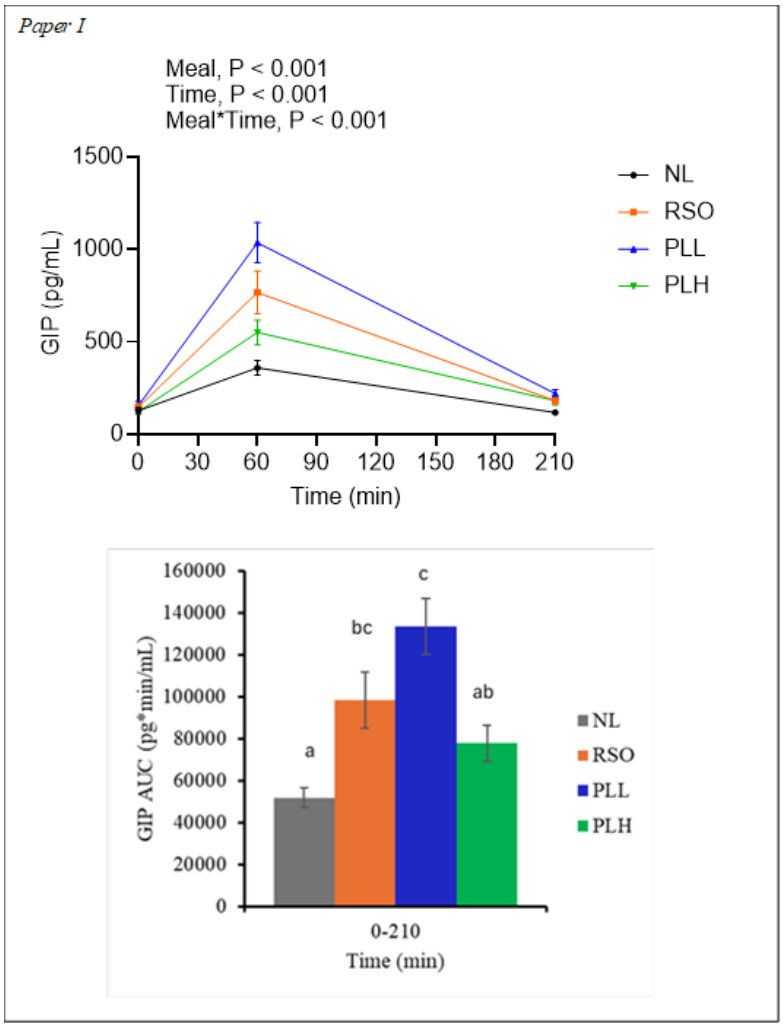

Figure 19: GIP responses after breakfast and lunch. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. NL, oat preparation without added lipids; RSO, oat preparation added with rapeseed oil; PLL, oat preparation with low concentration of polar lipids; PLH, oat preparation with high concentration of polar lipids. AUC, area under curve.

There were no significant main effects of the meals in *Paper II* on GIP concentrations over the study period (0–330 min, Figure 20). However, the results indicated a significant meal*time interaction, exhibiting that the breakfast consisting of PLH led to decreased postprandial GIP concentrations over the 0–210 min period compared to the RSO and PLL meals (AUC, $P < 0.001$).

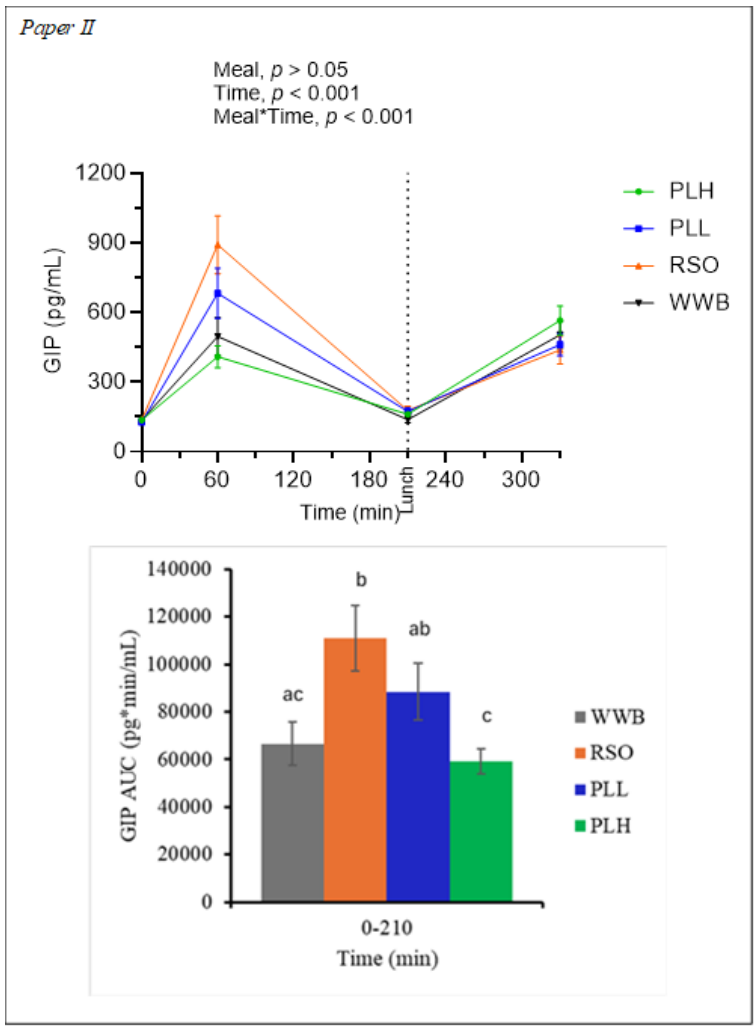

Figure 20: GIP responses after breakfast and lunch. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. WWB, white wheat bread; PLH, 15 g oat polar lipids; PLL, 7.5 g oat polar lipids and 8.3g rapeseed oil; RSO, 16.6 g rapeseed oil. AUC, area under curve.

The results in *Paper III* showed a significant main effect of the meal and meal*time on GIP concentrations over the study period 0–330 min. GIP concentrations (AUC) during the 0–210 min time period were significantly lower after breakfast containing OPL and LPL compared to RSO ($P < 0.05$, Figure 21). In addition, GIP concentrations during the whole period investigated (AUC 0–210 min and at 0–330 min) were significantly lower after OPL and LPL breakfasts compared to RSO breakfasts ($P < 0.05$).

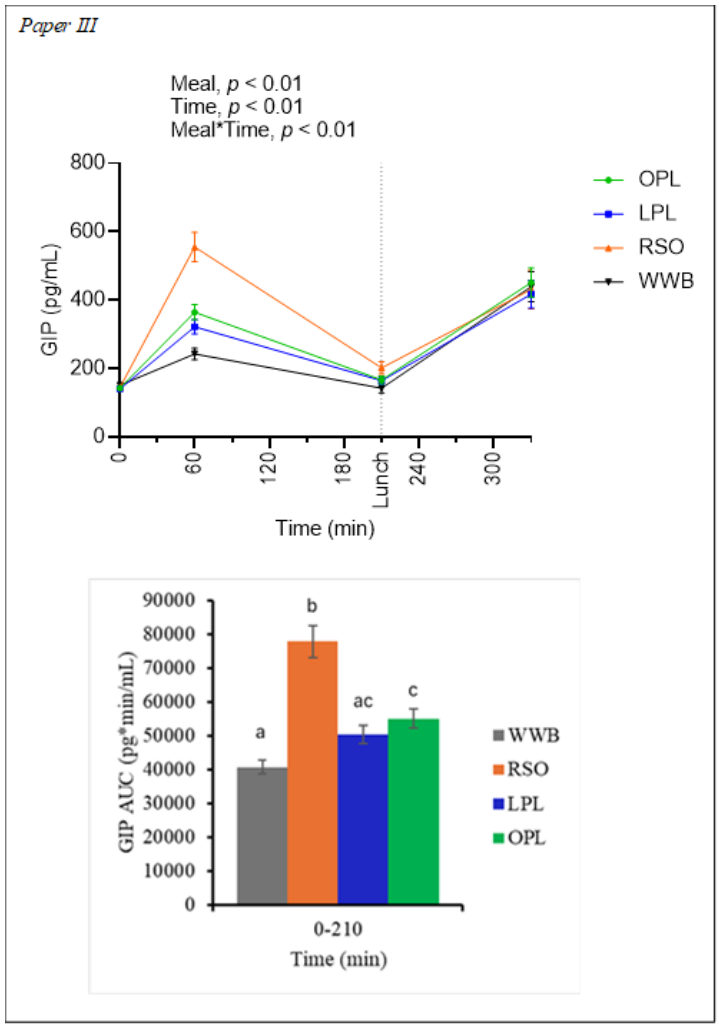

Figure 21: GIP responses after breakfast and lunch. Different letters (a, b and c) in the bar diagram indicate significant differences. WWB, white wheat bread; OPL, 15 g oat polar lipids; LPL, 15 g lecithin (polar lipids); RSO, 18 g rapeseed oil. AUC, area under curve.

Ghrelin

Results in *Paper I* revealed that ghrelin concentrations were significantly lower after the PLH breakfasts (0–210 min, Figure 22) compared to the NL breakfast ($P < 0.001$).

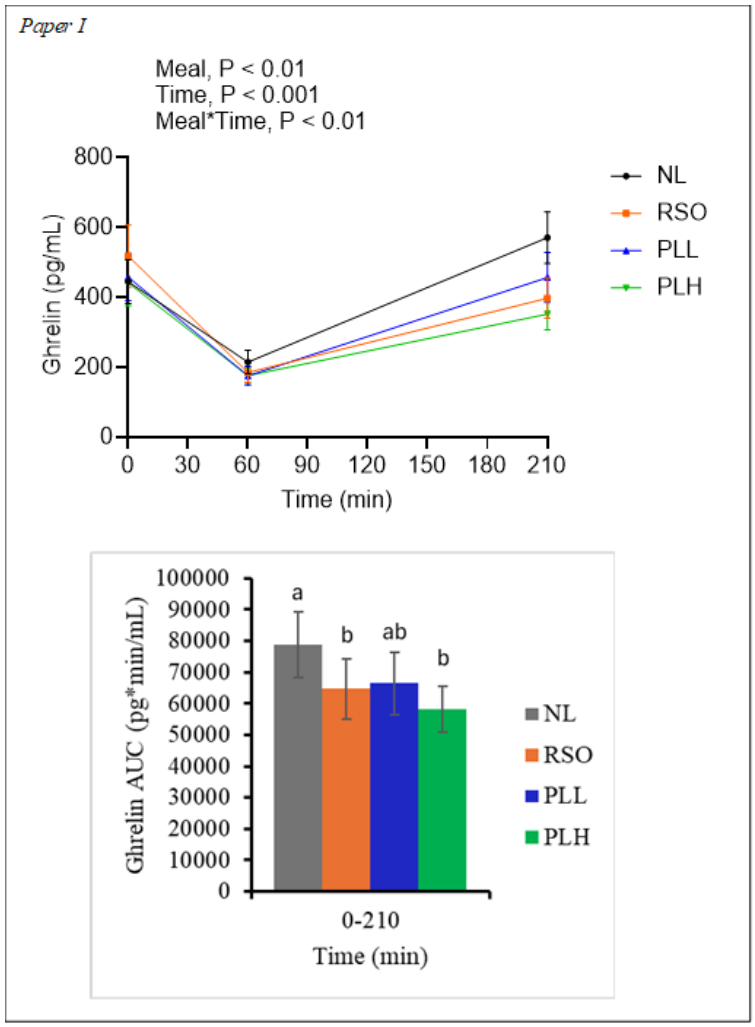

Figure 22: Ghrelin responses after breakfast and lunch. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. NL, oat preparation without added lipids; RSO, oat preparation added with rapeseed oil; PLL, oat preparation with low concentration of polar lipids; PLH, oat preparation with high concentration of polar lipids. AUC, area under curve.

In *Paper II*, ghrelin concentrations post breakfast (AUC 0–210 min, Figure 23) were significantly lower after PLH and PLL breakfasts compared to RSO and WWB ($P < 0.05$).

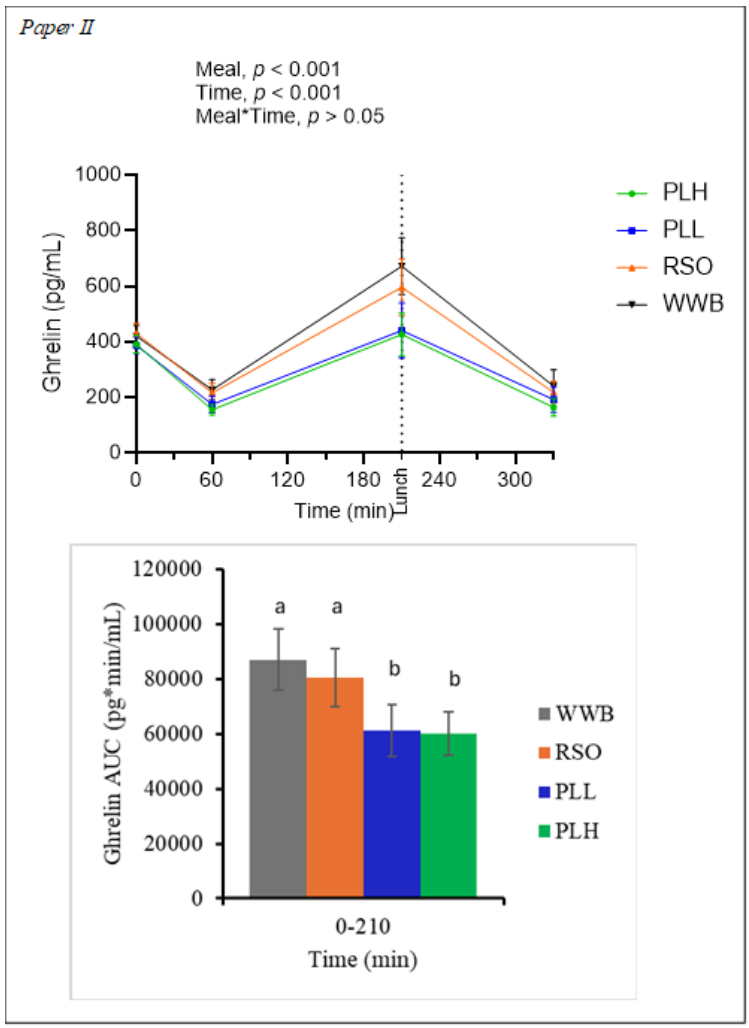

Figure 23: Ghrelin responses after breakfast and lunch. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. WWB, white wheat bread; PLH, 15 g oat polar lipids; PLL, 7.5 g oat polar lipids and 8.3g rapeseed oil; RSO, 16.6 g rapeseed oil. AUC, area under curve.

Postprandial ghrelin concentrations (AUC 0–210 and 0–330 min) in *Paper III* were significantly lower both after OPL and LPL breakfasts compared to RSO and WWB ($P < 0.05$, Figure 24).

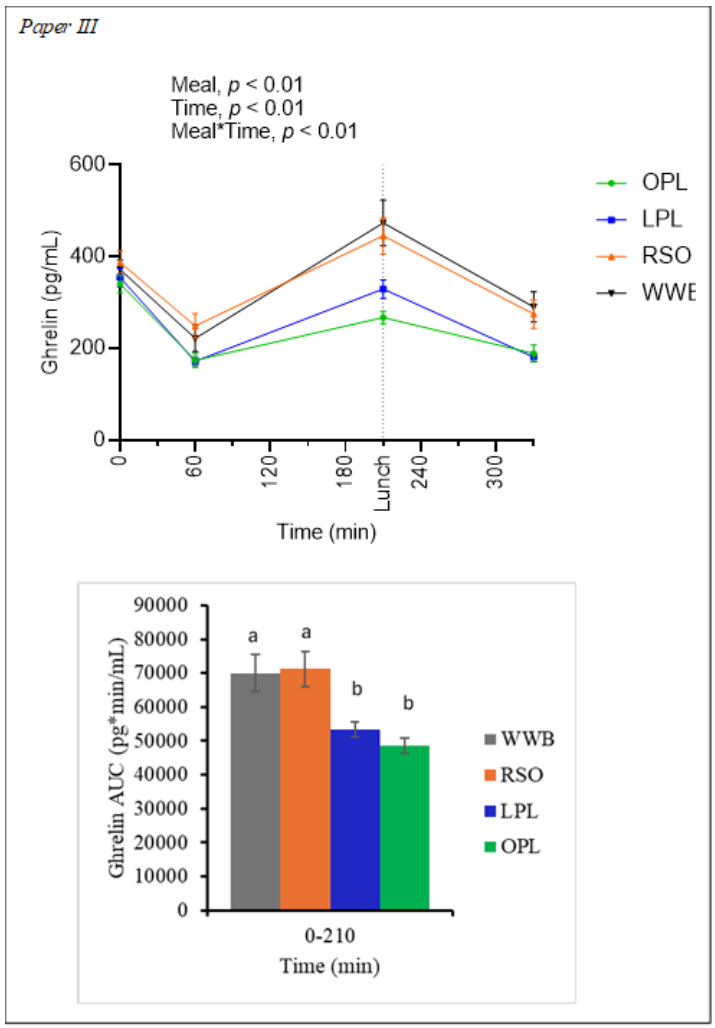

Figure 24: Ghrelin responses after breakfast and lunch. Different letters (a, b and c) in the bar diagram indicate significant differences. WWB, white wheat bread; OPL, 15 g oat polar lipids; LPL, 15 g lecithin (polar lipids); RSO, 18 g rapeseed oil. AUC, area under curve.

Triglycerides and FFA

Paper I. The results regarding FFA (Figure 25) and TG (Figure 26) showed a significant main effect of test meals during the whole experimental period (0–330 min). Intake of PLH resulted in lower TG concentrations compared to RSO and PLL. AUC (0–210 min) were significantly higher after RSO ($P < 0.05$) and PLL ($P < 0.01$) compared to after NL. At the end of the experimental session (at 330 min), the concentration of TG was significantly lower after the RSO breakfast compared with that observed after NL breakfast ($P < 0.05$). FFA responses after breakfast (AUC 0–210 min) and lunch AUC (210–330 min) were significantly lower after the PLH breakfast meal compared to RSO and PLL ($P < 0.05$).

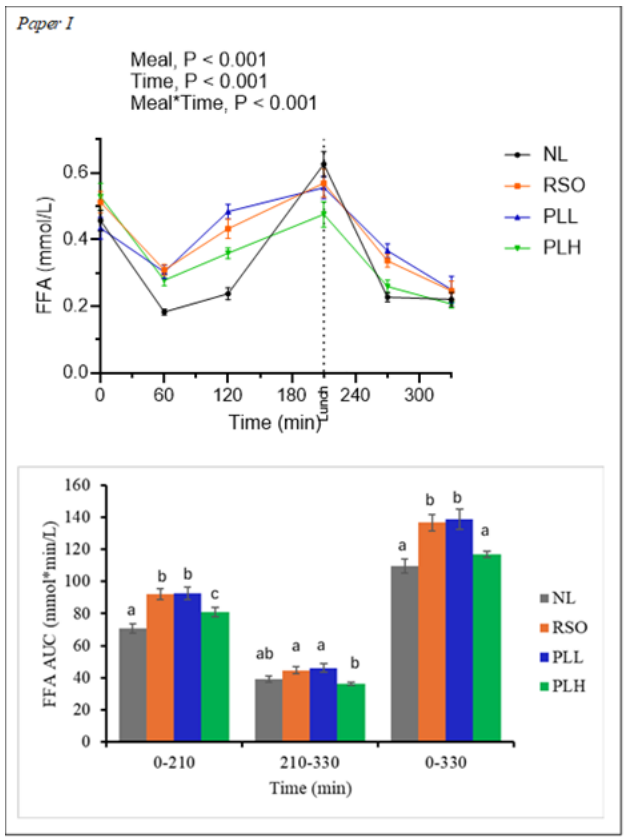

Figure 25: FFA responses after breakfast and lunch. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. NL, oat preparation without added lipids; RSO, oat preparation added with rapeseed oil; PLL, oat preparation with low concentration of polar lipids; PLH, oat preparation with high concentration of polar lipids. AUC, area under curve.

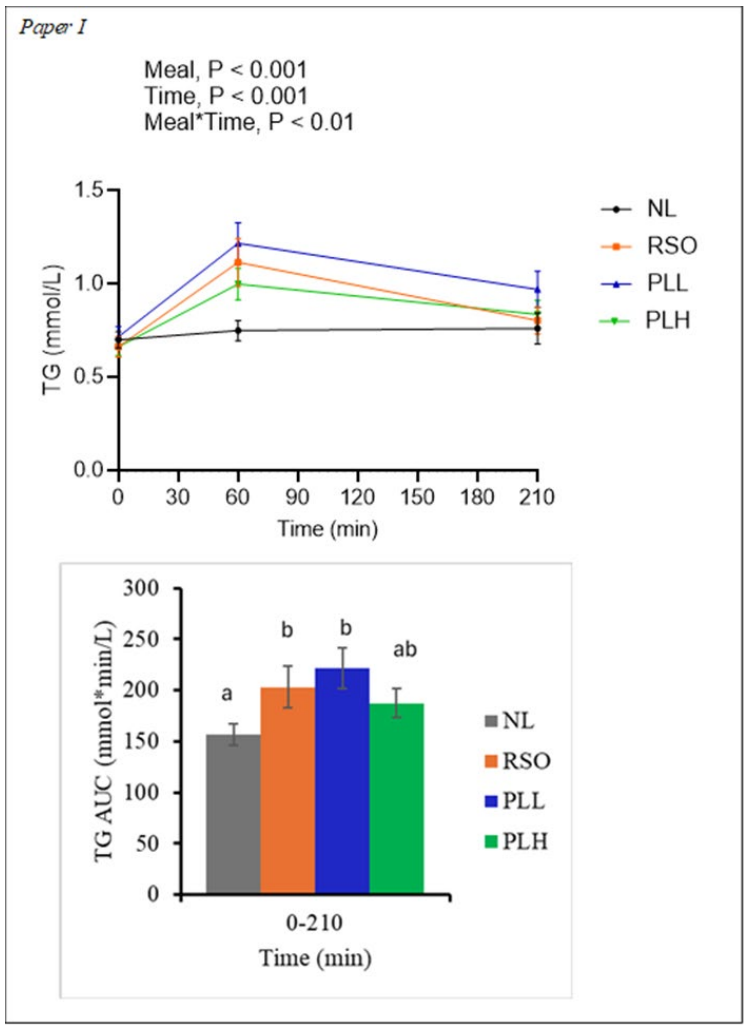

Figure 26: TG responses after breakfast and lunch. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. NL, oat preparation without added lipids; RSO, oat preparation added with rapeseed oil; PLL, oat preparation with low concentration of polar lipids; PLH, oat preparation with high concentration of polar lipids. AUC, area under curve.

Papers II and III. A significant main effect of test meals on TG concentration was found over the test period (0–330 min). The TG responses in *Paper II* (Figure 27) after the breakfast (AUC 0–210 min) and lunch (210–330 min) were significantly lower after intake of PLH compared to after RSO ($P < 0.05$). As expected, the WWB

breakfast resulted in the lowest concentration of TG during the test period, although no significant differences were detected in TG concentrations after intake of WWB compared with PLH. In *Paper III* (Figure 28), TG responses were significantly lower after intake of OPL and LPL compared to after RSO after the standardised lunch (210–330 min, $P < 0.05$). No significant differences were detected in TG concentrations during the experimental period after intake of OPL and LPL compared with WWB ($P > 0.05$).

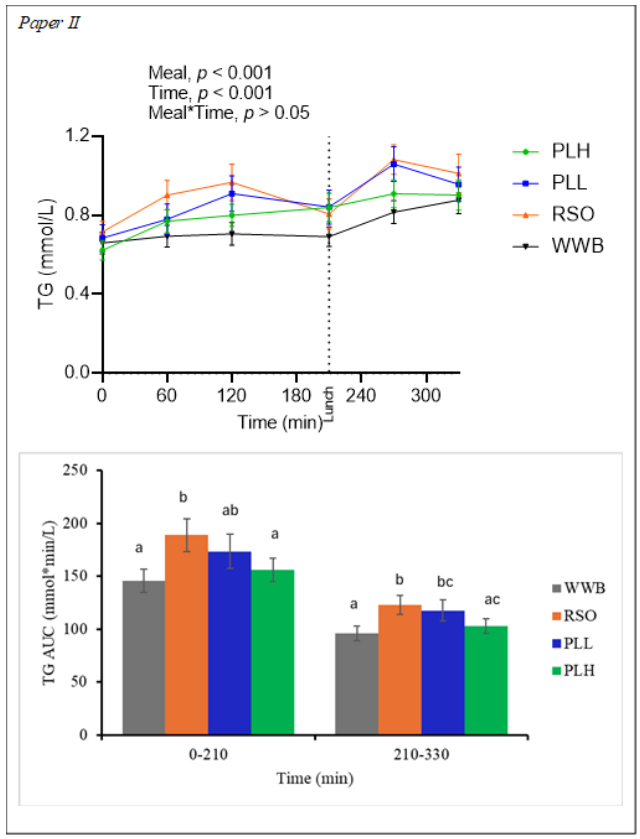

Figure 27: Changes in TG concentrations after test breakfasts and standardised lunch meals. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. WWB, white wheat bread; PLH, 15 g oat polar lipids; PLL, 7.5 g oat polar lipids and 8.3g rapeseed oil; RSO, 16.6 g rapeseed oil. AUC, area under curve.

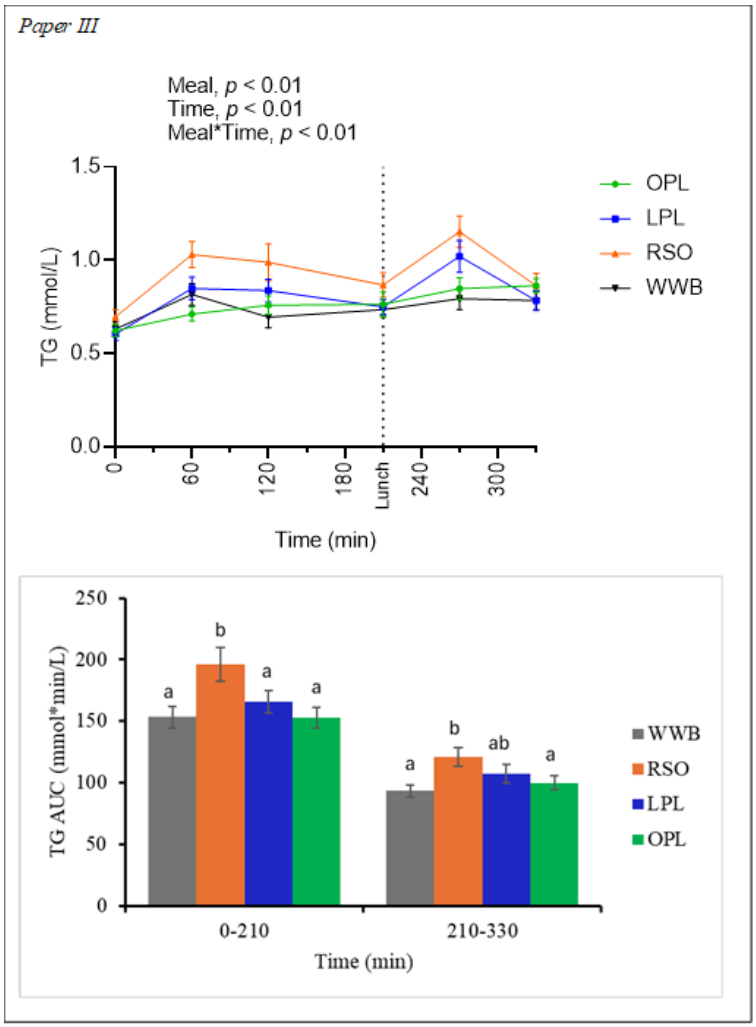

Figure 28: Changes in TG concentrations after test breakfasts and standardised lunch meals. Different letters (a, b and c) in the bar diagram indicate significant differences. WWB, white wheat bread; OPL, 15 g oat polar lipids; LPL, 15 g lecithin (polar lipids); RSO, 18 g rapeseed oil. AUC, area under curve.

In *Paper II*, no significant variations were found in FFA concentrations during the whole experimental period ($P > 0.05$). FFA were not determined in *Paper III*.

Subjective appetite ratings

In *Paper I*, no significant differences in subjective appetite ratings (desire to eat, hunger and satiety) were observed depending on meals after breakfast or after the standardised lunch ($P > 0.05$). Subjective appetite ratings were not determined in *Paper II* and *Paper III*.

Results, Paper IV

Baseline Characteristics

No statistical significance differences were seen in fasting glucose and insulin concentrations (i.e. before the start of test meals; $P > 0.05$). There was no significance difference of the appetite (hunger, satiety and desire to eat) rating score at fasting. Data can be found in *Paper IV*.

Glucose and Insulin Responses

The glucose iPeak ($P < 0.01$) after the BG4 test meal significantly decreased compared to the Ref. meal (-28%, $P < 0.01$). The study resulted in 28% reduced iAUC (0–60 min) after BG4 compared to Ref ($P < 0.01$). There was no statistically significant difference in iAUC at 0–120 min after all OBG test meals compared to Ref ($P > 0.05$). The iAUC after the standardised lunch with the test meal BG4 was 24% lower compared to Ref. breakfast ($P < 0.05$, Figure 29).

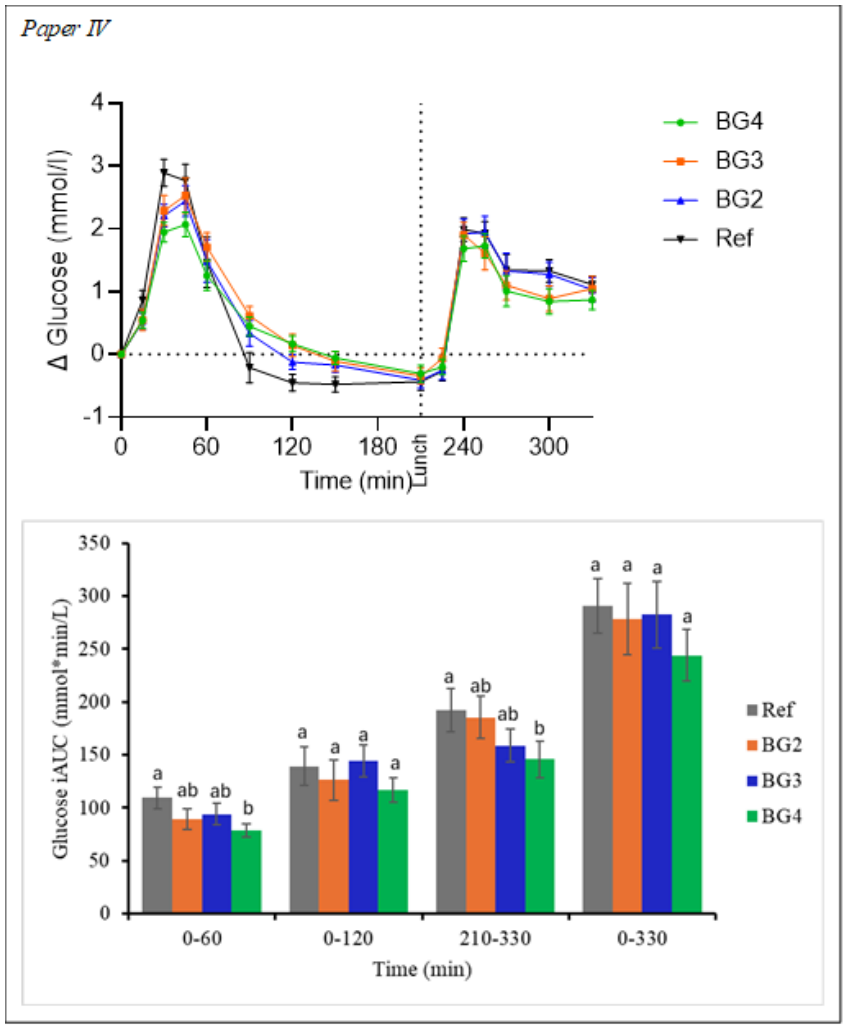

Figure 29: Incremental changes in blood glucose concentrations after test breakfasts and standardised lunch meals. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. BG2, glucose plus 2 g beta-glucan; BG3, glucose plus 3 g beta-glucan; BG4, glucose plus 4 g beta-glucan; Ref, glucose solution. iAUC, incremental area under curve.

The insulin iPeak was significantly reduced with the test product BG3 and BG4 compared to Ref. The iAUC during the course of entire investigation time was significantly lower after BG3 and BG4 compared to Ref (iAUC 0–330 min, $P < 0.05$). The iAUC during 0–60 min for BG3 and BG4 resulted in lower insulin concentration compared to Ref ($P < 0.01$). The iAUC during 0–120 min after BG2 and BG4 intake were significantly reduced compared to Ref. After the standardised

lunch, the iAUC was significantly reduced with BG3 and BG4 compared to Ref. ($P < 0.05$, Figure 30).

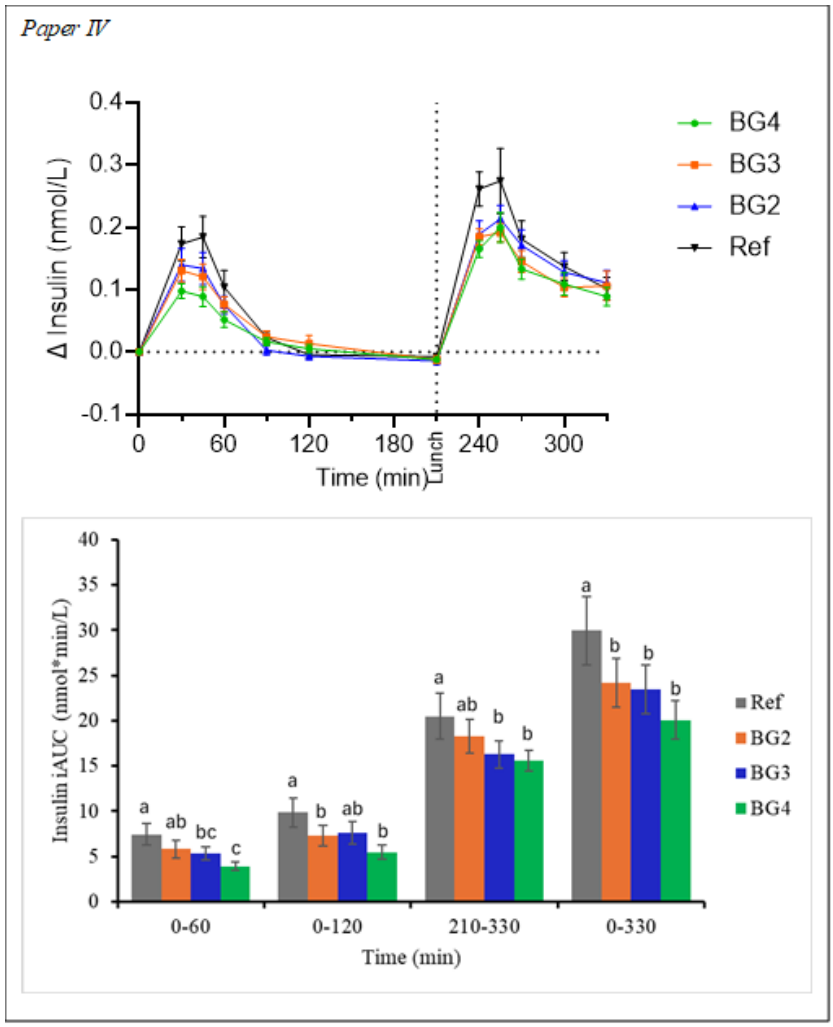

Figure 30: Incremental changes in blood glucose concentrations after test breakfasts and standardised lunch meals. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. BG2, glucose plus 2 g beta-glucan; BG3, glucose plus 3 g beta-glucan; BG4, glucose plus 4 g beta-glucan; Ref, glucose solution. iAUC, incremental area under curve.

Subjective Appetite rating

During the entire investigation period (0–330 min, Figure 31), the hunger AUC of BG4 was significantly lower compared to Ref. ($P < 0.05$). In addition, the AUC during 0–210 min was significantly lower with all BG-containing test meals compared to Ref. ($P < 0.01$). No significant differences were observed in the hunger score after lunch (210–330 min) within the test meals ($P > 0.05$).

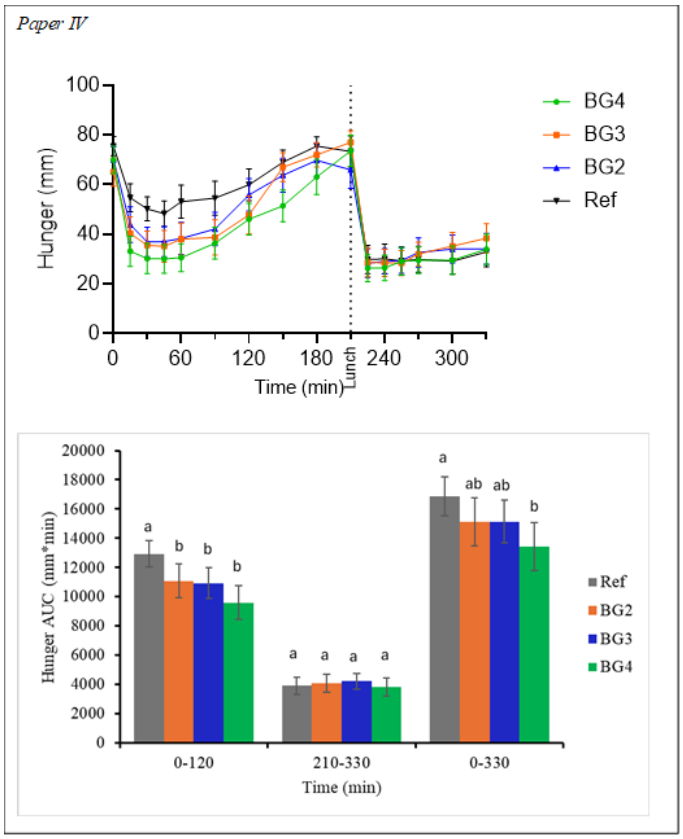

Figure 31: Changes in hunger rating after test breakfasts and standardised lunch meals. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. BG2, glucose plus 2 g beta-glucan; BG3, glucose plus 3 g beta-glucan; BG4, glucose plus 4 g beta-glucan; Ref, glucose solution. AUC, area under curve.

BG4 resulted in a higher subjective feeling of satiety compared to Ref. during the entire study duration (0–330 min, $P < 0.01$). The AUC during 0–210 min was

significantly higher with BG3 ($P < 0.01$) and BG4 ($P < 0.001$) test meals compared to Ref. No significant differences were observed in satiety score after lunch intake (210–330 min) among the test meals ($P > 0.05$, Figure 32).

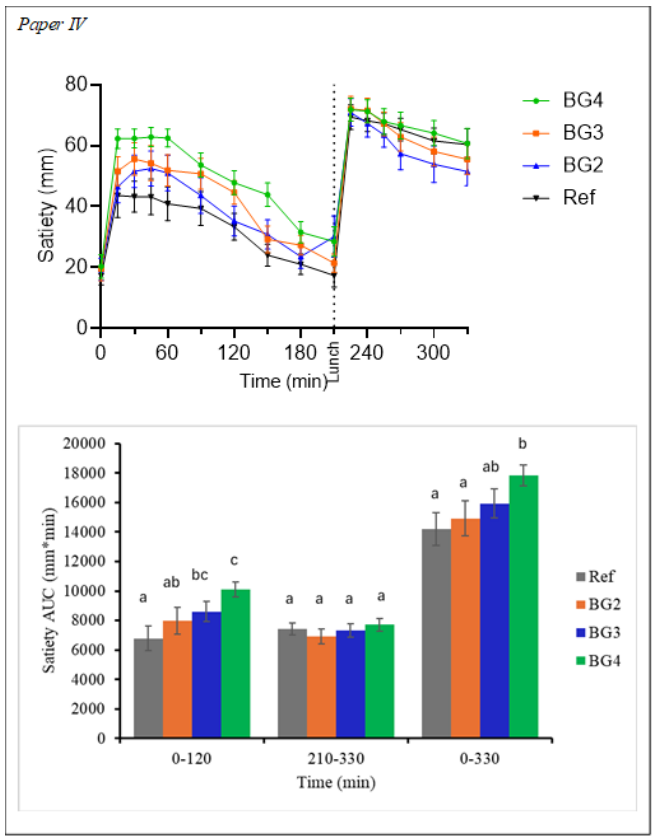

Figure 32: Changes in satiety rating after test breakfasts and standardised lunch meals. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. BG2, glucose plus 2 g beta-glucan; BG3, glucose plus 3 g beta-glucan; BG4, glucose plus 4 g beta-glucan; Ref, glucose solution. AUC, area under curve.

During the entire investigation period (0–330 min), the desire-to-eat AUC after all OBG test meals was significantly lower compared to Ref. ($P < 0.05$). The AUC during 0–210 min was significantly lower with all BG-containing test meals compared to Ref. No significant differences were observed in desire-to-eat score after lunch intake (210–330 min) within the test meals ($P > 0.05$, Figure 33).

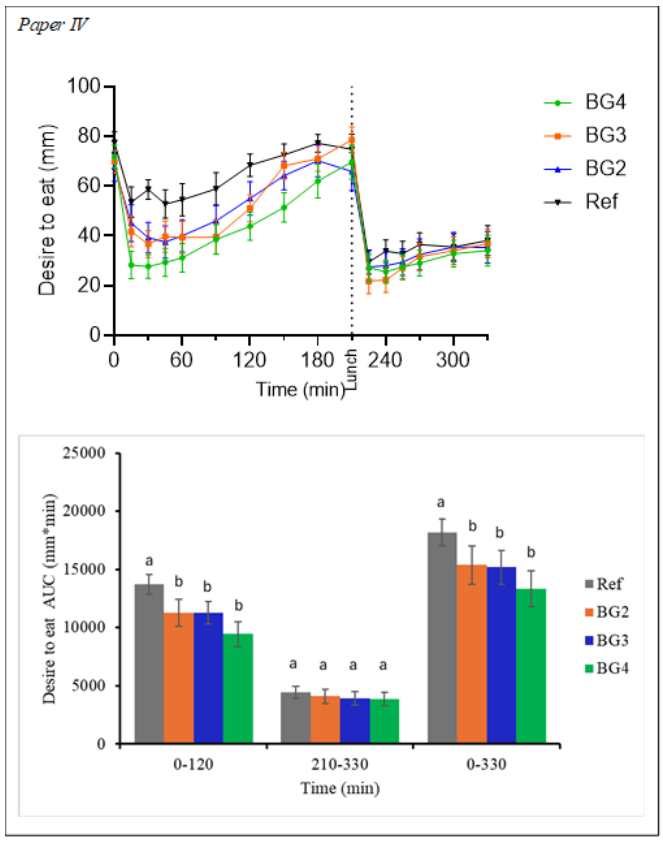

Figure 33: Changes in desire to eat rating after test breakfasts and standardised lunch meals. Values are means ± SEM. Different letters (a, b and c) in the bar diagram indicate significant differences. BG2, glucose plus 2 g beta-glucan; BG3, glucose plus 3 g beta-glucan; BG4, glucose plus 4 g beta-glucan; Ref, glucose solution. AUC, area under curve.

Discussion, Papers I–III

This thesis investigated the postprandial metabolic effects of oat polar lipids in an acute breakfast and a second-meal standardised lunch study design. The aim of *Paper I* was to study metabolic effects of OPL in a liquid oat base beverage and compare them with those of a widely used edible oil containing very low levels of polar lipids, i.e. rapeseed oil, included in the same food matrices [88]. *Paper II* studied the dose response effects of OPL and whether changing the physical form to solid meals affects the postprandial metabolic impact of OPL observed in *Paper I*. The results revealed that supplementation of the breakfast with OPL, which are particularly rich in galactolipids – e.g. digalactosyldiacylglycerols – has the potential to improve cardiometabolic risk-associated metabolic biomarkers, when incorporated into both a liquid and a solid food matrix.

Ingestion of polar lipids, of both animal and plant origin, has previously been suggested to exert beneficial effects with respect to supressing inflammatory mediators and improving gut health [91]. Most of those studies have been conducted to investigate effects of milk polar lipids and only a few have investigated health effects of plant polar lipids [12,91-97]. These studies were carried out using low doses of polar lipids (i.e. <3g) [91-94,96] and not focusing directly on their effects on postprandial glucose or insulin responses [12]. The present thesis work is the first to observe improved acute and second-meal postprandial glycaemic regulation following ingestion of a meal rich in oat polar lipids.

The results revealed that a breakfast meal containing 12g (*Paper I*), 7.5g (to some extent) and 15g (*Papers II–III*) polar lipids from oats reduced both glucose and insulin responses compared RSO or to a close to fat-free breakfast. In addition, OPL reduced after-lunch postprandial increments of TG and FFA compared to a fat-free meal and to RSO, respectively. The OPL breakfast also increased circulating concentrations of two gut hormones involved in metabolic and appetite regulation (GLP-1 and PYY) compared to RSO. In *Paper III*, the postprandial metabolic effects of OPL were compared with those of a commercially available polar lipid preparation, sunflower lecithin. The study showed that the impact of 15g sunflower lecithin on the metabolic variables investigated was similar to that of an equivalent OPL dose.

An interesting observation underpinning the importance of the results of this thesis is the beneficial impact of OPL and lecithin on postprandial metabolic test variables after a standardised meal consumed 3.5h after the ingestion of the polar lipids. For example, improved blood glucose regulation, lowering of triglycerides and increased concentrations of circulating GLP-1 and PYY were observed until the end of the experimental session (5.5h) in all three studies (*Papers I–III*). This constitutes an important finding since disrupted postprandial metabolic regulation is an established risk factor for the development of CMD. Thus, both postprandial

glycaemia and triglyceridaemia are risk factors for T2D [98] and/or CVD [99,100]. Consequently, the results indicate that OPL and sunflower lecithin have the potential to improve multiple risk markers encompassed by the MetS, and therefore can be suggested to be protective against T2D and CVD.

It must be noted that incorporation of fat in carbohydrate-rich meals in general reduces the acute postprandial glycaemic responses [101,102]. However, the present thesis demonstrates that OPL (12g and 15g) and LPL (15g) exert effects beyond the established knowledge regarding the impact of fat on postprandial glycaemic response. Consequently, glucose responses after OPL (*Papers I–II*) and LPL (*Paper III*) were more significantly reduced compared with the effect of similar amounts of RSO. While in *Papers I–III* both OPL and RSO resulted in reduced acute postprandial glucose response after breakfast compared to WWB, the OPL meal also resulted in a significantly reduced glucose response compared with the RSO meal. These results thus show that not all lipids are equally potent for lowering postprandial glucose concentrations.

Not so surprisingly, the dose of polar lipids in a meal has a significant impact on the metabolic effects observed. However, since for most people it is not desirable to add extra lipids, or calories in general, to a normal diet on a daily basis, it is important to establish an optimal (i.e. as low as possible) dose of polar lipids that can provide health benefits. In *Paper II*, the results demonstrate that a dose equal to 7.5g oat polar lipids increased GLP-1 and reduced ghrelin concentrations compared with RSO, but was not sufficient to lower postprandial glucose concentrations compared with RSO during the 5.5 h experimental session. However, 7.5g OPL improved postprandial glucose tolerance during the experimental period compared with the WWB reference, whereas no improvement was observed after RSO. In addition, post-meal triglyceride concentrations were less prominently increased after 7.5g OPL.

Insulin responses after the test meals followed the same pattern as the glucose responses in *Papers I–III*. Consequently, the OPL (12g and 15g) and lecithin meals resulted in lower postprandial insulin concentrations during both the test breakfast and the standardised lunch periods compared to RSO and fat-free meals (NL or WWB). No lowering effects on postprandial insulin concentrations were seen after RSO compared with WWB. The beneficial modulation of second-meal glucose regulation by OPL and sunflower lecithin is an interesting health effect, the explanation for which is as yet unclear. One possible mechanism could be related to a delayed or limited digestion of the polar lipids compared to rapeseed oil, with the consequent increase in the release of gastrointestinal hormones. The observations confirm the glycemia-modulating properties of oat polar lipids that go beyond the known action of dietary fats in general [103].

Food matrices are crucial in determining the bioavailability and absorption of nutrients. Numerous investigations have shown that the food matrix, calorie count,

types of available macronutrients, quantity and complexity of the meal have an influence on the rate and extent to which macronutrients are digested [104-108]. The digestion of solid meals requires more mechanical processing, which slows down the process of nutrient absorption and causes, for instance, a slower and more prolonged increase in blood glucose levels [109]. According to several reports, the rate of gastric emptying is noticeably lower for solid meals than for liquid meals [110,111], which can cause the macronutrients to be digested and absorbed more slowly. The rate of starch digestion affects the postprandial rise in blood glucose and consequent insulin responses. The overall number of calories from dietary fat in *Paper II* was approximately half that used in the *Paper I* (16.6g vs 33.0g, respectively), which may have reduced the generic influence of fat on digestion and absorption rates of macronutrients. Furthermore, all meals that were lipid-enriched had an equal amount of total fat, which underpins the suggestion that mechanisms underlying the effects observed on the metabolic variables relate to the polar properties of the lipids investigated.

Results in *Papers I–III* indicate that oat polar lipids and sunflower lecithin trigger the release of PYY and the incretin hormone GLP-1 in the gut. These hormones play important roles in metabolic and appetite regulation and are thus involved in a variety of physiological mechanisms, including reduction of the gastrointestinal motility and gastric emptying rate, and as signal molecules in the gut-brain axis, resulting in satiety sensations [79,112,113]. Actually, GLP-1 analogues are being used for the treatment of T2D, and have shown to be effective also in the treatment of obesity [114].

The effects of the polar lipids on gut hormones reported here are in line with the reduced postprandial blood glucose increments observed in all three papers, both after breakfast and following the second meal at lunch.

It has been reported that fat in general in a carbohydrate-containing meal promotes secretion of incretin hormones and modulates other appetite-regulating hormones such as PYY and ghrelin [115-118]. Consequently, studies conducted in T2D patients with olive oil (containing only a minor amount of polar lipids) [113] demonstrated that consuming fat 30 minutes prior to a meal rich in carbohydrates has a significant effect on the rate of gastric emptying, and thus contributes to improving postprandial glycaemic excursions. The results in this thesis do not support effects of lipids in general on gastrointestinal hormones in healthy humans. Consequently, intake of RSO did not result in increased concentrations of circulating of GLP-1 or PYY, whereas such effects were observed after oat polar lipids and LPL. It can be suggested that the mechanisms underlying the here-observed effects of LPL and OPL on glucose regulation are, at least partly, due to a slower gastro-intestinal transit time induced by delayed and/or decreased intestinal fat digestion, beyond what can be expected of dietary fat in general. Delayed fat absorption is a potential enhancer of the release of gut hormones [113].

In Paper I, ghrelin concentrations were significantly reduced both after the OPL and RSO (12g) breakfasts compared to a meal without added lipids, but no significant differences were recorded between the lipid-containing products. On the contrary, in *Paper II*, ghrelin was significantly reduced in the postprandial period after OPL breakfast meals compared to both WWB and RSO. Furthermore, the results in *Paper III* showed that both OPL and LPL significantly reduced postprandial ghrelin concentrations compared to RSO. Ghrelin stimulates appetite and accelerates gastric emptying, which triggers hunger sensations [119]. This indicates that both OPL and LPL included in solid meals may reduce the hunger sensation, and the reduced ghrelin concentration recorded before commencing lunch (at 210 minutes) may lead to reduced calorie intake during the meal intake. In *Paper I*, the effects on ghrelin were similarly reduced for OPL and RSO in a liquid food matrix, but the relatively high amount of total fat in the meal might have masked potential differential effects, complicating the interpretation of results. As already mentioned above, one possible mechanism behind the increased concentrations of GLP-1 and PYY after a meal rich in the polar lipids investigated relates to delayed digestion and absorption in the small intestine. This, in turn, can be suggested to originate from reduced pancreatic lipase activity, resulting in a slower hydrolysis of the lipids. Restricted digestion and absorption may potentially result in a prolonged stimulation of gut hormones release throughout the gastrointestinal tract. Such a hypothetical mechanism was already suggested by Ohlsson et al. [12], and is supported by in vitro observations showing delayed enzymatic hydrolysis of triglycerides in the presence of polar lipids from oats [120], suggesting the possibility of lipase inhibition by OPL.

GIP was another gut hormone investigated in the work on this thesis. Besides its initially described incretin action, a number of additional effects have been reported for this hormone, whose physiological importance is not yet clear. Consequently, while GLP-1 is known to suppress postprandial glucagon response, GIP has been suggested to exert the opposite effect, i.e. to promote an enhanced response [78]. In addition, GIP has also been shown to facilitate fat accumulation in adipocytes [78]. Interestingly, PLH promoted a lower GIP response than the RSO meal. However, interpretation of these results in terms of their physiological significance for healthy humans is difficult.

Oat oil contains relatively high amounts (3.5 pmol/mg) of branched fatty acid esters of hydroxy fatty acids (estolides) [37,121,122]. To our knowledge, no data have been reported regarding naturally occurring estolides in sunflower, but their presence in LPL cannot be ruled out. Estolides have drawn attention due to their potential effects on metabolic health. Some reports indicate that estolides may exert anti-diabetic and anti-inflammatory effects and are suggested as a potential nutraceutical lipid [12,123-125]. Thus, in addition to the aforementioned, another possible mechanism behind the beneficial metabolic effects of OPL and/or LPL could be linked to the presence of naturally occurring estolides in these PLs. Ohlsson et al., reported that fractionated oat oil liposomes containing PL, which naturally

contains a high proportion of DGDG estolides, delayed lipid digestion, reduced total energy intake and modified satiety and appetite in healthy humans [12]. Yore et. al, reported that endogenous estolides have the potential to improve glucose tolerance and stimulate GLP-1 and insulin secretion, both in humans and mice [125]. Additionally, a 12-week supplementation of estolides (0.37 mg per day) resulted in improved insulin sensitivity in a mouse model [123].

Paper I demonstrated that a breakfast meal containing 12g oat polar lipids resulted in lowered concentrations of circulating FFA at the time of the standardised lunch meal. Similar observations were reported by Ohlsson et al. [12] and are in agreement with a putative delayed hydrolysis of lipids and prolonged absorption time of the digestion products. It could be suggested that the reduced late postprandial concentrations of serum FFA promoted by the polar lipids as compared with the other test products contributed to the improved glycaemic response seen after lunch, in addition to increased gut hormones. Accordingly, it has been shown that elevated circulating concentrations of FFA correlate with impaired insulin signalling [126] and reduced glucose tolerance [127].

As energy providers and carriers of dietary fat, TG are essential to metabolism. Postprandial increased TG have, however, been suggested among cardiometabolic risk factors [128]. In comparison to meals containing rapeseed oil, findings of the thesis demonstrated a considerable decrease in postprandial triglyceridemia after consumption of a breakfast with oat or sunflower polar lipids (*Papers I–III*). Thus, this thesis provides important information of the possibility that oat polar lipids can lower postprandial triglyceridemia and hence reduce the risk of cardiovascular illnesses.

Reduced circulating concentrations of FFA and TG are significant effects of dietary polar lipids, since elevated concentrations are considered a cardiovascular risk factor [100,129,130]. However, the lower blood lipid concentration observed here after intake of polar lipids might also, at least partly, relate to differences in the actual TG/fatty acid concentration in the different lipids tested. Consequently, all test products in *Paper I*, (with the exception of the meal without added lipids) contained 33g added lipids. However, supplementation with PLH (12g oat polar lipids/meal), which significantly restricted postprandial TG and FFA increments, provided a significant proportion – 40%, of polar lipids and approximately 60% TG – while the PLL (1g oat polar lipids/meal) contained only 4% polar lipids and the remainder were mainly TG. Thus, both PLL and RSO are essentially made of TG. Therefore, the total amount of fatty acids ingested, and thus potentially absorbable as substrates for TG formation in the body, was lower in the PLH breakfast.

The results of this thesis indicate the significant role of oat polar lipids and sunflower lecithin in regulating postprandial metabolic responses. The results show that some dietary lipids may have a positive effect on the regulation of blood glucose and lipid profiles and some important gut hormones. This effect is evident in various

types of meals, whether they are in liquid or solid form. These findings suggest that particular dietary lipids play an important role in managing lifestyle-related diseases.

Discussion, Paper IV

Paper IV investigated the impact of OBG on postprandial glycaemic responses acutely after intake and following a standardised meal consumed after 3.5h. An important research question was to evaluate whether a dose lower than 4g of OBG per 30g avCHO can improve acute postprandial glucose responses. The results revealed that, in addition to a noticeable reduction in the acute postprandial glucose iPeak after 4g OBG compared to the Ref., a significantly reduced glucose iPeak was observed when 2g OBG were included in the meal. Including 3g OBG did not have a significant effect, but resulted in a strong trend ($p = 0.09$) towards a reduced glucose iPeak. These results thus indicate the potential postprandial blood glucose-reducing effect of a dose of BG lower than the 4g/30g avCHO, which is stated in the current EFSA regulation for approved claims as the lower limit for a glycemia-reducing effect of BG-containing foods [16].

The postprandial glucose response during the first 60 minutes (iAUC 0–60 min) after 4g OBG was significantly lower compared to the reference product, Ref. However, no significant effects on blood glucose responses were detected after 4g OBG when the iAUC was calculated based on a 2h postprandial period instead. The modulated postprandial blood glucose excursion observed after OBG, i.e. low iPeak but prolonged net increment of blood glucose concentrations above the fasting values, is probably related to increased viscosity of chyme, which reduces the gastric emptying rate and the absorption of glucose in the small intestine [40,131,132]. Such appearance of the postprandial blood glucose profile has been related to health benefits, both with respect to the lower blood glucose peak, but also due to the prolonged net increment of glucose levels, which may potentially increase insulin sensitivity at the following meal [133]. It is noteworthy that insulin response was significantly reduced after all doses (2g, 3g, 4g) of OBG during the entire test period (iAUC 0–330 min), compared with the Ref. Due to the specific impact on the acute postprandial blood glucose profile of viscous dietary fibre, i.e. low iPeak but a prolonged but low net increment above the fasting value, it can be hypothesised that, if solely taken into account as a measure of postprandial glycaemic impact, the 2h blood glucose increments do not show a correct picture of the OBG health effects. It can be suggested that the iPeak, or an iAUC for periods shorter than 120 minutes, would be more appropriate for judging glycaemic benefits of this, and perhaps other, viscous dietary fibres.

This work presents novel findings regarding second-meal effects of OGB on blood glucose regulation. Thus, intake of 4g OBG at breakfast resulted in improved postprandial glucose tolerance after a meal consumed 3.5h thereafter; i.e. OBG may induce a so called “second-meal effect” on glucose tolerance. Maintaining tightly controlled blood glucose concentrations over a prolonged period is important, as it can lead to a reduced risk of obesity, T2D and cardiovascular diseases [134,135].

Another important finding regarding the metabolic health potential of OBG is the effect on acute postprandial and second-meal attenuation of subjective appetite sensations. Such effects on appetite variables may lead to reduced energy intake and thus may help prevent and treat obesity.

Conclusions

The results from the present thesis provide novel insights into the health benefits of plant polar lipids and oat beta-glucans which, taken together, suggest significant potential of these molecules for the prevention of common lifestyle disorders, such as obesity, T2D and CVD.

In summary, the research demonstrates beneficial effects of polar lipids from oats and sunflower on postprandial glycaemic control, blood lipids and gut hormones in healthy volunteers. The health benefits were seen not only in the acute postprandial period, but also following a standardised meal consumed after 3.5h. Notably, a significant reduction in the acute postprandial blood glucose peak was observed after 2g of OBG / 30g avCHO, suggesting the effectiveness of OBG at lower doses than the current EFSA claim of 4g. Additionally, OBG exhibited potential to attenuate postprandial and second-meal subjective appetite sensations.

The main conclusions drawn from the present thesis are summarised as follows:

- Ingestion of 7.5g, 12g and 15g polar lipids from oats improves acute postprandial blood glucose and insulin responses.
- 12g and 15g oat polar lipids improve second-meal blood glucose and insulin responses.
- 12g oat polar lipids reduce circulating FFA levels (*Paper I*).
- 12g and 15g oat polar lipids reduce circulating TG concentration.
- 12g and 15g oat polar lipids increase postprandial release of GLP-1 and PYY.
- 15g oat polar lipids reduce postprandial ghrelin concentrations.
- 12g and 15g oat polar lipids reduce GIP concentrations.
- 15g sunflower lecithin improve blood glucose and insulin response, and led to reduced TG, increased GLP-1 and PYY, reduced ghrelin and GIP concentrations.
- 4g of OBG per 30g avCHO led to improved postprandial glucose tolerance both acutely and after a second meal.

- 2g OBG led to a reduction in acute postprandial glucose concentrations, suggesting the effectiveness of OBG at lower doses than the current EFSA recommendation of 4g.
- 3g and 4g OBG showed potential to attenuate acute and second-meal appetite sensations.

The results suggest that oat bioactives (oat polar lipids and beta-glucans), and also sunflower lecithin, have anti-obesogenic and anti-diabetic properties, and thus may be included in innovative foods aimed at preventing cardiometabolic illnesses.

Future Perspectives

In this thesis, the main focus has been on the acute postprandial and second-meal effects of oat polar lipids and beta-glucans on cardiometabolic risk-related markers in healthy subjects in the age range of 20–40 years. In future studies, it would be interesting to investigate the metabolic effects of polar lipids and beta-glucans in other population groups, such as patients with existing cardiometabolic conditions (e.g. obesity, T2D, MetS, hyperlipidemia), as well as different age groups. This would help to clarify whether the observed benefits can be generalised and identify possible group-specific recommendations.

Moreover, subsequent studies should focus on investigating the long-term metabolic effects of PL preparations, including detailed dose-response evaluation.

It would be important to dig deeper into the mechanistic pathways through which oat and sunflower polar lipids exert their beneficial effects on acute postprandial and second-meal metabolic regulation, and possibly also in a longer term. This could involve investigations of polar lipid structures formed in food matrices, and their influence on starch and lipid digestion in the small intestine. In longer-term intervention studies, it would be important to explore their interactions with gut microbiota.

Additionally, exploring additive or synergistic effects of oat-derived bioactive compounds investigated with other bioactives, e.g. avenanthramides, would likely generate important information that could lead to the formulation of multi-component functional diets with enhanced cardiometabolic benefits due to combined mechanistic pathways to yield a beneficial modulation of CMD risk-related markers.

Acknowledgements

I would like to extend my deepest gratitude to a number of individuals; without these incredible people I would never have been able to complete this work.

Foremost, I express my heartfelt thanks to my main supervisor, Anne, whose guidance, patience and unwavering faith in my abilities have been a pillar throughout this journey. Again, thanks Anne, for teaching me so much during my years as a doctoral student and for always taking the time to talk even though you didn't have to.

I am equally grateful to my co-supervisors: Juscelino, for his welcoming and supportive nature, critical thinking and for opening a new dimension and making my research experience enriching and enjoyable; and Lieselotte, whose support in all matters has been indispensable.

My research could not have been possible without funding from ScanOats. I am profoundly thankful for their financial support. Thanks to my fellow ScanOats PhD students for making this time enjoyable, inspiring, and for organising ScanOats "fikas".

A special thanks to the Research School LiFT, which provided an enriching academic environment through its courses, study visits and enjoyable excursions. I am particularly thankful to Fredric Prothon for being an inspiring mentor within the LiFT.

I extend my gratitude to Olex, who provided essential support in the meal studies and assistance with all the analyses.

My thanks also go to Hans, who adeptly handled all IT-related issues, ensuring that technical difficulties never impeded my research progress.

I am thankful for the dedication of all the master's students who supported the meal studies. Their contributions have been unforgettable for this work.

I would also like to thank Soraya for her assistance with the OPL-LPL meal study, and both Marina and Kiara for their support with the beta-glucan study. Their expertise and assistance were crucial to the success of these elements of my work.

Heartfelt thanks to all the study participants, without whom this thesis would not have been possible. Their participation and commitment were the foundation of my research.

Finally, I cannot express enough gratitude to my family for their love and unwavering support. To my wife, Rizwana, and my children, Anindo and my dear daughter Adrita – thank you for tolerating my mood swings, for your endless patience, and for standing by me through the ups and downs of this long journey. Your support has been my greatest strength.

Thank you all for making this thesis possible.

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Printed by Media-Tryck, Lund 2024 NORDIC SWAN ECOLABEL 3041 0903

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Department of Process and Life Science Engineering
Faculty of Engineering
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ISBN 978-91-8096-042-7