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“A new door to the Unbelievable, to the Possible,
a new day that can always bring you anything
if you have no objection to it”
- Tove Jansson -

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ABSTRACT

Obesity is a key factor leading to the development of insulin resistance, and its prevalence is increasing all over the world. The general benefits of exercise, both mentally and physically, are widely known, but in recent years, organs such as the intestine, its microbiota, and their crosstalk with other organs have exhibited high research interest. As genetic components affect the response to exercise, twin studies offer unique possibilities to minimize the confounding effects of genetics.

This thesis aimed to study the effects of long-term exercise training on liver and intestinal insulin-stimulated glucose uptake (GU), pancreatic and liver fat content, and intestinal microbiota composition. Tissue-specific GU was measured using positron emission tomography (PET), and fat content using magnetic resonance imaging and magnetic resonance spectroscopy, and microbiota composition was studied with 16s rRNA at baseline and after six months of regular exercise training in monozygotic twins discordant for BMI. To gain complementary data on liver GU and inflammation, a supplemental rat study with PET imaging and histological liver sample assessments was done.

At baseline, heavier twins had higher liver and pancreatic fat content, disrupted liver metabolism, and worse liver inflammatory state compared to leaner twins. Heavier twins also had lower intestinal GU, while no differences were seen in intestinal microbiota composition between the twin groups. Exercise tended to decrease liver fat in the heavier twins and decreased blood gamma-glutamyl transferase level, an oxidative stress marker. In rats, exercise decreased liver fat content, especially when combined with a dietary switch from a high-fat diet to chow, and reduced liver inflammation. Training increased colonic GU in leaner twins and caused significant changes in intestinal microbiota composition. No change was seen in pancreatic fat content.

In conclusion, exercise and exercise combined with dietary change from a high-fat diet to chow caused several improvements in the liver and intestine. The magnitude of the effects driven by exercise varies based on baseline obesity level, as leaner individuals seem to benefit most in colon GU and microbiota composition, while heavier individuals show a reduction in liver fat content and liver inflammation.

KEYWORDS: Liver, Pancreas, Intestine, Exercise training, Insulin resistance, Obesity, Positron Emission Tomography

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Sisätautioppi
Valtakunnallinen PET-keskus
MARTIN LIETZÉN: Lihavuuden ja liikunnan vaikutukset maksaan, haimaan ja suolistoon identtisillä kaksosilla
Väitöskirja, 180 s.
Turun kliininen tohtoriohjelma (TKT)
Toukokuu 2026

TIIVISTELMÄ

Lihavuus on maailmassa yleistyvä ilmiö ja yksi tärkeimmistä insuliiniresistenssiin johtavista tekijöistä. Liikunnan henkiset ja fyysiset hyödyt ovat laajalti tunnettuja. Viime vuosina erityisesti suolisto, ja suoliston mikrobisto ja niiden vuorovaikutus muiden elinten kanssa ovat herättäneet suurta tutkimuksellista kiinnostusta. Perimä vaikuttaa liikunnan vasteeseen yksilötasolla, ja siten identtiset kaksoset tarjoavat ainutlaatuisen mahdollisuuden minimoida perimän vaikutusta tutkimustuloksiin.

Tässä väitöskirjassa tutkittiin pitkäaikaisen liikuntaharjoittelun vaikutuksia maksan ja suoliston insuliinistimuloituun glukoosiaineenvaihduntaan, haiman ja maksan rasvapitoisuuteen ja suoliston mikrobistoon. Glukoosinottoa kudoksiin mitattiin positroniemissiotomografialla, rasvapitoisuutta magneettikuvauksella ja magneettispektroskopialla ja suoliston mikrobistoa 16s rRNA:lla lähtötilanteessa ja kuuden kuukauden liikuntaintervention jälkeen BMI:n osalta eroavilla identtisillä kaksosilla. Maksan glukoosinoton ja tulehduksen osalta toteutettiin täydentävä tutkimus rotilla käyttäen PET-kuvantamista, sekä tutkimalla maksan histologiaa.

Lähtötilanteessa painavammilla kaksosilla oli korkeampi maksan ja haiman rasvapitoisuus, maksan tulehdustila ja häiriintynyt maksan aineenvaihdunta verrattuna hoikempiin kaksosiin. Painavammilla kaksosilla oli myös vähäisempi glukoosinotto suolistossa, mutta kaksosten mikrobistossa ei havaittu eroja. Painavammilla kaksosilla liikunta vähensi maksan rasvapitoisuutta ja rotilla erityisesti yhdistettynä ruokavaliomuutokseen rasvaisesta tavalliseen ruokaan. Liikunta vähensi painavammilla kaksosilla glutamyylitransferaasia, joka mm. ilmentää oksidatiivista stressiä, ja rotilla maksan tulehdusmuutoksia. Harjoittelu lisäsi paksusuolen glukoosinottoa hoikemmilla kaksosilla ja muutti suoliston mikrobiomin koostumusta. Haiman rasvapitoisuudessa ei havaittu muutoksia.

Yhteenvetona, liikunta erityisesti yhdistettynä ruokavaliomuutokseen rasvaisesta ruokavaliosta tavalliseen ruokaan saa aikaan useita hyödyllisiä muutoksia maksassa ja suolistossa. Liikunnan vaikutukset vaihtelevat lähtötason lihavuuden mukaan, sillä hoikemmat henkilöt hyötyvät eniten paksusuolen glukoosinoton ja mikrobiston koostumuksen suhteen, kun taas painavammilla henkilöillä maksan rasvapitoisuus ja maksan tulehdus vähenevät.

AVAINSANAT: Maksa, Haima, Suolisto, Liikunta, Insuliiniherkkyys, Lihavuus, Positroniemissiotomografia

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Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASV	Amplicon sequencing variant
ATP	Adenosine triphosphate
BMI	Body mass index
CRP	C-reactive protein
CT	Computed tomography
DZ	Dizygotic
FDR	False discovery rate
FFA	Free fatty acid
GLUT	Glucose transporters
GT	Gamma-glutamyl transferase
GU	Glucose uptake
HFD	High-fat diet
HIIT	High-intensity interval training
HOMA-IR	Homeostatic model assessment for insulin resistance
HOMA2-β	Homeostasis Model Assessment 2 - Beta-cell function
HU	Hounsfield unit
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IVGTT	Intravenous glucose tolerance test
LFC	Liver fat content
MAFLD	Metabolic dysfunction-associated fatty liver disease
MASH	Metabolic dysfunction-associated steatohepatitis
MHO	Metabolically healthy obesity
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
M-value	Whole-body insulin-stimulated glucose uptake
MZ	Monozygotic
OGTT	Oral glucose tolerance test

PCoA	Principal Coordinate Analysis
PET	Positron emission tomography
PFC	Pancreatic fat content
RM	Repetition maximum
ROS	Reactive oxygen species
SAT	Subcutaneous adipose tissue
SGLT	Sodium glucose cotransporter
STAT3	Signal transducer and activator of transcription 3
T2D	Type 2 diabetes
TNF-α	Tumor necrosis factor alpha
TSPO	Translocator protein
VAT	Visceral adipose tissue
VOI	Volume of interest
VO2peak	Aerobic capacity
WHO	World Health Organization

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Lietzén MS, Mari A, Ojala R, Hentilä J, Koskensalo K, Lautamäki R, Löyttyniemi E, Parkkola R, Saunavaara V, Kirjavainen AK, Rajander J, Malm T, Lahti L, Rinne JO, Pietiläinen KH, Iozzo P, Hannukainen JC. Effects of Obesity and Exercise on Hepatic and Pancreatic Lipid Content and Glucose Metabolism: PET Studies in Twins Discordant for BMI. *Biomolecules*. 2024; 14(9):1070.

II Lietzén MS, Guzzardi MA, Ojala R, Hentilä J, Heiskanen MA, Honkala SM, Lautamäki R, Löyttyniemi E, Kirjavainen AK, Rajander J, Malm T, Lahti L, Rinne JO, Pietiläinen KH, Iozzo P, Hannukainen JC. Regular Exercise Training Induces More Changes on Intestinal Glucose Uptake from Blood and Microbiota Composition in Leaner Compared to Heavier Individuals in Monozygotic Twins Discordant for BMI. *Nutrients*. 2024; 16(20):3554.

III Lietzén MS, La Rosa F, Hentilä J, Jalo A, Helin JS, Nissinen TA, Löyttyniemi E, Laakso E, Eskola O, Rajander J, Iozzo P, Hannukainen JC. Exercise training combined with chow diet ameliorates high fat diet-induced hepatic steatosis, inflammation and downregulated TSPO availability in rats. *Manuscript.*

1 Introduction

Obesity is one of the main factors in the development of insulin resistance (DeFronzo 2010) and each unit of increased body mass index (BMI) has been estimated to increase the incidence of Type 2 diabetes (T2D) by 11-33% (Y. Chen et al. 2018; Ohno et al. 2023). This is especially important considering the fact that the prevalence of obesity is ever-increasing, and according to the 2022 World Health Organization (WHO) report, 43% of adults aged 18 or over are overweight (S. K. Ahmed and Mohammed 2025).

The pancreas, liver, and intestine are organs with a role in metabolic homeostasis found in the abdominal region. Each of these organs has a unique role in managing metabolic homeostasis and human health (Leung and Ip 2006; Beger et al. 2018; Trefts et al. 2017; J. T. Collins et al. 2025; Azzouz and Sharma 2025). The role of the pancreas in the disruptions of glucose metabolism was noticed early (Banting et al. 1922) and together with overall peripheral insulin resistance (Freeman et al. 2025) became the focus of studies such as drug trials. However, the pancreas is not the only abdominal organ relevant to glucose homeostasis, as studies have shown that other organs, such as the liver (Iozzo, Geisler, et al. 2003; Samuel et al. 2004; Immonen et al. 2014) and intestine (H. Honka et al. 2013; Motiani et al. 2017) are also insulin-sensitive organs. This has led to an interest in the crosstalk between human organs in the pathophysiology of T2D and insulin resistance.

Exercise training is known to be overall healthy and beneficial in multiple ways, such as improving physical fitness and quality of life (Ali et al. 2021; Dibben et al. 2023), reducing blood pressure and chronic pain (Cheng Wang et al. 2019; Owen et al. 2020) and improving cognition (Gallardo-Gómez et al. 2022). Organ-specific metabolic benefits of exercise include, but are not limited to, decreased pancreatic (Heiskanen et al. 2018) and liver (Cuthbertson et al. 2024) fat accumulation, improved insulin-stimulated glucose uptake (GU) in the skeletal muscle (Reichkendler et al. 2013), liver (Iozzo, Geisler, et al. 2003) and intestine (Motiani et al. 2017) and modulation of intestinal microbiota composition (Zheng et al. 2022).

Genetics play a role in human health by affecting the susceptibility for certain diseases such as T2D (Naukkarinen et al. 2012) and also affects the individual response to different interventions such as exercise (Solomon 2018). Thus, the

confounding effect of genetics cannot be forgotten when studying metabolism, obesity, and exercise.

While the benefits of exercise to function and composition in the abdominal organs are known to a degree (Cuthbertson et al. 2024; Slentz et al. 2011; Motiani et al. 2017; Heiskanen et al. 2018), the effects of long-term exercise interventions are sparse, especially when evaluated with state-of-the-art methods such as FDG-PET and euglycemic hyperinsulinemic clamp. Exercise training is often studied using epidemiological studies or cross-sectional comparisons of sedentary subjects with elite athletes, which may overemphasise the effect of exercise.

In this thesis, the main aim was to evaluate the effects of a six-month-long exercise intervention on pancreatic, liver, and intestinal metabolism and composition and microbiota using monozygotic twins (MZ) discordant for BMI. MZ twins, which have the same inherited genes, enabled us to investigate the pathology and exercise-induced improvements in the absence of the confounding effects of genetic factors. We hypothesized that obesity would disrupt target organ metabolism, cause increased intra-organ adiposity, and alter intestinal microbiota composition. We also hypothesized that these adaptations to obesity could be ameliorated with exercise.

2 Review of the Literature

2.1 Obesity and insulin resistance

Obesity is a condition where an individual has abnormal and/or excessive fat accumulation, presenting a risk to the individual's health. According to the definition of the WHO, obesity is defined as a BMI of over 30kg/m^2 (Nuttall 2015). The prevalence of obesity has long been increasing, and according to the latest WHO report, in 2022, 43% of adults aged 18 or over were overweight (S. K. Ahmed and Mohammed 2025).

The level of obesity is associated with the presence of comorbidities (Martin-Rodriguez et al. 2015; Luo et al. 2024) with increased prevalence in higher levels of obesity. In 2021, higher than optimal BMI caused an estimated 3.7 million deaths by noncommunicable diseases, such as T2D and cardiovascular diseases (Brauer et al. 2024). To further highlight the significance of increasing obesity, the association of BMI and all-cause mortality is steep, as the nadir is between 20 and 24 kg/m^2, after which, mortality increases linearly with BMI (Angelantonio et al. 2016; Aune et al. 2016). Due to the ever-increasing prevalence of obesity and the comorbidities associated with obesity, the need for effective interventions towards obesity is greater than ever before.

Insulin is a peptide hormone produced by the β-cells of the pancreas, which acts as one of the main anabolic hormones of the body by regulating glucose metabolism. Insulin regulates the uptake of glucose in several organs, such as muscle (Norton et al. 2022), liver (Iozzo, Hallsten, et al. 2003) and intestine (H. Honka et al. 2013). In normal conditions, when insulin binds to the target organ receptors, it allows glucose to enter the target organ cells for energy metabolism.

Insulin resistance is a phenomenon defined as an impaired response of target tissues to insulin stimulation (Freeman et al. 2025). The development of insulin resistance and finally T2D can be divided into three main stages. The first stage is the phase where insulin secretion increases to compensate for the blunted response to regular insulin levels. The second stage is where the β-cells can no longer fully compensate for the increasing insulin resistance through insulin production. At the second stage of insulin resistance, blood glucose levels start to increase due to β-cells being unable to compensate for the insulin resistance, and the individual begins

to exhibit signs of prediabetes such as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) as defined by the American diabetes Association (Table 1). (Tabák et al. 2012). If this discrepancy between increasing blood glucose and a blunted response to insulin keeps progressing, the third stage is reached, and the diagnostic criteria of T2D are met (Brunton 2016).

Table 1. The diagnostic criteria for impaired fasting glucose and impaired glucose tolerance according to the American Diabetes Association (Tabák et al. 2012).

	Fasting plasma glucose, mmol/l	**2h glucose in OGTT, mmol/l**
Impaired fasting glucose (IFG)	5.6–6.9	<7.8
Impaired glucose tolerance (IGT)	<7.0	7.8–11.0
T2D	>7.0	>11.0

OGTT, Oral glucose tolerance test. Own drawing.

Obesity is one of the main components in the development of insulin resistance (DeFronzo 2010) and the risk of developing T2D increases linearly with the increase in BMI (Colditz et al. 1995). Previously, it has been estimated that each unit of increase in BMI increases the incidence of T2D by 11–33% (Y. Chen et al. 2018; Ohno et al. 2023) and managing obesity alone has been shown to be an effective way to improve insulin sensitivity (Immonen et al. 2014; McLaughlin et al. 2019). The clear mechanism of improved insulin sensitivity by isolated dietary weight loss is not clear, but obesity driven adipocyte hypertrophy is hypothesized to cause cellular hypoxia, which induces endoplasmic reticulum stress, lipolysis, and inflammation, leading to insulin resistance (Klöting and Blüher 2014). Weight loss is thought to improve insulin sensitivity by decreasing adipocyte size and thus reversing the negative effects caused by adipocyte hypertrophy (McLaughlin et al. 2019).

However, not all obesity is equal when it comes to insulin resistance, as obesity can be roughly categorized into two main manifestations: visceral (VAT) and subcutaneous (SAT) adipose tissue accumulation, which possess different effects on health (Bays et al. 2008). The total amount and distribution between VAT and SAT vary among individuals (Bays et al. 2008). Of these two main types of obesity, SAT accumulation, especially in the gluteofemoral region, has been thought of as a less harmful type of obesity (Manolopoulos et al. 2010). In the absence of insulin resistance, ectopic fat accumulation, and lipid profile abnormalities, this type of obesity has been called metabolically healthy obesity (MHO) by some (Blüher 2020). Though obesity with predominantly SAT accumulation may exhibit a more favourable risk profile in regard to the general comorbidities of obesity, MHO still

should not be considered a safe condition as the risks are still higher compared to lean individuals (Caleyachetty et al. 2017; Blüher 2020; Tanriover et al. 2023).

VAT accumulation, especially with the presence of ectopic fat accumulation in organs such as the liver and pancreas, is seen as the more harmful type of obesity. One of the reasons for this is that VAT is seen as the more metabolically active adipose tissue that causes inflammatory responses, such as increased expression of the inflammation regulator nuclear factor-kB and production of inflammation-inducing signals such as interleukin-6 in excessive VAT accumulation (Stenkula and Erlanson-Albertsson 2018; Lemmer et al. 2021). The proposed mechanism leading to insulin resistance due to VAT excreted pro-inflammatory cytokines is thought to be due to blockade of insulin action in tissues and organs such as skeletal muscle and the liver (Ota 2014; B. Ahmed et al. 2021). VAT accumulation is also considered harmful because VAT is thought to be highly lipolytic. Increased lipolysis is thought to lead to excessive release of fatty free acids into the portal vein and thus into organs such as the liver. (Gastaldelli and Basta 2010). Fatty free acid overload in the liver has been associated with worsening hepatic steatosis and hepatic insulin resistance (Gastaldelli and Basta 2010; Sancar and Birkenfeld 2024). Excessive VAT accumulation has been linked as a risk factor for developing comorbidities of obesity, such as insulin resistance (Neeland et al. 2013; Arner et al. 2013), hypertension (Zhong et al. 2025) and some cancer types (Du et al. 2017).

2.2 Exercise training and insulin sensitivity

Exercise training is physical activity that enhances fitness and overall health. Exercise can be performed in multiple different ways, which include, but are not limited to, strength and endurance training. López-Otín and Kroemer proposed eight hallmarks of health based on three main criteria (López-Otín and Kroemer 2021):

1. It should be associated with the healthy state
2. Its experimental or real-life perturbation should be vastly pathogenic
3. Its experimental or medical maintenance or restoration should have a broad pro-health activity.

Based on these criteria, the eight hallmarks of health were integrity of barriers, containment of local perturbations, recycling and turnover, integration of circuitries, rhythmic oscillations, homeostatic resilience, hormetic regulation, and repair and regeneration. Although more studies are needed, a large amount of evidence suggests that exercise affects most of the eight hallmarks of health (Qiu et al. 2023). Figure 1 summarises the main regulatory mechanisms by which exercise sustains health.

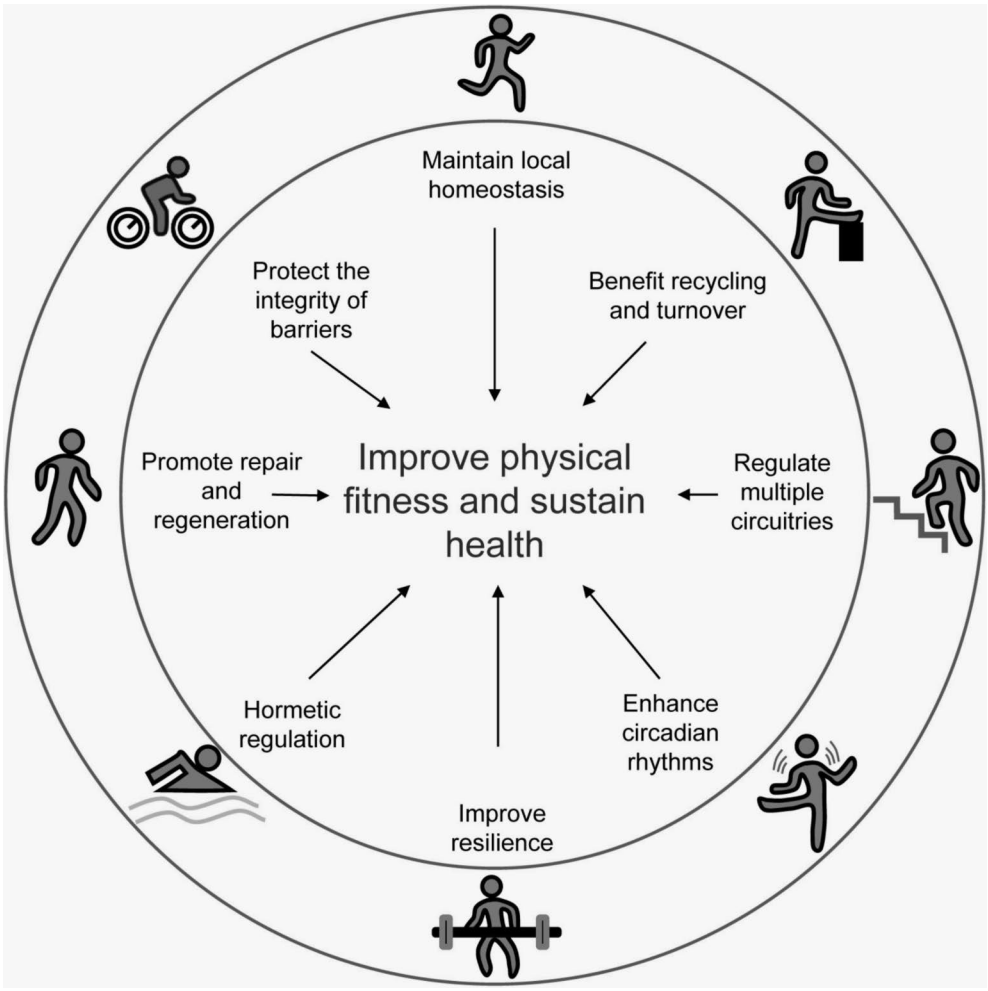

Figure 1. Exercise impacts the major hallmarks of health, including the integrity of barriers, containment of local perturbations, recycling and turnover, integration of circuitries, rhythmic oscillations, homeostatic resilience, hormetic regulation, as well as repair and regeneration. Reprinted with permission from (Qiu et al. 2023).

The benefits of regular exercise are so significant that the WHO global recommendations on physical activity for health recommend that adults aged 18–64 should follow the following recommendations (Bull et al. 2020):

WHO Guidelines on Physical Activity and Sedentary Behaviour.

1. All adults should undertake regular physical activity.
2. Adults should do at least 150-300 minutes of moderate-intensity aerobic physical activity; or at least 75-150 minutes of vigorous-intensity aerobic

physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week, for substantial health benefits

3. Adults should also do muscle-strengthening activities at moderate or greater intensity that involve all major muscle groups on 2 or more days a week, as these provide additional health benefits.
4. Adults may increase moderate-intensity aerobic physical activity to more than 300 minutes; or do more than 150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week for additional health benefits.

Similarly, the Finnish Institute for Health and Welfare has made recommendations on physical exercise, which also include recommendations for children. (THL 2023)

1. Adults should engage in moderately stressful aerobic exercise, such as walking, running, cycling, swimming, or dancing, for at least 2 hours and 30 minutes per week or vigorous aerobic exercise for at least 1 hour and 15 minutes per week.
2. Physical activity that supports muscle fitness and motor control should be practiced at least 2 times a week.
3. All children and adolescents should aim to be physically active every day of the week, most of the physical activity being endurance activity.
4. All children and adolescents should partake in vigorous endurance-type activity and physical activity that increases the strength of the muscular and skeletal system at least three days a week.

Exercise has an important role in insulin resistance, as insulin resistance is especially prevalent in overweight and sedentary individuals (Keshel and Coker 2015). Exercise can be used as a supportive method for weight loss and weight maintenance after weight loss (Petridou et al. 2019) especially when diet changes are combined with exercise (Johns et al. 2014). When comparing the effects of diet and exercise on obesity, studies have seen that exercise tends to decrease VAT when compared to diet only (Verheggen et al. 2016).

However, the benefits of exercise on insulin sensitivity do not require weight loss, as exercise has been shown to improve insulin sensitivity even without significant weight loss (Heiskanen et al. 2018; Ojala et al. 2024). This is because the skeletal muscle organ system is the largest one in the body, being about 40% of the total body weight of a young man (K. M. Kim et al. 2016). Around 80% of GU occurs in skeletal muscle under euglycemic hyperinsulinemic conditions (Thiebaud

et al. 1982), which is why skeletal muscle has been considered the main driver of whole-body insulin resistance (Merz and Thurmond 2020). In skeletal muscle, insulin binds to the tyrosine kinase receptor, which initiates a signalling cascade leading to the translocation of the facilitative glucose transporter (GLUT) 4 to the muscle cell plasma membrane and thus permitting GU (Carmichael et al. 2019). One of the main mechanisms in skeletal muscle insulin resistance is decreased transposition of GLUT4 into the plasma membrane as a response to insulin (van Gerwen et al. 2023).

Exercise modality affects the effect on insulin sensitivity. Both aerobic training and resistance training have been shown to be effective ways to improve insulin sensitivity (Suh et al. 2011; Motiani et al. 2017), but some studies have also seen that aerobic exercise or a combined protocol of resistance training and aerobic exercise is more effective at improving insulin sensitivity when compared to only resistance training (Slentz et al. 2011). Even within the modality of exercise, there may be differences in the effects of exercise intensity on insulin sensitivity, as higher intensity aerobic training has been shown to be more effective than training at a lower intensity in some (DiPietro et al. 2006), but not in all studies (K. A. Collins et al. 2022).

2.3 Twin studies

Twins are two individuals born from the same pregnancy. Twins can develop from a single divided zygote (monozygotic twins) or from two separate zygotes (dizygotic twins). In layman's terms, monozygotic twins are often called "identical twins" and dizygotic (DZ) twins "non-identical twins".

Twins offer unique insight into science, especially with MZ twins, where the genetic variance can be minimized. Due to being born of the same zygote, MZ twins are identical at the level of DNA, precluding somatic mutations, epigenetic modifications, and other later genetic changes. Twins often also share the same childhood environment and conditions until adulthood, which decreases the confounding effects of environmental factors.

Genetic background has a significant effect on the susceptibility to many conditions and diseases, such as obesity and T2D (Naukkarinen et al. 2012), with the concordance rate of T2D in MZ twins reaching as high as 70% (J. Kaprio et al. 1992). Genetic background also influences the distribution of fat between SAT and VAT, as previously it has been shown that there is a high correlation between MZ twins in SAT and VAT quantities (Jermendy et al. 2018). The magnitude of the beneficial effect of exercise also differs between individuals, and genetics has been shown to influence the effects of exercise on health (Solomon 2018).

While genetics influence human health as a whole, the effects of lifestyle choices cannot be forgotten. Previously, twin studies have shown that in twins discordant for obesity, the heavier twins have a significantly lower whole-body insulin sensitivity measured with euglycemic hyperinsulinemic clamp (Pietiläinen et al. 2006; Ojala et al. 2024). Finnish longitudinal twin studies spanning over 30 years have shown that less physically active twins measured by leisure-time physical activity questionnaires have lower VO_{2peak}, higher total fat percentage, and visceral adipose tissue area and liver fat index (Kujala et al. 2022). Twin studies on MZ twins discordant for BMI have also shown that heavier twins have higher incidences of disinhibited eating and higher binge-eating scores compared to their leaner co-twins (Berntzen et al. 2019).

Because of these unique features among twins, twin studies enable us to study the other factors affecting phenomena, such as acquired obesity and glucose metabolism outside genetics. While it is quite rare due to the similarities between twins, situations where the twins differ significantly in a studied variable, such as body weight, are one of the most valuable settings for a study. This is especially true in the case of multicomponent variables such as body weight, where genetic factors explain as high as 77% of individual variation in BMI in young adulthood (Silventoinen et al. 2017). Though this percentage decreases as individuals age, and even if the twins have been discordant for BMI, the differences often decrease during aging (Berntzen et al. 2023). Still, even later in life, twins show similar degrees of obesity (Berntzen et al. 2023) indicating that the intrapair differences may be mostly due to environmental factors. Because of this, the twins can act as “control” groups for their co-twins, as they share most of the same genes, age, sex, etc.

2.4 Imaging studies and metabolism

Imaging in the context of human metabolism means the process of creating visual representations of the interior of the body. Imaging can be used to find and measure various things in the body that would either not be possible without imaging or would require invasive methods.

Imaging includes but is not limited to computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine techniques such as positron emission tomography (PET).

CT imaging was invented by the Nobel Prize winner Godfrey Hounsfield and was introduced into medical practice in 1.10.1971 (Bhattacharyya 2016). CT imaging uses X-rays taken multiple times from various directions. As X-Rays pass through the patient, they are attenuated differently by various tissues according to the tissue density (Meredith and Massey 1977). Passed X-rays are detected with X-ray detectors, and the data is formed into a 3D image. CT imaging offers good tissue

resolution and, as an example, can detect small fractures or abnormalities that are not visible with regular X-ray images. The resolution can be further improved with the administration of radiocontrast agents. When compared to MRI imaging, CT imaging is also relatively fast, which can be beneficial if longer imaging studies are not possible.

MRI imaging technique uses strong magnetic fields to generate 3D images of various tissues. The first ever MRI imaging of a human being was done in 1977 by Sir Damadian, Sir Minkoff, and Sir M. Goldsmith (Damadian et al. 1977). MRI uses a strong external magnetic field to align hydrogen atoms with the magnetic field. Hydrogen atoms abundant in the body absorb targeted radiofrequency pulses applied by the MRI scanner and emit this energy when returning to their original state. The emitted energy is detected by a receiving coil, and 3D images are formed from the data acquired (Happonen 2025). The benefits of MRI compared to CT and PET imaging are that the image quality in soft tissues is the highest, and MRI does not use ionizing radiation.

PET imaging is a functional imaging technique that can be used to study a specific biological function in both health and disease (Lameka et al. 2016). ME Phelps, E Hoffman, and M Ter-Pogossian built the first true PET tomograph in 1973 (Ter-Pogossian et al. 1975). During PET imaging, positron-emitting pharmaceuticals are administered, and the pharmaceutical undergoes beta plus decay, emitting positrons. Emitted positrons interact with electrons, and due to annihilation, gamma rays are emitted. These gamma rays are registered with cameras, and the data is used to form a 3D image.

PET imaging offers the possibility to study the metabolism depending on the radiotracer used, whereas CT and MRI are best suited for studying the morphological changes in the body. PET imaging has been used to measure uptake of radiotracers in specific tissues and organs, such as the intestine (H. Honka et al. 2013), the liver (Iozzo et al. 2007) and the pancreas (Heiskanen et al. 2018). The downsides of PET are that PET imaging has poor tissue resolution when compared to CT and MRI. PET imaging also exposes the patient to a small dose of radiation. The problem of poor tissue resolution can be solved by combining either CT or MRI with PET imaging. Thus, both PET/CT and PET/MRI imaging offer great tissue resolution and the possibility to study metabolism.

2.5 Pancreas

The pancreas is an organ located in the abdomen behind the stomach, weighing about 80g in adults, and its length generally ranges from 12 to 15 centimetres. Anatomically, the four main parts of the pancreas include: the tail, the body, the neck, and the head. The pancreas has a role in digestive and endocrine functions.

The digestive role of the pancreas is carried out by acinar cells that comprise around 80% of the pancreas. Acinar cells produce amylase, lipase, and proteases, which are hydrolytic enzymes. These enzymes are secreted to the duodenum, where they assist digestion by hydrolysing carbohydrates (amylase), fats (lipase), and proteins (proteases) from food eaten by the body (Leung and Ip 2006).

The endocrine function of the pancreas is carried out by pancreatic islets of Langerhans. Islets of Langerhans are scattered throughout the whole pancreas, constitute up to 2% of the total mass of the pancreas, and each islet contains up to a few thousand endocrine cells (Shahid and Singh 2025). There are five recognized cell types within the islets: α, β, δ, ε, and PP cells, producing glucagon, insulin, somatostatin, ghrelin, and pancreatic polypeptide, respectively (Beger et al. 2018). All of these play a crucial role in regulating blood glucose metabolism in both fasting and post-prandial states.

2.5.1 Pancreatic glucose metabolism and β-cell function

The most common cell type in the islets of Langerhans are the β-cells. β-cells have a crucial role in regulating the blood glucose level by producing insulin and releasing it to the bloodstream. Insulin increases cellular GU, stimulates glycolysis, and promotes the synthesis of glycogen in the muscles and liver, adipose triglycerides, and skeletal muscle protein via the tyrosine kinase receptor pathway (Hardie 2012; B.-Y. Yang et al. 2018). The insulin gene encodes a prohormone called preproinsulin, which is cleaved into proinsulin in the endoplasmic reticulum. Proinsulin is transported to the Golgi apparatus, where in the secretory granules, C-peptide is excised from a proinsulin molecule to form mature insulin. Insulin is then exocytosed from the cell into the circulation (Lawrence 2011). Glucagon is a hormone secreted by pancreatic alpha cells and acts partially opposite to insulin by raising the concentration of glucose and fatty acids in the bloodstream (Wewer Albrechtsen et al. 2023).

Blood glucose is the metabolic signal that elicits insulin production and secretion (Tokarz et al. 2018). Blood glucose levels affect insulin secretion from the β-cells and glucagon secretion from pancreatic α-cells in an opposite way. Hypoglycaemia causes inhibition of insulin secretion, whereas hyperglycaemia inhibits glucagon secretion (Sohn and Ho 2020).

In the pancreas, similarly to muscle, the members of the GLUT family control the facilitated GU from blood into pancreatic cells (D. Deng and Yan 2016). Glucose enters the pancreatic cell via GLUT1, GLUT2, and GLUT3 in humans (McCulloch et al. 2011), after which glucose is quickly phosphorylated by glucokinase to generate glucose-6-phosphate, which goes through glycolysis and then proceeds to the mitochondrial citric acid cycle. Glucokinase generates downstream signaling

metabolites such as adenosine triphosphate (ATP) and pyruvate within a range of glucose concentrations that match the normal range for plasma glucose homeostasis. (Meglasson et al. 1983). The rise in cytoplasmic ATP causes the closure of K_{ATP} channels that leads to membrane depolarization, calcium influx, and finally insulin secretion (Christensen and Gannon 2019). However, the secretory insulin response to glucose is also regulated by various signals coming from outside of the pancreas. The gut is one of the organs that affects insulin secretion with hormones such as glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, which amplify the insulin secretion (Drucker et al. 2017).

It is worth noting that while insulin sensitivity can be measured accurately with methods such as the euglycemic hyperinsulinemic clamp (DeFronzo et al. 1979), other methods are needed to evaluate the insulin secretion itself.

There are different ways to evaluate insulin secretion, such as the intravenous glucose tolerance test (IVGTT) or the oral glucose tolerance test (OGTT). The main difference between these methods is the administration route of the glucose bolus. It has been shown through these methods that when glucose is ingested orally, a higher acute insulin response, coined the incretin effect, can be seen compared to intravenously administered glucose, even when preceded by intravenous glucose (Natali et al. 1998). However, the benefits of IVGTT are that, due to the absence of the incretin effect, it may reflect more specifically the β-cell function when compared to OGTT, even though OGTT may reflect a more physiological response (Ele Ferrannini and Mari 2014).

It has been shown in both IVGTT and OGTT that the insulin secretion rate dynamically and quickly increases at the beginning of the test, showing an acute insulin response to increasing blood glucose levels, and then decreases steadily in OGTT and quickly to a steady state in IVGTT. Patients with T2D show a blunted acute insulin response when compared to healthy individuals in both IVGTT and OGTT. (A. Mari et al. 2008).

Progression of insulin resistance to T2D is a multiphase process that begins with compensatory increases in insulin secretion and ends with the inability of β-cells to respond to elevated blood glucose levels. While regular physiological glucose stimulation is essential for the normal function of β-cells, chronic hyperglycemia and persistent glucose metabolism lead to pathological compensatory β-cell hypertrophy due to increased insulin demand (Park et al. 2007) and a concept called glucotoxicity (Bensellam et al. 2012). Glucotoxicity as a term, refers to the direct negative properties of chronic hyperglycemia. Reactive oxygen species (ROS) are normal byproducts created by mitochondria during oxidative phosphorylation. Under normal circumstances, ROS production is kept at a level where the β-cells can handle the stress caused by ROS. In the early stages of insulin resistance and T2D, prolonged hyperglycemia and simultaneous increased insulin production cause ROS

overproduction and endoplasmic reticulum stress, which trigger apoptosis in β-cells (Pu et al. 2020). This leads to the decrease of functional β-cells mass and, eventually, to the cessation of insulin secretion, which is thought to be the key mechanism in the development of T2D (Eizirik et al. 2020).

2.5.2 Pancreatic fat content

The type of fat that accumulates within or around the organ is often called ectopic fat. Ectopic fat accumulation has been shown to increase with obesity, first by Ogilvie in 1933, when he showed that pancreatic fat content (PFC) was higher in obese individuals when compared to leaner individuals (17% vs. 9%, respectively) (Ogilvie 1933). Pancreatic ectopic fat and lipid accumulation have also been shown to increase with aging (Tong et al. 2020).

Individuals with pancreatic ectopic fat have been shown to have a higher prevalence of diabetes when compared to individuals without significant pancreatic ectopic fat (Chih-Yuan Wang et al. 2014). The risk ratio for diabetes is 2.08 in the presence of a fatty pancreas when compared to individuals without excess pancreatic ectopic fat (Singh et al. 2017). Similarly, the risk ratio for metabolic syndrome is 2.37 in the presence of increased PFC.

The effect of pancreatic ectopic fat on β-cells' function is not clear. Some studies are linking fatty pancreas to insulin resistance and β-cells dysfunction (Tushuizen et al. 2007; van der Zijl et al. 2011; Della Corte et al. 2015), but not all (Wong et al. 2014).

Decrease in pancreatic β-cell function associated with increased ectopic fat is not clear, but one possible explanation is glucolipotoxicity caused by insulin resistance-induced increase in circulating fatty free acids. In glucolipotoxicity, chronic hyperglycemia decreases mitochondrial β-oxidation in the pancreatic β-cells. This, together with exposure to high levels of free fatty acids, promotes intracellular triglyceride accumulation in these cells. Chronic exposure to high fatty free acids leads to further increased triglyceride content, blunted insulin secretion, and decreased insulin gene expression. (Poitout et al. 2010). However, the same authors suggested that intrapancreatic triglyceride accumulation may be more of a symptom than the cause of the effects seen in glucolipotoxicity. Sphingolipid metabolites such as ceramide, glycosphingolipids, sphingosine 1-phosphate, and gangliosides play an important role in the pancreas as they modulate several β-cell signaling pathways (Boslem et al. 2012). Similar to triglycerides, ceramide accumulation in the pancreas has been associated with late stages of declining β-cell function (Boslem et al. 2012). One of the suggested mechanisms in the declining β-cell function caused by sphingolipid metabolites, such as ceramides, is that ceramide may decrease β-cell insulin production by increasing ROS production (Yano et al. 2011) and

downregulating Per-Arnt-Sim domain-containing kinase, leading to decreased insulin gene transcription (Guo et al. 2010; Véret et al. 2014).

The negative associations of increased pancreatic ectopic fat are not limited to pancreatic β-cells function or risk for developing T2D. Increased PFC has been shown to increase the prevalence and is suggested as a significant risk factor for pancreatic ductal adenocarcinoma (Papalamprakopoulou et al. 2025).

2.5.3 Effects of exercise on the pancreas

The benefits of exercise extend to the pancreas. Many exercise trials have been conducted to assess the effects of exercise on pancreatic β-cell function (Table 2.). As the trials on pancreatic β-cell function and exercise are numerous, the table 2 includes a representative, though not exhaustive, sample of relatively new and long (three months minimum) studies. Long-term aerobic, resistance, and combined training protocols have been shown to improve pancreatic β-cell function by multiple measuring methods, such as homeostatic model assessment of insulin resistance (HOMA-IR) (a model that quantifies insulin resistance based on fasting insulin and glucose), homeostasis model assessment 2 - beta-cell function (HOMA2-β) (a model that measures the percentage of functioning β-cells based on fasting insulin and glucose taking the variations in peripheral tissue and liver glucose resistance into account), and disposition index (an index measuring insulin sensitivity and first-phase insulin secretion) (Shih and Kwok 2018; Fortuin-de Smidt et al. 2020; Yuan et al. 2020; M. Li et al. 2022; Legaard et al. 2023; S. B. K. Jensen et al. 2023). Of these studies, only Yuan et al. saw an improvement without concomitant weight loss, as others either did not report weight change (S. B. K. Jensen et al. 2023) or saw a decrease in body weight (Shih and Kwok 2018; Fortuin-de Smidt et al. 2020; M. Li et al. 2022; Legaard et al. 2023), but did not assess whether the result in β-cell function was significant after adjusting for weight loss.

Table 2. Exercise-induced changes in β-cell function.

Reference	n	Duration	Effect on β-cell function	Main result
(Legaard et al. 2023)	82	16 weeks	Diet +/- exercise (both aerobic and resistance training) 3 or 6x/wk vs controls	β-cell function measured by disposition index improved in all intervention groups. No difference 3 (+105%) vs 6 (+137) x/wk
(S. B. K. Jensen et al. 2023)	195	52 weeks	Aerobic exercise +/- liraglutide vs controls	β-cell function measured by disposition index improved only in exercise + liraglutide group (+20%) vs controls
(Yuan et al. 2020)	248	26 weeks	Aerobic training or resistance training 3x/wk vs controls	β-cell function measured by HOMA-IR tended to improve in resistance training group and HOMA2-β improved in both groups (AT +1.6%, RT +4%)
(M. Li et al. 2022)	86	26 weeks	Aerobic exercise 3x/wk vs controls	β-cell function measured by HOMA2-β improved (+7%). No change in HOMA-IR
(Shih and Kwok 2018)	47	12 weeks	Moderate intensity running 5x/wk	β-cell function measured by HOMA-IR (+77%) and disposition index improved
(Fortuin-de Smidt et al. 2020)	45	12 weeks	Aerobic and resistance training 4x/wk	β-cell function measured by disposition index improved (+7%)

HOMA-IR; Homeostatic Model Assessment of Insulin Resistance, HOMA2-β; Homeostasis Model Assessment 2 - Beta-cell function, AT; aerobic training, RT; resistance training. Percentages represent relative change. Own drawing.

Compared to pancreatic β-cell function, studies examining the effects of exercise on PFC are sparse. Table 3 includes a representative, though not exhaustive, sample of studies examining the effects of exercise on PFC. Due to the sparsity of the studies examining the effects of exercise on PFC, all methods for measuring pancreatic fat were accepted (MRI, MRS, and CT). In addition, the results are not as consistent as some studies have shown decreases in PFC (M. Li et al. 2022; Heiskanen et al. 2018), while others have not (Fortuin-de Smidt et al. 2020; Kuk 2007). It is worth noting, however, that Kuk et al used CT and all others used MRI-based approaches, which may affect the results, as currently, MRI is seen as the most accurate way to quantify PFC (Kato et al. 2019). Of the studies with significant decreases in PFC, Li et al. saw a decrease in body weight, while Heiskanen et al. did not. Li et al. did not report whether the decrease in PFC is significant when adjusted for the decrease in body weight.

Table 3. Exercise-induced changes in pancreatic fat content.

Reference	n	Duration	Effect on pancreatic fat content	Main result
(M. Li et al. 2022)	86	26 weeks	Aerobic exercise 3x/wk vs controls	PFC decreased (-19%)
(Heiskanen et al. 2018)	54	2 weeks	Moderate intensity continuous exercise or sprint interval training in healthy and prediabetic/T2D	PFC decreased when participants were divided into high or low PFC (6.2% cutoff point), only in high PFC group (-31%)
(Fortuin-de Smidt et al. 2020)	45	12 weeks	Aerobic and resistance training 4x/wk vs controls	No difference in PFC
(Kuk 2007)	424	26 weeks	Three different aerobic exercise loads (3-4x/wk) vs controls	No significant changes in PFC

T2D; Type 2 diabetes. Percentages represent relative change. Own drawing.

Possible mechanisms behind the protective effects of exercise on β-cells function may be through the signal transducer and activator of transcription 3 (STAT3) mediated pathway. The STAT3 pathway has been shown to be more active in trained mice and humans, where the STAT3 pathway was linked to protection of the β-cells from cytokine-induced apoptosis and endoplasmic reticulum stress (Paula et al. 2018).

Exercise has also been shown in mice to ameliorate early markers of β-cells aging, a phenomenon seen as a risk factor for developing T2D (Childs et al. 2015), in insulin-sensitive animals, and also late markers in insulin-resistant mice (Carapeto et al. 2024). In that study, decreased β-cells aging was accompanied by improved β-cell function due to reduced basal insulin secretion.

Another possible mechanism is through the insulin receptor substrate 2. In rats, a high-fat diet caused insulin receptor substrate 2 degradation, which was ameliorated by exercise (Park et al. 2007). Insulin receptor substrate 2 has been suggested to play a crucial role in the increase of β-cell mass through hyperplasia (Withers et al. 1999) and a reduction of apoptosis as a result of potentiated insulin or insulin-like growth factor-I signalling (Choi et al. 2005).

2.6 Liver

The liver is a large organ located in the right upper quadrant of the abdominal cavity below the diaphragm. Anatomically, the liver can be divided into four distinct parts: right, left, caudate, and the quadrate lobes. The liver plays a significant role in various physiological processes necessary for life, such as macronutrient

metabolism, blood volume regulation, immune system support, endocrine control of growth signalling pathways, production of digestive enzymes, synthesis of proteins, and breakdown of various xenobiotic compounds (Trefts et al. 2017).

The liver is composed of several cell types, such as hepatocytes, cholangiocytes, stellate cells, Kupffer cells, and liver sinusoidal endothelial cells. Each of these cells is unique in its function and forms the basis for liver function at various levels.

Hepatocytes are the most abundant cell type of the liver that can convert absorbed nutrients into substances fit for other organs to use and can also store these substances and release them later for use. Hepatocytes also take up many foreign products, such as alcohol and medication, and metabolize them into harmless substances or prepare them for excretion out of the body (Schulze et al. 2019).

Cholangiocytes are the second most abundant cell type in the liver and function as a more traditional epithelial cell type lining the lumen of bile ducts. Cholangiocytes produce bile and uphold homeostasis of the bile ducts by inflammatory and fibrotic mediators such as tumor necrosis factor alpha (TNF-α) and interleukin 6, and by modulating cell apoptosis, senescence, and proliferation (Yoo et al. 2016).

Stellate cells are resident perisinusoidal cells distributed throughout the liver. Stellate cells can store vitamin A into cytoplasmic perinuclear droplets and participate in vasoregulation, extracellular matrix homeostasis, and drug detoxification. Liver damage leads to stellate cell proliferation and organisation of collagen in the liver (Puche et al. 2013).

Kupffer cells are a specialised type of macrophage located in the liver that are self-sustaining and a locally proliferating cell type. Kupffer cells migrate between liver sinusoids and the space of Disse. Kupffer cells act as one of the liver's main defence mechanisms against bacteria and toxins (J. Chen et al. 2020).

Liver sinusoidal endothelial cells are cells specialized in forming a semipermeable wall in the sinusoidal lumen, allowing certain-sized particles and proteins to go from the plasma to the cells of the liver.

2.6.1 Liver glucose metabolism and function

The liver is one of the central organs controlling glucose metabolism in the body. It has a different role depending on the nutritional status. The liver has a role in forming and breaking energy substrates fit for long-term storage. Glycogen is a multibranched polysaccharide formed by the liver from glucose. In Glycogenesis, glucose is converted in a multiphase process into uridine diphosphate glucose, which is bonded into a growing glycogen strand by glycogen synthase (Daghlas and Mohiuddin 2025). It has been estimated that in a healthy person weighing 70kg, the amount of circulating glucose in the blood is around 4g (Wasserman 2009). The four

grams of glucose is roughly the amount needed to fill a teaspoon. Because only the brain consumes around 60% of the blood glucose used in a sedentary fasted person, this highlights the need for a sustainable way of ensuring the necessary amounts of blood glucose. The liver can store around 100 g or 400 kilocalories worth of glycogen, which it can use to release glucose at rates equal to the uptake of blood glucose by other tissues and organs (Wasserman 2009).

At the postprandial state, the excess part of the substrate not needed for short-term metabolic needs is converted into fatty acids and glycerol through lipogenesis, which takes place in the liver (Rui 2014). After lipogenesis, the fatty acids and glycerol are esterified into triglycerides for storage. Excess glycerol can also be converted to glucose with gluconeogenesis (Shah et al. 2022). In healthy individuals, some of the triglycerides are stored locally in the liver, but most are packaged into very low-density lipoproteins for exportation to adipose tissue (Frayn and Kingman 1995).

The liver is able to change between net output and net uptake depending on nutritional status. The transition is mandated by hormonal level changes, such as the decrease of glucagon and increase of insulin in the presence of feeding. During feeding, the absence of glucagon and an increase of insulin leads to decreased gluconeogenesis and glucose formation from glycogen stores. At a fasting state, the opposite happens, and insulin levels decrease while glucagon increases, which leads to glycogen breakdown and gluconeogenesis (Trefts et al. 2017). Glycogen breakdown in the liver offers a way to produce glucose, especially in short-term fasting, while gluconeogenesis offers a solution to depleted glycogen storage during prolonged fasting (Rui 2014). In gluconeogenesis, the liver can utilize substrates such as lactate, pyruvate, glycerol, and amino acids, either generated in the liver or delivered through circulation from extrahepatic tissues, to produce glucose in the blood (Rui 2014).

The liver receives glucose both from the intestine via the portal vein and from systemic circulation via the hepatic artery. Blood glucose enters hepatocytes mainly via GLUT2, based on mice models showing that with GLUT2 deletion, the GU of hepatocytes decreases significantly, and the role of diffusion through hepatocytic plasma membrane increases (Seyer et al. 2013). However, interestingly, during fasted states, the deletion of GLUT2 does not lead to decreased liver glucose output, suggesting that glucose can be released from the hepatocytes by other transporters such as GLUT1 (Seyer et al. 2013).

The liver has been shown to be an insulin-sensitive organ, and that insulin stimulates liver GU in humans (Iozzo, Geisler, et al. 2003). Development of diabetes can impair insulin sensitivity in the liver, as insulin-stimulated liver GU has been shown to be decreased in T2D (Iozzo, Hallsten, et al. 2003). In the liver, when glucose enters the hepatocyte via GLUT2, it is soon met by glucokinase, an enzyme

that aids in the phosphorylation of glucose to glucose-6-phosphate (Nozaki et al. 2020). This phosphorylation of glucose is a crucial step, as it initiates liver GU and is a necessary step in the cascade leading to the formation of glycogen (Nakamura et al. 2021). The mechanism behind decreased liver GU in insulin resistance is proposed to be due to impaired glucokinase activity, as it is the rate-limiting step in liver glycogen synthesis (Basu et al. 2001; Nozaki et al. 2020). Insulin sensitivity of the liver can also be seen in gluconeogenesis and glycogenolysis, as hyperinsulinemia suppresses glycogenolysis, directly suppresses hepatic gluconeogenesis, and indirectly decreases hepatic gluconeogenesis by extrahepatic pathways, such as limiting glucagon production in the pancreas (Hatting et al. 2018). Insulin resistance leads to excessive gluconeogenesis in the liver by blunting the suppressive effect of insulin directly in the liver and also indirectly via extrahepatic pathways (Hatting et al. 2018).

2.6.2 Liver fat content

Excessive Liver fat content (LFC) without the presence of high alcoholic intake is called metabolic dysfunction-associated fatty liver disease (MAFLD) (formerly known as non-alcoholic fatty liver disease (NAFLD) (Gofton et al. 2023). MAFLD is defined as increased LFC, mainly consisting of neutral lipids with intracellular lipid droplets exceeding 5% of liver mass that cannot be explained by at-risk alcohol intake (over 14 units for men and 7 for women per week according to Finnish Institute for Health and Welfare) (Pelusi and Valenti 2019). MAFLD has become one of the leading causes of chronic liver disease worldwide (Asrani et al. 2019). The estimated global incidence of MAFLD is 47 cases per 1,000 population, with 40% of adult men and 26% of adult women affected (Teng et al. 2023).

Liver fat accumulation happens due to the increase in hepatocellular lipid droplets formed by triglycerides. Excess triglyceride accumulation comes from various sources, such as dietary fatty acids, elevated liver lipogenesis due to hyperinsulinemia, and peripheral lipolysis due to adipose tissue insulin resistance (Fabbrini et al. 2008; Yao et al. 2023). The more exact subtype of the dietary fatty acids also matters in LFC accumulation, as a diet rich in saturated fatty acids has been shown to increase LFC more than a diet rich in unsaturated fatty acids in already obese or overweight individuals (Luukkonen et al. 2018).

The progressive, inflammatory form of MAFLD is metabolic dysfunction-associated steatohepatitis (MASH), previously known as non-alcoholic steatohepatitis (NASH). MASH includes the increased LFC seen in MAFLD, but also cellular injury, with or without fibrosis and inflammation (Rinella et al. 2023).

In liver function tests, MAFLD is the most common cause of asymptomatic transaminase (alanine aminotransferase, aspartate aminotransferase, gamma-

glutamyl transferase) elevation, accounting for approximately 25% of them (Radcke et al. 2015). The relationship between MAFLD and transaminase elevation has been further strengthened by studies showing dietary interventions, such as a ketogenic diet, leading to a concomitant decrease in LFC and gamma-glutamyl transferase (GT) (Luukkonen et al. 2020). Transaminases such as GT can be used to evaluate hepatocellular injury (Iluz-Freundlich et al. 2020) and inflammation (Bo et al. 2005). Under normal conditions, the liver strives to maintain metabolic homeostasis through adipokines (Y. Deng and Scherer 2010) and growth factors (Fisher and Maratos-Flier 2016). However, it has been shown that, most commonly, in the presence of a hypercaloric diet and physical inactivity combined with epigenetic factors, such as liver-specific DNA-methylation and microRNAs, fat accumulation starts to occur in the liver (Dongiovanni and Valenti 2017). As a highly prevalent condition, MAFLD has epidemiologically been associated with overall obesity, T2D, hyperlipidaemia, and metabolic syndrome (Younossi et al. 2019).

Obesity has been seen as one of the main components leading to increased LFC (Pár and Pár 2017), and both obesity and metabolic syndrome have been established as major risk factors when identifying individuals who are at risk for developing liver-related events, such as hospitalisations or even deaths, in the long term (Åberg et al. 2025). It has been shown that losing ten percent or more of body weight leads to resolution of MASH in as many as 90% of individuals with MASH (Vilar-Gomez et al. 2015), and what makes this especially relevant clinically is that MASH is one of the major causes leading to liver transplantation (Younossi et al. 2019).

As obesity and diabetes are known to be closely related (Hossain et al. 2007), it is no surprise that insulin resistance has been epidemiologically linked with MAFLD, with the prevalence of T2D coexisting with MAFLD being estimated as 22.5% (Younossi et al. 2019). Alongside insulin resistance, genetic components have also been shown to have a role in the pathogenesis of MAFLD, independently but additively with insulin resistance (Luukkonen et al. 2022).

Insulin resistance contributes to the pathogenesis of MAFLD, and liver-specific inhibition of insulin receptors IRS1 and IRS2 leads to increased liver gluconeogenesis, hyperglycaemia, and T2D (Dong et al. 2006) while genetic components increase liver mitochondrial redox state, leading to more profound features of MAFLD, such as increased LFC and lobular inflammation (Luukkonen et al. 2022).

Liver steatosis and liver inflammation form a spectrum where the advanced stages of MAFLD also exhibit inflammatory findings all the way to MASH. Rat studies have linked MASH with increased GU, which was thought to reflect a transition from MAFLD to MASH, with GU starting to decrease in the most severe forms of MASH (Guzzardi et al. 2022). However, the relationship between increased LFC and liver glucose metabolism is not clear, as in ^{18}F-FDG-PET studies done in

humans (a representative, though not exhaustive, sample of available studies that used ^{18}F-FDG-PET to measure liver GU) (Table 4.), some studies show that obesity decreases liver GU (Immonen et al. 2014), while some see no difference (Viljanen et al. 2009; Ustsinau et al. 2024; Tuomola et al. 2025), and some show that obesity increases liver GU (Batallés et al. 2013). What makes drawing conclusions on the relationship between obesity and liver GU even harder is that the results vary greatly based on the normalizations used and the method used for measuring GU. Of the studies in table 4, Immonen et al., Viljanen et al., and Tuomola et al. used euglycemic hyperinsulinemic clamp, while Ustsinau et al. and Batallés did not. It is worth noting that in Immonen et al., the average BMIs of the groups were 44.1 vs 23.7 kg/m^2, while in Tuomola et al., the averages were 29.4 vs 25.2 kg/m^2. In the studies that did not use euglycemic hyperinsulinemic clamp (Ustsinau et al. 2024; Batallés et al. 2013), Batallés et al. found that liver GU increases with BMI, whereas Ustsinau et al. did not see similar results after normalising the results by lean body mass and body surface area.

Table 4. Effects of obesity on liver glucose uptake in 18F-FDG-PET studies.

Reference	n	Method for measurement	Effect on liver GU	Main result
(Immonen et al. 2014)	24	^{18}F-FDG-PET during euglycemic hyperinsulinemic clamp	Morbidly obese individuals who undergo bariatric surgery vs lean controls	Liver GU was lower in obesity
(Viljanen et al. 2009)	33	^{18}F-FDG-PET during euglycemic hyperinsulinemic clamp	Obese individuals before and after a very-low-calorie diet	No change in liver GU
(Tuomola et al. 2025)	124	^{18}F-FDG-PET during euglycemic hyperinsulinemic clamp	Mildly elevated LFC (1.86-5.56%) individuals vs low LFC (<1.86%) individuals	No significant differences between groups in liver GU
(Ustsinau et al. 2024)	33	Non-insulin-stimulated [^{18}F]FDG-PET	Individuals with obesity vs lean controls	After adjusting to LBM and BSA, no differences in liver GU
(Batallés et al. 2013)	603	Non-insulin stimulated [^{18}F]FDG-PET	Relationship between BMI and liver GU	Liver GU increases with BMI (not normalised with LBM)

BMI; Body mass index, GU; Glucose uptake, LBM; lean body mass, LFC; liver fat content, BSA; body surface area. Own drawing.

As liver steatosis is associated with liver inflammation, methods to evaluate inflammation, especially in the early stages, are of great academic interest. Liver

biopsy is widely considered to be the "gold standard" method for evaluating liver steatosis and inflammation, but it is invasive, has high inter-observer variability, and is associated with adverse effects (Karanjia et al. 2016; Loomba 2018). Thus, effective minimally invasive methods are needed.

PK11195 is a mitochondrial translocator protein (TSPO) inhibitor (D. Zhang et al. 2023; Kumar et al. 2010) that can be used for evaluating inflammatory hypermetabolism in organs non-invasively, as it has been shown to be elevated in various pathological conditions such as breast cancer, stroke, HIV encephalitis, Alzheimer's, and Parkinson's disease (Batarseh and Papadopoulos 2010). Liver inflammation has been shown to upregulate TSPO (L. Xie et al. 2012). However, the exact relationship between inflammation and TSPO is unclear, as loss of TSPO has also been shown to worsen simple steatosis by accumulation of cholesterol and triacylglycerol, while on the other hand, mitigating fibrosis in MASH (Y. Li et al. 2021). To further highlight the uncertain relationship between TSPO and liver steatosis, there are preclinical studies indicating that obesity may, in fact, downregulate TSPO expression in the liver (Dimitrova-Shumkovska et al. 2010; Thompson et al. 2013). In rat studies, liver TSPO downregulation due to a high-energy diet correlates with increased oxidative stress in the liver (Dimitrova-Shumkovska et al. 2010). TSPO mRNA expression has been shown to correlate negatively with several methylation genes that are associated with high liver short fatty chain levels.

The role of inflammation in liver steatosis may also have an autoimmune component, as the depletion of liver Kupffer cells has been shown to protect against liver steatosis and insulin resistance (W. Huang et al. 2010). The mechanism behind this was suggested to be mediated by macrophage-produced cytokines such as TNF-α, and this is further strengthened by studies showing increased steatosis following a TNF-α-inducing injection (Endo et al. 2007).

2.6.3 Effects of exercise on the liver

Like many other organs, the liver also benefits from exercise training. As previously mentioned, exercise is an additional method for the management of obesity (Petridou et al. 2019) and the benefits of weight loss can be seen in the amelioration of MASH in most individuals (Vilar-Gomez et al. 2015).

A representative, though not exhaustive, sample of studies examining the effect of exercise on liver fat content (LFC) using MRI-based techniques can be seen in Table 5. Multiple studies have shown that exercise decreases LFC (Johnson et al. 2009; Hallsworth et al. 2011; S. Lee et al. 2012, 2013; Bacchi et al. 2013; H.-J. Zhang et al. 2016; Motiani et al. 2019), while there are studies where no difference in LFC was seen (Fortuin-de Smidt et al. 2020; M.-J. Honka et al. 2016; Van Der Heijden et

al. 2010). Even a short exercise intervention of two weeks can be enough to elicit liver fat loss (Motiani et al. 2019). In the studies that saw a decrease in LFC with concomitant decrease in body weight (Table 5.), Lee et al. and Bacchi et al. did not report LFC results adjusted for the decrease in body weight. Zhang et al. adjusted the LFC results with changes in body weight, and the decrease in LFC became non-significant. However, what makes exercise especially effective at improving liver steatosis is that the reduction of steatosis from exercise interventions can be seen even without clinically significant reductions in body weight (Johnson et al. 2009; Hallsworth et al. 2011; Motiani et al. 2019; Cuthbertson et al. 2024).

Multiple exercise modalities can decrease LFC, as both resistance training (Hallsworth et al. 2011; S. Lee et al. 2012; Bacchi et al. 2013) and aerobic training (Johnson et al. 2009; S. Lee et al. 2012, 2013; Bacchi et al. 2013) have been shown to be effective. Recent clinical guidelines have thus suggested that aerobic training, resistance training, high-intensity interval training, and combined training are all effective at reducing liver steatosis without a clear optimal exercise modality (Tacke et al. 2024). The baseline severity of liver steatosis has been suggested to affect the response to exercise, as some studies have shown that the decrease in liver steatosis is greater in individuals with higher LFC before starting to exercise (Motiani et al. 2019) While genetics have a role in the response to exercise, even in MZ twins, the twin that has a higher overall activity has a lower LFC (Hannukainen et al. 2011). Because of the effectiveness of exercise in reducing liver steatosis, exercise protocols with preferably >150 min/week of moderate or 75 min/week of vigorous-intensity physical activity, independent of modality, have been recommended (Tacke et al. 2024).

Table 5. Effects of exercise on liver fat content.

Reference	n	Duration	Effect on LFC	Main result
(Fortuin-de Smidt et al. 2020)	45	12 weeks	Aerobic and resistance training 4x/wk vs controls	No difference in LFC
(S. Lee et al. 2012)	45	12 weeks	Aerobic or resistance training 3x/wk vs controls	Both aerobic (-40%) and resistance training (-69%) decreased LFC
(M.-J. Honka et al. 2016)	35	17 weeks	Resistance training in elderly women	No change in LFC
(Motiani et al. 2019)	54	2 weeks	Moderate intensity continuous training or sprint interval training normoglycemic and prediabetes/T2D individuals	When divided to >5.6% LFC and <5.6% LFC groups by baseline results, liver fat content decreased in >5.6% LFC group (-13%)
(Van Der Heijden et al. 2010)	12	12 weeks	Resistance training 2/wk before and after	No change in LFC
(S. Lee et al. 2013)	44	12 weeks	Aerobic or resistance training vs controls	Aerobic exercise decreased LFC (-72%)
(Bacchi et al. 2013)	31	17 weeks	Aerobic training 3x/wk vs resistance training 3x/wk	Both training modalities decreased LFC (AT -33%, RT -26%)
(Hallsworth et al. 2011)	21	8 weeks	Resistance training 3x/wk vs controls	Resistance training decreased LFC (-13%)
(Johnson et al. 2009)	19	4 weeks	Aerobic training 3x/wk vs controls	Aerobic training decreased LFC (-21%)
(H.-J. Zhang et al. 2016)	220	52 weeks	Vigorous or moderate aerobic exercise vs controls	Both modalities decreased LFC, but change nonsignificant after adjusting for weight loss

LFC; liver fat content, AT; aerobic training, RT; resistance training. Percentages represent relative change. Own drawing.

The benefits of exercise are not limited to reduced liver adiposity; as metabolic improvements in liver FFA uptake has been shown to be decreased in the more active twins when studied in monozygotic twins discordant for physical activity. (Hannukainen et al. 2007). Effects of exercise on liver glucose uptake measured by FDG-PET are sparse, and a representative, though not exhaustive, sample of available studies that use FDG-PET to measure liver glucose uptake can be seen in table 6. Insulin-stimulated GU has been shown to be higher in athletes than in patients with coronary artery disease (Iozzo, Geisler, et al. 2003). However, the effects of exercise training on liver insulin sensitivity are unclear, as some exercise intervention studies have shown exercise to be effective in improving liver insulin sensitivity (Motiani et al. 2019) while others have found no change (M.-J. Honka et

al. 2016). In both Motiani et al. and Honka et al., there were no significant changes in body weight. Meta-analysis by Sargeant et al found that exercise tends to improve liver insulin sensitivity, but warrants further evidence to draw clear conclusions (Sargeant et al. 2018). While both endurance and resistance exercise have been shown to be effective at improving liver insulin sensitivity (Van Der Heijden et al. 2010; Motiani et al. 2019), there is variation in the effects of exercise on liver insulin sensitivity based on the modality, as moderate intensity continuous exercise may be more effective at improving liver insulin sensitivity when compared to sprint interval training (Motiani et al. 2019).

Table 6. Effects of exercise on Liver insulin sensitivity or glucose uptake.

Reference	n	Duration	Effect on insulin sensitivity or glucose uptake	Main result
(M.-J. Honka et al. 2016)	35	17 weeks	Resistance training on elderly women	No change in liver GU measured by PET
(Motiani et al. 2019)	54	2 weeks	Moderate intensity continuous training or sprint interval training normoglycemic and prediabetes/T2D individuals	When divided to >5.6% LFC and <5.6% LFC groups by baseline results, only MICT increased liver GU (+7%) measured by PET

GU; Glucose uptake, MICT; moderate intensity continuous training. Percentages represent relative change. Own drawing.

2.7 Intestine

The intestine is a long tubulous digestive organ that consists of two main components, the small intestine and the large intestine. Anatomically, the small intestine starts from the gastric pylorus' distal tip and continues to the ileocecal valve, where the large intestine begins. The small intestine can be further divided from proximal to distal into the duodenum, jejunum, and ileum. The small intestine aids in the enzymatic digestion and absorption of ingested nutrients, immune functions by acting as a barrier to intraluminal bacteria, and has an endocrinologic role by producing digestive and energy-regulating hormones like cholecystokinin, secretin, gastric inhibitory peptide, and glucagon-like peptide-1 (J. T. Collins et al. 2025).

The large intestine is the distal part of the digestive tract that can be anatomically divided from proximal to distal into the cecum, ascending colon, transverse colon, descending colon, and sigmoid colon. By the time ingested food reaches the large intestine, most nutrients have been absorbed by the small intestine. The ascending colon absorbs the remaining water and some of the nutrients left, solidifying the

remaining material into stool (Azzouz and Sharma 2025). The descending colon stores the stool that will move to the rectum to be emptied. The large intestine also acts as a large host for trillions of bacteria called the gut microbiome. The gut microbiome assists in the fermentation of unabsorbed material. Important vitamins produced by the gut microbiome include vitamin K and B vitamins, such as biotin (Azzouz and Sharma 2025).

2.7.1 Intestinal glucose metabolism

Intestinal enterocytes have a crucial role in trafficking glucose between the gut and circulation. Intestinal glucose metabolism is modulated mainly by two glucose transporters, the sodium glucose cotransporter 1 (SGLT1) and GLUT2 (Ait-Omar et al. 2011). SGLT1 works in conjunction with the sodium gradient to actively transport glucose across the brush border membrane of enterocytes, while GLUT2 works via facilitated diffusion driven by the concentration gradient (Cottam et al. 2024). Of these transporters, SGLT1 is predominantly expressed in the small intestine, while GLUT2 can be found in both the small and large intestine (Lehmann and Hornby 2016).

Different parts of the intestine have different rates of GUs, which has been suggested to be due to the differences in GLUT2 location in enterocytes. In the small intestine, GLUT2 has been observed in the basolateral membrane, while in the colon, GLUT2 is mainly present in the short epithelial portions (Merigo et al. 2018). Under postprandial conditions, GLUT2 mainly provides basolateral exit for glucose to portal blood, but can translocate into the brush border membranes to assist absorption of glucose at high luminal concentrations (Ait-Omar et al. 2011; Koepsell 2020), though studies where this translocation was not seen exist (Röder et al. 2014). GLUT2 can be mobilized based on need from the enterocyte cytosol to the brush border membrane and vice versa by vesicle exocytosis to uphold glucose homeostasis in the body (Shen et al. 2024). However, the production and release mechanisms of the vesicles coupled with glucose concentration remain unknown.

The intestine has been shown to be an insulin-sensitive organ (H. Honka et al. 2013; Motiani et al. 2017), with Honka et al. showing that insulin increased GU in the duodenum and jejunum and further showing that the radiotracer labelled glucose injected into the blood was located in the mucosal layer during fasting. Insulin has also been shown to affect GLUT2 receptor localization in enterocytes, as brush membrane border GLUT2 was decreased by insulin, while intracellular membrane GLUT2 was increased in mice (Tobin et al. 2008). This translocation mechanism has been shown to be blunted in insulin-resistant mice, where GLUT2 remains in the brush membrane despite being subjected to a hyperinsulinemic-euglycemic clamp (Shen et al. 2024). Obesity and T2D have been shown to decrease insulin-stimulated

GU from blood to intestinal enterocytes (Holst et al. 2009; Mäkinen et al. 2015), and visceral fat has been shown to negatively correlate with intestinal GU (Motiani et al. 2017). The reduction in insulin-stimulated intestinal GU is thought to be due to reduced insulin effect on GLUT2, which leads to GLUT2 permanently staying on the brush border membrane of the enterocyte and not relocating to adjust glucose homeostasis, leading to decreased intestinal uptake because of constant blood-to-lumen efflux (Ait-Omar et al. 2011).

2.7.2 Gut microbiota

The gut microbiome is an ever-changing organism that individuals have from birth to the grave. The gut microbiota goes through changes during life, and the first big change occurs in the birth environment, after which diversity is built over the first few years of life and thereafter shaped largely by environmental factors (Goodrich et al. 2016; Martino et al. 2022). Because of the strong connection between gut microbiota composition and environmental factors, there are studies highlighting the role of diet, shared household, and aging as the main components shaping human gut microbiota (Vilchez-Vargas et al. 2022; Rothschild et al. 2018). Genetics may also affect microbiota composition, as MZ and DZ twin pairs have significantly fewer differences in their microbiota composition when compared to unrelated individuals (H. Xie et al. 2016). Studies that have compared the microbiota of twins with one of the twins having inflammatory bowel disease or Parkinson's disease, while the other co-twin is healthy, have shown minimal differences in microbiota composition (Brand et al. 2021; Bolliri et al. 2022). However, it is worth noting that Brand et al. did not report dietary patterns, and Bolliri et al. showed that there were no significant differences in the dietary patterns of the studied twins, which limits the possible conclusions on the relationship between genetics and microbiome composition. While twins may exhibit similarities in microbiota composition, the difference between the twins seems to increase slowly if the twins live apart from the other co-twin for multiple years (H. Xie et al. 2016).

Gut microbiota can be divided into several different taxonomical ranks, of which at the phylum level, the four most diverse and abundant are *Actinobacteria*, *Bacteroidetes*, *Firmicutes,* and *Proteobacteria,* of which *Bacteroidetes* and *Firmicutes* are the most prevalent (Rajilić-Stojanović and de Vos 2014). In healthy conditions, the gut microbiota exhibits stability and a symbiotic interaction with the host, often demonstrating high taxonomic diversity and a high microbial richness (Hou et al. 2022). Advanced sequencing technologies and bioinformatics have led to most research being focused on the relationship between gut microbiota and diseases, and intestinal microbiota composition has been shown to differ between healthy individuals and individuals with obesity and insulin resistance (Munukka et

al. 2012; Cronin et al. 2017; C. J. Lee et al. 2020), inflammatory bowel diseases, liver diseases, and brain disorders (Hou et al. 2022). Dysbiotic gut microbiota composition may be associated with obesity by increasing intestinal permeability and by increasing inflammation, inducing toll-like receptor 5 signalling in the adipocytes of the obese (Pekkala et al. 2015). The exact localisation of obesity also plays a role as a link between ectopic fat in organs such as the liver and gut microbiota composition have been suggested by showing a lower microbial balance index in individuals with high LFC (Munukka et al. 2014). The role of microbiota in obesity has also been strengthened with studies showing reductions in body weight of obese adult individuals after fecal matter transplantation therapy in some (Hu et al. 2023), but not all (Wilson et al. 2025) studies. However, it is worth noting that while Wilson et al. did not see a decrease in BMI after adjusting to diet and physical activity, they saw other favourable differences, such as lower total body fat and smaller waist circumference in the fecal matter transplantation group.

In the context of obesity and T2D, the most commonly studied phyla are *Firmicutes* and *Bacteroidetes*. *Firmicutes* tend to be proportionally increased relative to *Bacteroidetes* in obesity and vice versa in weight loss, which has led to the belief that *Firmicutes* have a role in obesity (Ley et al. 2006; Jian et al. 2021). Similar observations have been made in gestational diabetes mellitus patients who showed an increased *Firmicutes* to *Bacteroidetes* ratio (Cortez et al. 2019). As obesity and T2D are closely related, it is perhaps expected that, similarly, *Firmicutes* are increased compared to *Bacteroidetes* in T2D (Bahar-Tokman et al. 2022). However, there are also studies with opposite results (Larsen et al. 2010). Even the response to bariatric surgery may differ significantly based on diabetic status, as diabetic participants saw an increase in the relative abundance of *Firmicutes*, while non-diabetic participants saw a decrease (Masoumi et al. 2024). Thus, the link between obesity and T2D is not so clear in the context of gut microbiota.

2.7.3 Effects of exercise on the intestine and the gut microbiota

While the effects of exercise on tissues such as muscle and liver are widely studied, studies on the effects of exercise on intestinal GU are sparse. The intestine has, however, been shown to be an insulin-sensitive organ (H. Honka et al. 2013), and decreases in body weight have been shown to improve intestinal GU in both the small and large intestine (Mäkinen et al. 2015; Franquet et al. 2019), which may imply that exercise has positive effects on intestinal insulin sensitivity at least when exercise leads to weight loss. There are studies that have examined the effects of exercise on splanchnic organs as a whole and have seen adaptations leading to

improved reactive mesenteric vasodilatation, which was speculated to enhance nutrient absorption and utilization during exercise (Padilla et al. 2011).

However, knowledge on the direct effects of exercise on GU from blood to enterocytes is lacking. Previously, short-term moderate-intensity continuous training has been shown to be effective at improving intestinal insulin-stimulated GU (Motiani et al. 2017). The same team also noted that the modality of exercise used may also affect intestinal insulin-stimulated GU, as high-intensity training did not cause improvements, while moderate-intensity continuous training did. The team saw improvements in colonic GU, while in the small intestine, it only tended to increase in the jejunum. Thus, more studies on the effects of exercise directly on the intestine are warranted to be able to draw conclusions.

The microbiome is susceptible to the effects of exercise, as its composition (Motiani et al. 2020) and microbial metagenome pathways (Hintikka et al. 2023) can be altered with exercise. Similarly, microbiome diversity, a marker of a healthy gut microbiome, has been shown to be increased in athletes when compared to sedentary individuals (Clarke et al. 2014; Barton et al. 2018). However, there are also studies where differences in gut microbiome composition were not found between athletes and sedentary individuals (Jang et al. 2019). Cardiorespiratory fitness has also been shown to improve microbiota diversity (Estaki et al. 2016). Min et al showed in their meta-analysis that exercise interventions significantly improve Shannon index, a biodiversity index that considers both the number of species and their relative abundance in an ecosystem (Min et al. 2024). Similarly, Zheng et al. showed in their meta-analysis that exercise-induced gut microbiota changes can be especially beneficial to obese individuals, as exercise shows positive changes in the gut microbiota of the obese by altering beta diversity, which is associated with the weight-lowering effect of exercise, especially when exercise is continued for eight or more weeks (Zheng et al. 2022).

A recent systematic review compared different exercise prescriptions and their effect on microbiota. In the review, it was noted that alpha diversity (representing the variation of species within a particular ecosystem) improves more from a combined exercise intervention of both aerobic and resistance training when compared to aerobic-only interventions (Boytar et al. 2023). In the review, strength training-only interventions were not included, and the role of strength training is not as clear on the effects on microbiota as previously; no differences between the gut microbiota of bodybuilders and sedentary controls were found (Szurkowska et al. 2021).

Exercise intensity and duration also have varied effects on gut microbiota. While in amateur athletes generally, exercise and especially high intensity exercise leads to beneficial changes in the gut microbiome, in higher level athletes, negative findings such as an upsurge in serum intestinal fatty acid binding protein (a biomarker that

rises when the intestinal wall is damaged) concentration, and intestinal permeability are more common (Bonomini-Gnutzmann et al. 2022). These negative findings were more common, especially in long endurance athletes such as triathletes and ultramarathoners, which may imply that there is an upper limit of exercise duration and metabolic strain for the beneficial changes in microbiota caused by exercise.

Exercise frequency also matters when assessing the effect on the microbiota profile. While increases in beta diversity (a ratio between regional and local species diversity) can be seen with as few as two to three exercise sessions per week, increases in alpha diversity can be seen with four to five weekly exercise sessions, with more than five sessions per week showing a greater increase (Boytar et al. 2023).

3 Aims of the study

Obesity is associated with impaired whole-body and tissue-specific metabolism in multiple organs, such as muscle (Norton et al. 2022), liver (Iozzo, Hallsten, et al. 2003) and intestine (H. Honka et al. 2013) and also the composition of intestinal microbiota (C. J. Lee et al. 2020) in the multiphase progression to T2D (Ohno et al. 2023).

Exercise training is a medicine-free alternative to improve tissue and organ metabolism and fat content, and has been shown to be effective, especially in muscle, liver, and pancreas (Heiskanen et al. 2018; Motiani et al. 2019; Tacke et al. 2024; Carapeto et al. 2024). However, it is still unclear what effects exercise has on intestinal metabolism and microbiota (Motiani et al. 2017; Boytar et al. 2023).

Also, the role of genetics remains unclear, as the effects of exercise vary between individuals (Solomon 2018) and genetics have a significant effect on the susceptibility to many diseases, such as obesity and T2D (Naukkarinen et al. 2012).

The specific aims of this thesis were:

1. To study, independent of genetic factors in monozygotic twins discordant for BMI, the effects of obesity on pancreatic and liver fat content, β-cell function, and liver metabolism, and whether possible obesity-induced impairments can be ameliorated by long-term exercise training (Study I).
2. To study, independent of genetic factors in monozygotic twins discordant for BMI, the effects of obesity on insulin-stimulated intestinal glucose uptake and microbiota composition, and whether possible obesity-induced impairments can be ameliorated by long-term exercise training (Study II).
3. To study the role of obesity-induced liver fat accumulation on liver inflammation and liver insulin-stimulated GU, and whether liver fat content and inflammation can be ameliorated by regular exercise training, studied in rats (Study III).

We hypothesized that:

1. Obesity increases liver and pancreatic fat content, lowers insulin-stimulated liver GU, and impairs beta-cell function. Long-term exercise training reduces liver and pancreatic fat content, enhances beta-cell function, and improves liver insulin-stimulated GU. These training-induced improvements are observed in both leaner and heavier twins, but especially in the heavier twins. (Study I)
2. Insulin-stimulated intestinal GU and microbiota diversity are decreased in heavier twins compared to their leaner co-twins. Long-term exercise training improves intestinal GU and microbiota diversity in both leaner and heavier twins, but especially in the heavier twins. (Study II)
3. A high-fat diet increases liver fat accumulation, leading to liver inflammation, and abnormal liver GU and TSPO availability. Exercise training prevents and ameliorates the impairments in liver metabolism induced by a high-fat diet. (Study III)

4 Materials and Methods

4.1 Human studies

4.1.1 Participants and study design (Studies I and II)

Studies I and II were part of a larger study entitled Systemic cross-talk between brain, gut, and peripheral tissues in glucose homeostasis: effects of exercise training (CROSSYS) (NCT03730610). The study protocol was approved by the Ethical Committee of the Hospital District of South-Western Finland (100/1801/2018/438§). Good Clinical Practises and the Declaration of Helsinki were followed. Each participant provided written informed consent after being told of the study's goals and possible risks. The studies were conducted at Turku PET Centre (University of Turku, Turku, Finland), Paavo Nurmi Centre (Turku, Finland), and Turku University Hospital (Turku, Finland).

MZ twin pairs were recruited as participants from three population-based longitudinal twin studies in collaboration with the University of Helsinki (Jaakko Kaprio et al. 2019; Rose et al. 2019; Kaidesoja et al. 2019). The twins were identified through Finland´s central population registry. Every participant was born in Finland and had European ancestry.

Inclusion criteria for CROSSYS were:

- All participants must be MZ twins
- Within twin pairs, there must be a BMI difference of $\geq 2 kg/m^2$ and/or insulin resistance
- At least one from the twin pair must be overweight (BMI over $25 kg/m^2$)

Exclusion criteria were:

- BMI over $60 kg/m^2$
- Body weight over 170kg
- Waist circumference over 150cm
- Mental or eating disorder
- Excess use of alcohol
- Claustrophobia or poor compliance
- Active ulcus disease
- Diabetes requiring insulin treatment or fasting glucose over 10 $mmol \cdot l^{-1}$
- Pregnancy
- Past dose of radiation
- Ferromagnetic objects in the body
- Physical disability that prohibits exercising or would jeopardise participants health or interfere with the interpretation of the results

The study design can be seen in Figure 2. An initial phone interview was used to assess eligibility. Individuals who were willing to engage and without specific exclusion criteria underwent a screening visit where the requirements for participation were verified. After 1-4 weeks from the screening visit, Baseline measurements were taken as described below. For six months, both co-twins trained four times a week. Participants received weekly instruction from a personal trainer during the training program, which took place at their own residences. The identical measurements were repeated after six months.

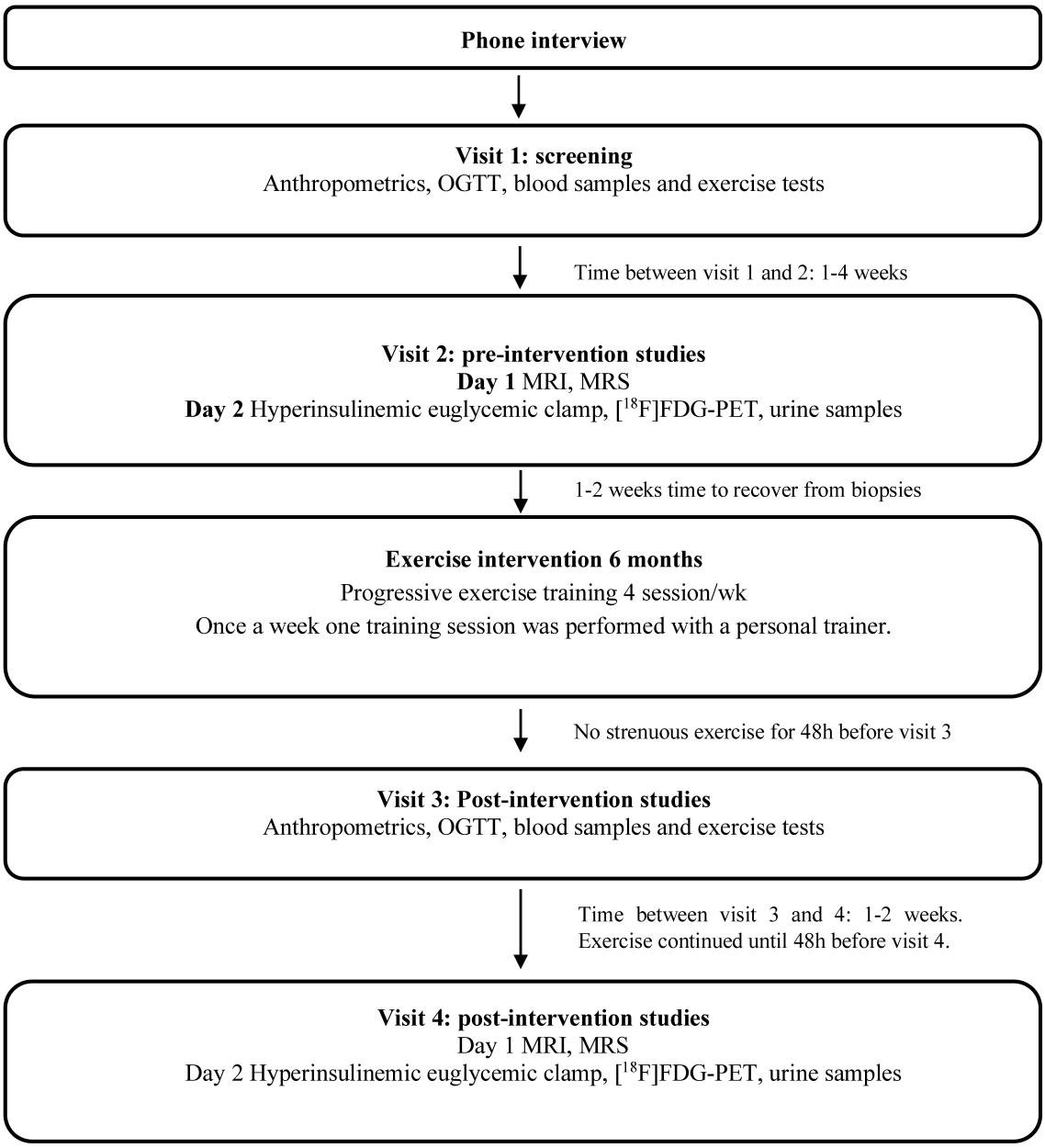

Figure 2. Overview of the study protocol. Abbreviations: [^{18}F]FDG, 2–deoxy–2– [^{18}F]fluoro–D–glucose; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; OGTT, oral glucose tolerance test; PET, positron emission tomography. Reprinted with permission from study I.

Twelve pairs were available and willing to participate and met the inclusion criteria, and 10 pairs completed this study. From the twelve MZ twin pairs, eight were female, four were male, with the average age of 40.4 ± 4.5 years and the average BMI of 32.9 ± 7.6 kg/m^2. The mean BMI difference between co-twins was 7.6 kg/m^2 (min 2.2 kg/m^2, max 18.4 kg/m^2). According to the American Diabetes Association's standards, five had impaired fasting glucose (IFG), and two of the leaner co-twins had impaired glucose tolerance (IGT) (Table 1). Two of the heavier twins were receiving treatment for hypertension, seven had impaired fasting glucose, and two had impaired glucose tolerance. The prediabetes status of seven twin pairs was discordant. None of the subjects used diabetes medication, had diabetes, or were receiving treatment for hyperlipidemia. All the female participants were premenopausal. Two of the leaner twins smoked, and two used nicotine pouches. One of the heavier twins smoked, and one used nicotine pouches. None of the twins consumed more alcohol than the general safe limits (two units/day and three units/day for women and men, respectively). The participants were told not to change their food or way of life during the intervention. At baseline, mid-intervention, and post-intervention, the participants kept a dietary journal for three to four days. Although they were free to select the precise days, participants were told to finish the diaries near the intervention time points. Before providing the faeces sample, food diaries were to be filled out. The logbook had both working and non-working days, depending on the selected time point. The participant evaluated the portion size using the appropriate measurement units, such as grams or decilitres. Macro- and micro-nutrients were calculated based on the completed diaries using the online food diary calculator provided by Fineli from the Finnish Institute for Health and Welfare.

4.1.2 Body composition and peak exercise capacity tests (studies I and II)

Body composition measurements and a peak oxygen uptake (VO_{2peak}) exercise test were performed on each participant before and after the training intervention. The tests were performed at the Paavo Nurmi Centre (Turku, Finland). Participants' body composition was measured using a bioimpedance analysis machine (Inbody 720; Biospace Co, Korea). The machine measured participants' total mass, skeletal muscle mass, body fat mass, body mass index, and body fat percentage.

VO_{2peak} was measured using a stationary bicycle ergometer (Ergoline 800 s; VIASYS Healthcare, Germany). For men, the test started with 50 W, which was increased by 30 W every 2 min until volitional exhaustion. For women, the test started with 40 W, which was increased by 20 W every 2 min until volitional exhaustion. The same device was used for each pair before and after the intervention.

4.1.3 Exercise intervention (studies I and II)

The exercise training intervention for studies I and II consisted of 27 ± 2 weeks of a progressive exercise training regime (Heiskanen et al. 2021). The training program consisted of two endurance training sessions, one resistance training session, and one high-intensity interval training (HIIT) session weekly (Table 7.). Exercise was done at the residences of the participants. The participants could do one of the training sessions with a local personal trainer of their choice. Unsupervised exercise training made up the remaining three sessions. In order to accommodate their everyday schedules, the participants selected the day and time for the workouts. The specific exercises could be changed based on the gym equipment and injury history of the participant. The endurance workouts were done twice weekly with training intensities set as a percentage of the maximum heart rate measured during the VO_{2peak} test before the intervention, and the training time and intensity were increased as the training intervention progressed.

The resistance training workouts used individually determined loads for ten-repetition sets. The exact training loads were determined together with a personal trainer, corresponding to approximately 75% of the external load that could be lifted once, i.e., one-repetition maximum (1 RM). The resistance training loads were increased when sets of ten repetitions were easy to perform.

The high-intensity interval training sessions were conducted in a rotation of three different types of training. The rotation included circuit workout, cross-training workout, and HIIT workout. Circuit workout included four rounds of different movements done in a certain order, cross-training included three blocks of two movements done to a certain timepoint and then moved to the next block. HIIT training sessions included maximal bouts of a single exercise modality, followed by short rest and then repeated 4–6 times.

To prevent overtraining and injuries, the training schedule includes two deload weeks. These deload periods were weeks 9 and 18. A heart rate monitor (Polar A370, Polar, Kempele, Finland) and a training log were used to monitor training adherence, intensity, and duration of individual workout sessions. More in-depth description of the exercise intervention can be found in table 7.

Table 7. Overview of the exercise intervention.

ENDURANCE TRAINING (twice a week: one Session 1 and one Session 2)						
	Weeks 1–2	*Weeks 3–4*	*Weeks 5–6*	*Weeks 7–9*	*Weeks 10–19*	*Weeks 20–26*
Session 1	70% HR_{max} 30 min	70% HR_{max} 35 min	70% HR_{max} 40 min	70% HR_{max} 45 min	75% HR_{max} 45 min	80% HR_{max} 45 min
Session 2	60% HR_{max} 40 min	60% HR_{max} 50 min	60% HR_{max} 60 min	60 % HR_{max} 60 min	60 % HR_{max} 60 min	60 % HR_{max} 60 min

HIGH INTENSITY INTERVAL TRAINING (once a week, one type of training)		
Type	*Completion method*	*Content of the training*
Circuit	Perform 4 rounds of the movements in chronological order. Every round, spend 1 min in each movement: do as many repetitions as you can in 40 s and then rest for 20 s. Rest 1 min between the rounds after completing all movements (1–6).	1. Lunges
	Above 80% of HR_{max}	2. X-jump/jumping rope/mountain climber
		3. Back extension
		4. Abdominal crunches (obliqual)
		5. Burpee
		6. Hip thrust
		7. Rest
Cross training	First, perform 12 min of section A (switch between two movements). Rest 1 min.	A. 500-m row/cycling/run
	Second, perform 6 min of section B. Rest 1 min.	10 air squats
	Third, perform 6 min of section C.	B. 20 kettlebell swings
	Above 80% of HR_{max}	10 push-ups/pull-ups
		C. 30 sit-ups
		30 box step-ups
HIIT	Make each bout as hard as possible. Return between bouts by walking calmly back to the starting point. Repeat 4–6 times.	Choose one:
	Above 90% of HR_{max}	Running/cycling/rowing
		Stair-running
		Uphill running

RESISTANCE TRAINING (once a week)			
Weeks 1–9	*Weeks 10–19*	*Weeks 20–26*	*Repetitions (load)*
Leg press	Leg press/back squat	Leg press/ back squat	3 × 10, (75% of 1RM)
Leg extension	Bulgarian squats	Hip extensions	3 × 10, (75% of 1RM)
Push-ups[a]	Cable seated row	Bent-over row	3 × 10, (75% of 1RM)
Peck-deck	Bench press	Bench press	3 × 10, (75% of 1RM)
Lat pulldown	Lat pulldown	Lat pulldown/ Pull-ups	3 × 10, (75% of 1RM)
Shoulder press	Shoulder press	Shoulder press	3 × 10, (75% of 1RM)
Abdominal crunches[a]	Abdominal crunches[a]	Abdominal crunches[a]	3 × 10

Abbreviations: HRpeak peak heart rate, 1 RM: external load that can be lifted once i.e. one repetition maximum, aBody weight exercise. Modified from (Heiskanen et al. 2021).

4.1.4 Euglycemic-hyperinsulinemic clamp and whole-body insulin sensitivity (M-value)

For the euglycemic-hyperinsulinemic clamp and whole-body insulin sensitivity, participants fasted overnight (for at least 10 h) and avoided excess physical activity for 48 h before the FDG-PET study. They were placed in a supine position in the PET scanner (Discovery MI (DMI), GE Healthcare, Chicago, IL, USA) and instructed to avoid excess muscle contractions. The euglycemic-hyperinsulinemic clamp was performed, as originally described by DeFronzo et al. (DeFronzo et al. 1979). Primed-constant insulin (Actrapid 100 U mL^{-1}, Novo Nordisk, Bagsværd, Denmark) infusion was started at a rate of 192 $mU \cdot m^{-2} \cdot min^{-1}$ during the first 4 min. Then, the infusion rate was reduced to 96 $mU \cdot m^{-2} \cdot min^{-1}$ for 4–7 min. After 7 min, the infusion rate was reduced to 48 $mU \cdot m^{-2} \cdot min^{-1}$ for the remaining clamp protocol. The exogenous glucose infusion was initiated 4–10 minutes after the insulin infusion began, and it was further adjusted based on the blood glucose concentration measured using the glucose oxidase method with the goal of reaching a stable level of 5 mmol/l. Before and every five minutes during the clamp, arterialized venous blood samples were taken. The glucose levels acquired in the steady state of 5 mmol·l−1 for at least 20 minutes were analysed to determine the whole-body insulin sensitivity (M-value). (DeFronzo et al. 1979).

4.1.5 Imaging studies and image analysis

In preparation for the PET studies, participants had their antecubital veins cannulated in both arms. Radiotracers were injected using one catheter, and blood was drawn using the other. To arterialize venous blood, an electrically powered heating pad was positioned surrounding the arm from where the blood samples were drawn.

MRI and magnetic resonance spectroscopy (MRS) were used to measure visceral fat mass, PFC, and LFC. Siemens MAGNETOM Skyra fit 3 T MRI system (Siemens Healthcare, Erlangen, Germany) was used for the imaging. MRI was used to evaluate visceral fat mass from the fat fraction maps by 2-dimensional regions of interest drawn in every 5–9 slices and transforming them to a 3-dimensional volume of interest (VOI) using the interpolation feature of Carimas software. From the 3-dimensional volume of interest, all the voxels with intensity below 0.5 were excluded. The cut-off point of 0.5 was chosen as above 0.5, the fat fraction is thought to be over 50%, meaning that within the accuracy of the MRI, most of the content in the voxel represents visceral adipose tissue.

For the measurements of PFC and LFC, a voxel was manually placed into the target organ, and a magnetic resonance spectrum was collected. Amplitudes of triglycerides in the frequency range of 0.9 to 2.8 ppm and the water in the MRS spectra were differentiated using LCModel program (version 6.3-1N). LFC and PFC

were calculated by dividing the triglyceride amplitudes by the sum of water and triglyceride amplitudes (Provencher 1993).

4.1.5.1 [^{18}F]-FDG PET

During the euglycemic-hyperinsulinemic clamp, once a steady state in the blood glucose was achieved, participants were positioned in a supine position in the PET scanner (Discovery MI (DMI), GE Healthcare, US), while all unnecessary movement and muscle activity of the participant was avoided during the transition. [^{18}F]FDG (155 ± 8 MBq) tracer injection was given, and PET imaging started ~84 min after the start of the clamp. The liver PET scan started 43 ± 1.6 minutes post-[^{18}F]FDG injection, while the abdominal area PET scan started 56 ± 3.2 minutes post-injection. During the FDG-PET imaging, blood samples were collected to determine plasma radioactivity (input function) (Heiskanen et al. 2021). Other blood samples collected were lactate at time points 0, 20, and 80 minutes, insulin at 0, 30, 60, 90, 120, and 150 minutes, and free fatty acids at 0, 60, and 120 minutes. These samples were collected to ensure that the clamp is performed successfully. All obtained imaging data were corrected for attenuation, dead time, and decay and then reconstructed.

Together with PET images, CT images served as an anatomical reference. Carimas software 2.10.3.0 (http://turkupetcentre.fi) was used to analyze the PET/CT images.

Four distinct VOIs were used to average the small intestine activity levels. One cylinder and one tube-shaped VOI were placed in the upper left quadrant of the abdomen into the jejunum, and a similar configuration was used for the lower left quadrant of the abdomen into the ileum. The left quadrant of the abdomen was selected to prevent spillover effects from organs with high GU, including the liver. The VOIs were manually positioned in relation to the target organs using the CT anatomical reference images, and they were shaped to closely resemble the anatomical landmarks. The PET images were used to check that there were no clear high-intensity radioactive spots that would indicate either a different organ or tissue. It was also ensured that the distance to organs with high GU, including the liver, was maximized using VOI shape-modifying features in the Carimas software.

One cylinder-shaped VOI and one tube-shaped VOI (a tube on the left side of the transverse colon and a cylinder on the right) were used to average the colon activity levels. The transverse colon was selected because it was the most dependable portion of the colon to locate from the abdomen. By averaging several VOIs, the aim was to reduce potential spillover activity from adjacent organs like the liver. Two distinct shapes were employed to assess if the colon's internal composition causes noticeably different outcomes.

In the liver, the activity values were averaged over three spherical volumes of interest (two in the upper and one in the lower half of the right lobe of the liver), as drawn in a total of 25 image planes. The right lobe was selected because it provides the farthest distance from the heart's apex, which could have resulted in spillover activity if the VOIs had been drawn too near. To obtain data mostly from hepatic tissue, big veins that were evident in the liver were avoided.

Tissue time activity curves were extracted from the VOIs, and the data was analysed using the fractional uptake ratio model (Thie 1995).

4.1.6 β-cell function tests

During visits 1 and 3 (Figure 2), a two-hour OGTT was performed after at least 10 h fast. Blood samples were collected before and at 15, 30, 45, 60, 90, and 120 min after ingestion of 250 mL of a solution containing 75 g of glucose (GlucosePro, Comed Oy, Ylöjärvi, Finland), to measure glucose, C-peptide, and insulin concentrations. Blood samples were examined in the Turku University Hospital laboratory (Tykslab, Turku, Finland) on the same day. C-peptide and insulin were determined using electrochemiluminescence immunoassay, and glucose using photometry.

The "Pisa-Podova" model and the C-peptide deconvolution technique were utilized to characterize the β-cell function based on the OGTT results. Modelling previously reported by Mari et al. was used to estimate the β-cell function parameters, which included a basal insulin secretion rate, glucose sensitivity, rate sensitivity, and the two-hour to baseline potentiation factor ratio (PFR). (Andrea Mari, Tura, et al. 2002; Andrea Mari, Schmitz, et al. 2002). OGTT-derived glucose sensitivity was calculated as the mean slope of the glucose-insulin secretion dose-response curve, and rate sensitivity was defined as the dependence of insulin secretion on the rate of change in the plasma glucose levels (A. Mari and Ferrannini 2008). A potentiation factor was calculated every 5 min from the 2-h OGTT, and the ratio mean (potentiation 110-120) divided by mean (potentiation 0-10) was defined as the potentiation factor ratio. The early- and late-phase insulin secretion rates (ISR early and ISR late) were calculated from the area under the curve from 0 to 30 min and from 30 to 120 min. Total ISR was calculated using the area under the curve of the whole 2 h OGTT.

4.1.7 Faecal DNA extraction and 16S rRNA gene sequencing

During the intervention, participants were told not to alter their regular eating habits or level of physical exercise. Samples of faeces were taken before, during, and after

the intervention. Participants provided the faeces sample to the testing site on the same day and at the same time during the pre and post visits, while mid-point samples were collected at home. The mid samples were brought to the post-visit and previously kept in a standard freezer at -20 °C at the participants' residences. The mid-point faeces samples were told to be kept in a cooler bag while being transported to the study location. Samples of faeces were kept at room temperature for a maximum of four hours. Every sample was gathered and placed in a sterile faeces tube (Sarstedt Group with its head office in Nümbrecht, Germany) with a screw cover and spoon.

The Faeces samples were stored in a freezer (−70 °C) as soon as they were obtained. DNA libraries were performed with the amplification of the Specific 16S ribosomal RNA (rRNA) gene region (V3–V4) following Illumina protocols. 16S rRNA gene sequencing analysis was performed using PE250 Illumina. During DNA extraction and PCR amplification, the reagent contamination was controlled and ruled out by using blanks not containing a sample. Taxonomic assignment was conducted using SILVA taxonomy 138 database, QIIME 2.0. Samples with less than 1000 reads were removed from the final analysis. Sequences not assigned to Bacteria domain level, also, those sequences classified as cyanobacteria and chloroplasts, likely represent ingested plant material, were removed from the dataset as previously described (Heiskanen et al. 2021).

4.1.8 Blood tests

Blood samples were collected before (Visit 1) and after the intervention (Visit 3) from the antecubital vein. Fasting state (≥10 h) blood samples were collected between 8 and 10 am using VACUETTE or Vacutainer EDTA tubes, and plasma and serum samples were centrifuged according to the tube manufacturer's recommendations. With the exception of FFA and HbA1c tests, all blood samples were examined in the Turku University Hospital laboratory (Tykslab, Turku, Finland) on the same day. FFA samples were frozen at -70 °C and subsequently examined in a bigger batch. HbA1c samples were examined on the same day or, at the latest, the following day. Samples of HbA1c were kept at +4 °C. Extra serum and plasma samples were transferred to lithium heparin tubes and centrifuged in accordance with the instructions provided by the tube manufacturer. Extra samples were stored in a freezer (− 70 °C) for further analyses.

4.2 Animal Studies

4.2.1 Study design

This study III was conducted as a part of a larger study entitled CROSRAT, detailed previously (Jalo et al. 2024). Approval for the study was admitted by the State Provincial Office of Southern Finland (permission number ESAVI/4080/2019). Male Sprague Dawley rats (housed in an environmentally controlled facility of 12/12 h light-dark cycle, 21 °C, 55% humidity) were obtained from the Central Animal Laboratory of the University of Turku (Turku, Finland) and were given food and water ad libitum.

The rats were split up into eight intervention groups for either 12 or 24 weeks once they were eight weeks old. Rat groups varied from one another in terms of exercise and/or food. A more detailed view of the study design is shown in figure 3.

Rats in the exercise groups were housed individually in cages with free access to running wheels (Intellibio, Seichamps, France) from 4 pm to 8 am for four consecutive days a week, followed by three days of rest. Activity wheel system ActiviWheel v.4.4 software (Intellibio, Seichamps, France) was used to record daily running distances.

The animals were weighed, and the body composition of the animals was analyzed with EchoMRI™ 700 Analyzer (EchoMRI LLC, Houston, TX, USA) at 0, 12, and 24 weeks of the intervention to measure total body fat and lean mass.

The rats were fed either standard chow (RM3 (E) Soya free; Special Diets Services, Shropshire, United Kingdom; 15.43 MJ/kg: 11.5% from fat, 27.0% from protein, 61.5% from carbohydrates, or high fat diet (HFD) (Western diet, 1.5% cholesterol; ssniff Spezialdiäten GmbH, Soest, Germany; 21.8 MJ/kg: 42.0% from fat, 15.0% from protein, 43.0% from carbohydrates according to the study design (Jalo et al. 2024).

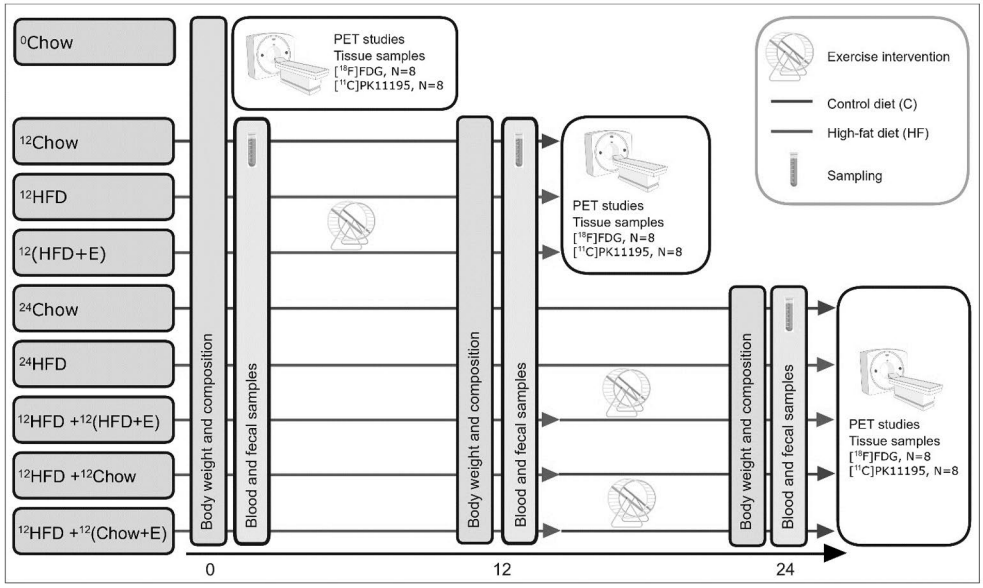

Figure 3. At eight weeks of age, the rats were divided into eight intervention groups (N = 7-24/group) for either 12 or 24 weeks. The groups were :(I) age-control group fed with chow diet for 12 weeks (^{12}Chow); (II) group fed with HFD for 12 weeks (^{12}HFD); (III) exercise intervention group fed with HFD for 12 weeks with the possibility of voluntary running exercise (^{12}(HFD+E); (IV) age-control group fed with chow diet for 24 weeks (^{24}Chow); (V) group fed with HFD for 24 weeks (^{24}HFD); (VI) exercise intervention group fed with HFD for 24 weeks with the possibility of voluntary running exercise for the last 12 weeks of the intervention ^{12}HFD+^{12}(HFD+E)); (VII) diet intervention group with an initial 12 weeks of HFD then a switch to chow diet for another 12 weeks (^{12}HFD+^{12}Chow); and (VIII) combined intervention group with an initial 12 weeks of HFD then a switch to chow diet with a possibility of voluntary running exercise for the last 12 weeks of the intervention (^{12}HFD+^{12}(Chow+E)). Reprinted with permission from study III.

4.2.2 Euglycemic-hyperinsulinemic clamp and [^{18}F]-FDG and [^{11}C]PK11195 PET and liver Hounsfield units

The rats in both PET trials were weighed, given 0.05 mg/kg buprenorphine for analgesia, and then put to sleep with a mixture of oxygen and isoflurane (2.5% for maintenance, 4% for induction).

To evaluate tissue-specific insulin-stimulated GU, a hyperinsulinemic-euglycemic clamp combined with PET imaging with [18F]FDG was performed on half of the rats (n = 8) from each of the eight groups at the end of the intervention. After a 4-hour fast, sedated rats underwent surgical femoral artery and vein catheterization. Catheterizations were done on the same day as the clamp and imaging studies. A 120 mU/kg/min insulin infusion was used to start the insulin clamp for three minutes. This was followed by a 60 mU/kg/min infusion until the

blood glucose level fell to 6.0 mmol/L. Then the insulin infusion was lowered to 18 mU/kg/min for the rest of the clamp protocol. Arterial blood glucose was measured (Contour XT, Bayer, Leverkusen, Germany) before the initiation of the clamp, every 3 minutes for the first 25 minutes, and every 5 minutes onwards. The animals were transported to the PET-CT scanner, and after a CT scan, the catheters were combined with a peristaltic pump and a Swisstrace Twilite II coincidence detector for blood arterial input function measurement without blood loss during the PET scan. After a steady blood glucose level of approximately 5 mmol/L was reached, a 45-min PET scan with 30 × 10 s, 15 × 60 s, and 5 × 300 s framing was started simultaneously with an intravenous injection of 20.7 MBq (SD 1.1) [^{18}F]FDG.

The other half of the rats (n=8) from each of the eight groups underwent PET imaging with 11C-labelled R isomer of [1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3-isoquinolinecarboxamide] ([^{11}C]-(R)-PK11195) (Charbonneau et al. 1986). The lateral tail vein of the [11C]-(R)-PK11195 group was cannulated in order to administer [11C]-(R)-PK11195. A 10-min CT scan was conducted for anatomical reference images and the attenuation correction of the PET imaging data. Then, [^{11}C]-(R)-PK11195 (50 MBq) was administered intravenously, and a 30-min PET scan was started in tandem with 30 × 10 s, 15 × 60 s, and 2 × 300 s framing. The liver's radioactivity curves were obtained using PET-CT images in a manner identical to that of the animals administered FDG. A Logan plot with a reference tissue input was used to compute PK11195 uptake. The left ventricle's lumen provided the input (from 60 seconds to 30 minutes).

CT-based Hounsfield units (HU) were used to measure liver fat alongside the histological samples. HU quantifies the radiodensity of tissues in computed tomography images. In general, low negative values indicate tissues like fat, whereas higher positive values indicate more dense tissues like soft tissue and water.

4.2.3 Liver histological analysis

Liver samples were collected 5 days after the last exercise session for protein expression and mRNA expression analyses, respectively. Following the completion of the in vivo PET/CT scans, harvested tissue samples were flash-frozen in liquid nitrogen and kept at -80 °C. The liver samples were sent for processing once every rat had finished the intervention. Depending on the sample size, the samples were divided into four to seven pieces, which were then embedded in paraffin blocks. One slide was created for each liver from 3 μm-thick slices. Hematoxylin and eosin stain was applied to the slides. Once the slides were finished, an expert biologist who was blind to the study design and group allocations examined them under a microscope to assess and measure the samples' histological characteristics.

The histological analyses were adapted from the method of Kleiner et al (Kleiner et al. 2005), addressing portal inflammation and lobular damage, with particular attention to micro- and macrovesicular steatosis, inflammatory foci, and the number of lipogranulomas. Micro- and macrovesicular steatosis were quantified at 20x magnification and graded based on the percentage of affected hepatocytes, with the final total percentage derived from the combined total of both types (grade 0: healthy, <5%, grade 1: 6%-33%, grade 2: 34%-66%, and grade 3: >66%).
The following categories were used to evaluate the degree of inflammation surrounding the portal veins (portal inflammation grade): grade 0: None (no inflammation), grade 1: Low (some portal vessels have low/very low inflammation), grade 2, Low-Mild (low-mild inflammation), grade 3: Mild (mild inflammation), Mild-Moderate (mild-moderate inflammation), or Moderate (extensive inflammation). At 20x magnification, the total number of lipogranulomas on the slide was assessed. The size of the inflammatory foci was also used to determine an observational grade, which was subsequently translated into a numerical score for statistical analysis (Foci size Score: Very Small or Small=0; Small-Medium=1; Medium=2; Medium-Large or Large=3).

4.3 Statistics

4.3.1 Studies I and II (CROSSYS)

For studies I and II, the normality assumption was checked from studentized residuals, and logarithmic transformations were performed to fulfill the normal distribution when needed. A linear mixed model for repeated time points using compound symmetry covariance structure was used to analyse the data. The model consisted of two within-factors: time (before and after intervention) and group (heavier and leaner co-twin), and their interaction term (time × group). The same model was applied to baseline group differences, but only the pre-intervention data were employed. If there was a significant time × group outcome following the intervention, the within-group time effect was calculated using the same model to examine if the groups responded differently to the intervention or if one of the groups had a significant time effect. Participants' missing data points were incorporated into the statistical analysis utilizing the linear mixed models' restricted maximum likelihood estimate. As a result, 95% confidence intervals and model-based means are presented. All statistical tests were performed as two-sided, and *p*-values less than 0.05 were considered statistically significant. The SAS System, version 9.4 for Windows (SAS Institute, Cary, NC, USA), was used for the analyses.

The gut microbiota alpha diversity indices in study II were subjected to the same statistical analysis at the amplicon sequencing variant (ASV) level. Total-sum

scaling normalization was applied to the gut microbiota in study II. The Bray-Curtis index, Jensen-Shannon Divergence, and Jaccard Index were then used to calculate beta diversity, which was then visualized on a Principal Coordinate Analysis (PCoA) plot. Multivariate analysis was used to examine group differences in the relative taxon abundances at the phylum, genus, and ASV taxonomic levels. To reduce the quantity of false positives, false discovery rate (FDR) correction was used. FDR-corrected *p*-values ≤ 0.05 were considered statistically significant. Analyses were conducted on the free online software MicrobiomeAnalyst, version 2.0. The association of exercise and nutrition with microbiota was analysed using an additional calculation method (type 1 method), where effects are tested sequentially, fitting one additional effect at each step. With this method, it was possible to see whether the following explanatory variable is significant when the model includes all other explanatory variables, i.e., all variations explained by earlier factors have already been taken into account. These analyses were carried out using a JMP® Pro 16.0.0 for Windows (SAS Institute, Cary, NC, USA).

In study I, correlation analyses were performed using Pearson's product–moment correlation coefficient for normally distributed data and Spearman's rank correlation coefficient for non-normally distributed data. P-values less than 0.05 were regarded as statistically significant, and all statistical tests were conducted in a two-sided manner. Because of the short sample size, p-values between 0.05 and 0.15 were considered as tendencies in study I. SAS system version 9.4 for Windows (SAS Institute, Cary, NC, USA) was used for the analyses.

4.3.2 Study III (CROSRAT)

The normality assumption was checked both visually and using the Shapiro-Wilk test. Student's t-test was employed to compare each group while analysing normally distributed continuous data. The Wilcoxon rank sum test was applied to continuous variables that were not normally distributed. Wilcoxon rank sum test was used for nominal variables. Pearson's product-moment correlation coefficient for normally distributed data and Spearman's rank correlation coefficient for non-normally distributed data were used for correlation analysis. *p*-values less than 0.05 were considered statistically significant. A JMP Pro, version 17 for Windows (JMP Statistical Discovery LLC 920 SAS Campus Drive, Cary, NC, USA) was used for the analyses.

5 Results

The following section presents the main results of this thesis. More detailed results can be found in the original articles (Studies I-III).

5.1 Subject characteristics (I-III)

In the human (studies I and II) baseline results, the heavier twins had both a lower VO_{2peak} and a whole-body insulin-stimulated glucose uptake (M-value) (Table 8.) compared to the leaner co-twins. The exercise intervention improved the VO_{2peak} and M-value in both groups (time $p < 0.05$ in both variables). Exercise had no effect on whole-body mass or fat percentage, but it tended to decrease visceral fat mass in the whole population (time $p = 0.07$).

Table 8. Subject characteristics (95% CI) of the heavier and leaner twin groups before and after exercise intervention

	Heavier		**Leaner**		***p*-Value**		
	Pre	Post	Pre	Post	Baseline	Time	Time *group
n	12	11	12	10			
Male/female	4/8	4/7	4/8	4/6			
Age, years	40.4 (37.5;43.4)		40.4 (37.5;43.4)				
Weight, kg	108.7 (91.8;125.7)	108.0 (93.1;122.9)	86.4 (72.4;100.3)	86.9 (72.6;101.2)	0.001 *	0.95	0.37
BMI, kg/m2	36.7 (32.2;41.1)	36.4 (32.4;40.4)	29.1 (25.1;33.1)	29.3 (25.3;33.2)	0.001 *	0.92	0.41
Waist circumference, cm	117.7 (106.3;129.2)	115.0 (106.8;123.1)	96.5 (84.7;108.3)	94.4 (82.3;106.6)	0.001 *	0.17	0.74
Fat-free mass, kg	35.9 (31.0;40.7)	36.2 (32.1;40.3)	33.1 (29.0;37.2)	33.9 (30.6;37.2)	0.003 *†	0.14	0.10
Fat mass, kg	45.5 (33.8;57.3)	44.5 (34.6;54.4)	27.8 (17.9;37.7)	26.9 (14.4;39.4)	0.001 *†	0.70 †	0.97 †
Visceral fat mass, kg	5.9 (4.5;7.3)	5.5 (4.4;6.5)	3.1 (2.0;4.3)	3.2 (2.0;4.4)	0.002 *†	0.07	0.29
Fat percentage, %	40.6 (35.5;45.7)	40.0 (35.9;44.1)	30.4 (24.0;36.9)	29.5 (20.3;38.7)	0.001 *	0.37	0.72
V̇O2peak, mL·kg−1·min−1	25.6 (22.7;28.5)	28.3 (26.1;30.6)	32.4 (27.3;37.4)	35.1 (29.9;40.2)	0.003 *	0.001 *	0.94
Triglycerides, mmol/L	1.4 (0.9;1.9)	1.2 (0.9;1.5)	0.8 (0.6;1.0)	0.8 (0.6;1.0)	0.040 *	0.54 †	0.49 †
FFA, mmol/L	0.59 (0.51;0.67)	0.68 (0.45; 0.91)	0.52 (0.34;0.69)	0.54 (0.14; 0.94)	0.29	0.63	0.63
ALT, u/L	33.8 (23.3;44.2)	31.4 (22.3;40.6)	31.6 (13.1;50.1)	31.5 (17.7;45.3)	0.30 †	0.95 †	0.42 †
ALP, u/L	59.4 (51.4;67.4)	59.6 (51.5;67.8)	51.8 (43.2;60.3)	56.9 (47.2;66.7)	0.08 †	0.31 †	0.11 †
AST, u/L	22.2 (18.7;25.6)	22.6 (18.3;26.9)	27.5 (15.8;39.2)	25.8 (14.8;36.9)	0.28 †	0.86 †	0.92 †
CRP, mg/L	2.8 (1.4;4.2)	3.7 (1.3;6.2)	2.1 (0.3;3.9)	1.2 (−0.6;3.1)	0.050 *	0.69 †	0.50 †
M-value, µmol/kg*min	23.1 (16.3;30.0)	31.4 (20.4;42.3)	37.6 (26.7;48.5)	46.9 (31.7;62.1)	0.007 *	0.022 *	0.82

p-value (linear mixed model) for a baseline: within-pair difference before the intervention, time: pre- and post-difference in the whole group, Time*group: did the training response differ within twin pairs. For M-value heavier co-twins: pre n = 11, post n = 9, leaner co-twins: pre n = 11, post n = 10. Abbreviations: BMI, body mass index; VO2peak, aerobic capacity; FFA, free fatty acid; ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CRP, C-reactive protein; M-value, whole-body insulin sensitivity. *Statistically significant p-value ($p \leq 0.05$). † Logarithmic transformation. Reprinted with permission from study I.

In the rat study (study III), ^{24}HFD rats were significantly heavier and had a higher overall fat percentage when compared to the ^{24}Chow group ($p<0.05$ in both). While in HOMA-IR, the ^{24}HFD group did not differ from the ^{24}Chow group, the ^{24}HFD group had a significantly higher HOMA-IR when compared to the group that switched the diet and exercised mid-point (^{12}HFD+^{12}(Chow+E)) ($p<0.05$) (Figure 4).

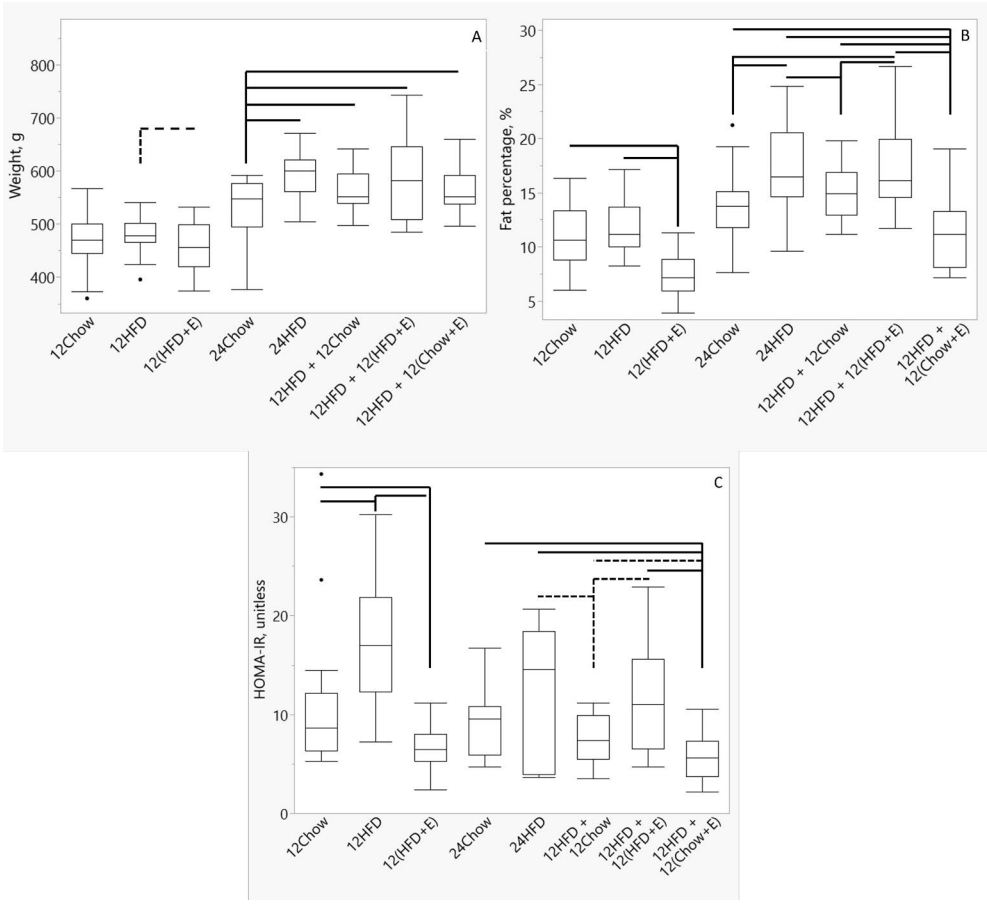

Figure 4. (A) Body weight (n = 16–24/group), (B) whole-body fat percentage at the end of study (n = 16–24/group), and (C) homeostatic model assessment for insulin resistance, HOMA-IR index (n = 8–20/group). Data is presented as boxes representing quartiles and whiskers representing the 10th and 90th percentiles. Median is marked with a single line. Student's t-test was used for A and B, Wilcoxon rank sum test was used for C. The black line indicates a significant difference ($p<0.05$) between groups. The dotted line indicates a tendency ($p<0.10$). Reprinted with permission from study III.

5.2 Obesity increases both liver and pancreatic fat content and disrupts liver insulin-stimulated GU and pancreatic β-cell function (I and III)

In the human study (study I), both pancreatic and liver fat content were significantly higher at baseline in the heavier twins compared to the leaner co-twins (p=0.035 and p=0.018, respectively) (Figure 5). Similar findings were seen in rats (study III), as the younger ^{12}HFD rats had higher total liver steatosis (Figure 6A) and lower HU (Figure 6B) compared to ^{12}Chow ($p<0.03$ for both). The 24-week-old rats also showed similar findings, as ^{24}HFD rats had a higher total liver steatosis (Figure 6A) compared to ^{24}Chow ($p<0.05$).

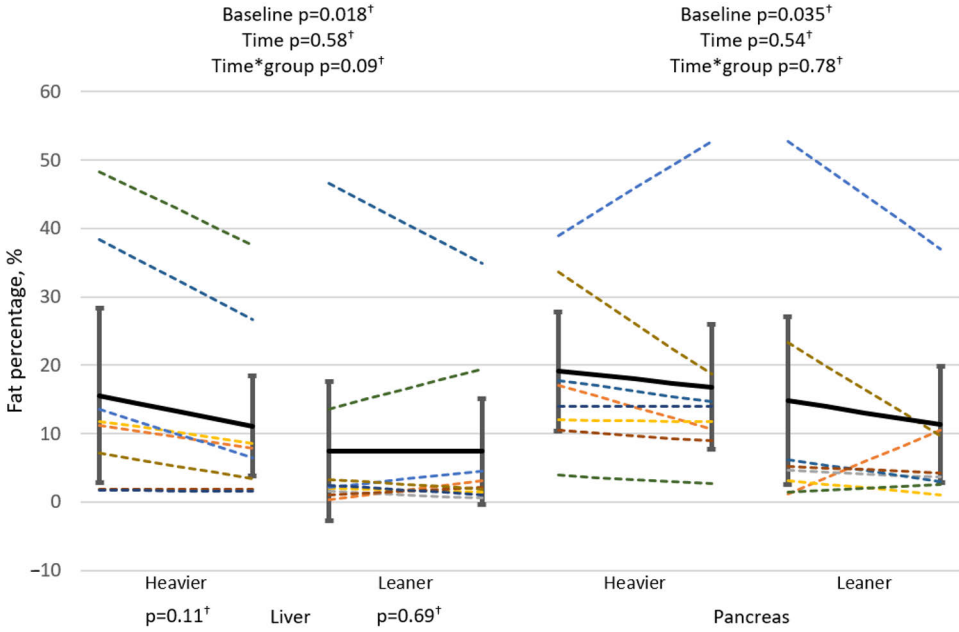

Figure 5. At baseline, the liver and pancreatic fat percentage were higher in the heavier twins compared to the leaner co-twins. In the heavier twins, liver fat percentage tended to decrease with exercise, while it was unchanged in the leaner twins. In the pancreatic fat percentage, no changes were observed after the intervention. Linear mixed model used for analysis. A single color represents a twin pair. The black line with confidence intervals represents the group average. Color coding is the same in both organs. Pancreatic fat percentage heavier twins: pre n = 8, post n = 9, and leaner twins: pre n = 10, post n = 9. Liver fat percentage heavier twins: pre n = 8, post n = 8, and leaner twins: pre n = 10, post n = 10, † Logarithmic transformation. Reprinted with permission from study I.

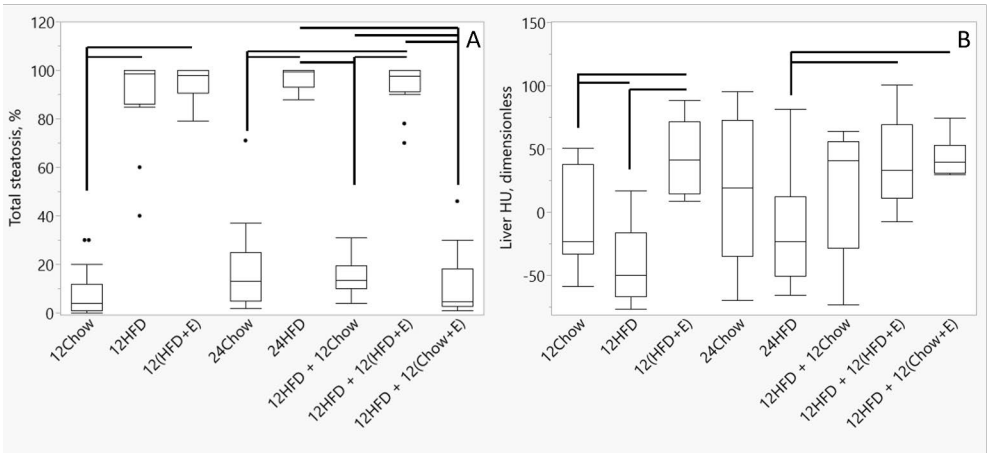

Figure 6. Total steatosis (n = 16–19/group), **(A)** Data is presented as boxes representing quartiles and whiskers representing the 10th and 90th percentiles. Median is marked with a single line. Wilcoxon rank sum test was used for both. The black line indicates a significant difference ($p<0.05$) between groups. Modified from study III.

In the human study (study I), insulin-stimulated liver GU was higher at baseline in the heavier twins when compared to the leaner co-twins ($p = 0.01$) (Figure 7). In rats, the younger rat group saw similar results to humans, as ^{12}HFD rats had the highest liver GU, which was significantly higher when compared to the group that exercised ^{12}HFD+E ($p<0.05$) (Figure 8A). The older 24-week rats, however, did not follow the same pattern as the ^{24}HFD rats had their liver GU on the lower end and significantly lower compared to the diet change group ^{12}HFD+^{12}Chow ($p<0.03$) (Figure 8A). In the PK11195 group, ^{24}HFD rats had lower liver PK uptake compared to ^{24}Chow ($p<0.05$) (Figure 8B).

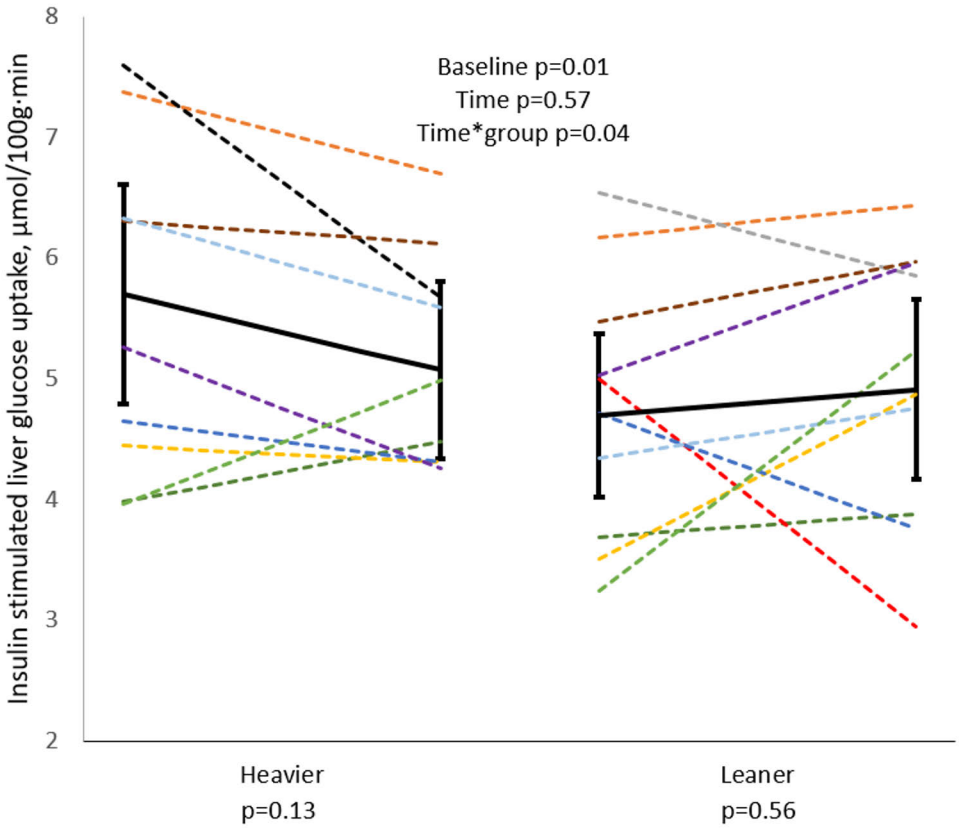

Figure 7. At baseline, liver GU was higher in the heavier twins compared to the leaner co-twins. The effect of exercise training differs between the twin groups, as training seems to decrease liver GU in the heavier twins while increasing it in the leaner co-twins. Linear mixed model used for analysis. A single color represents a twin pair. The black line with confidence intervals represents the group average. Heavier twins: pre n = 11, post n = 9, and leaner twins: pre n = 11, post n = 10. Reprinted with permission from study I.

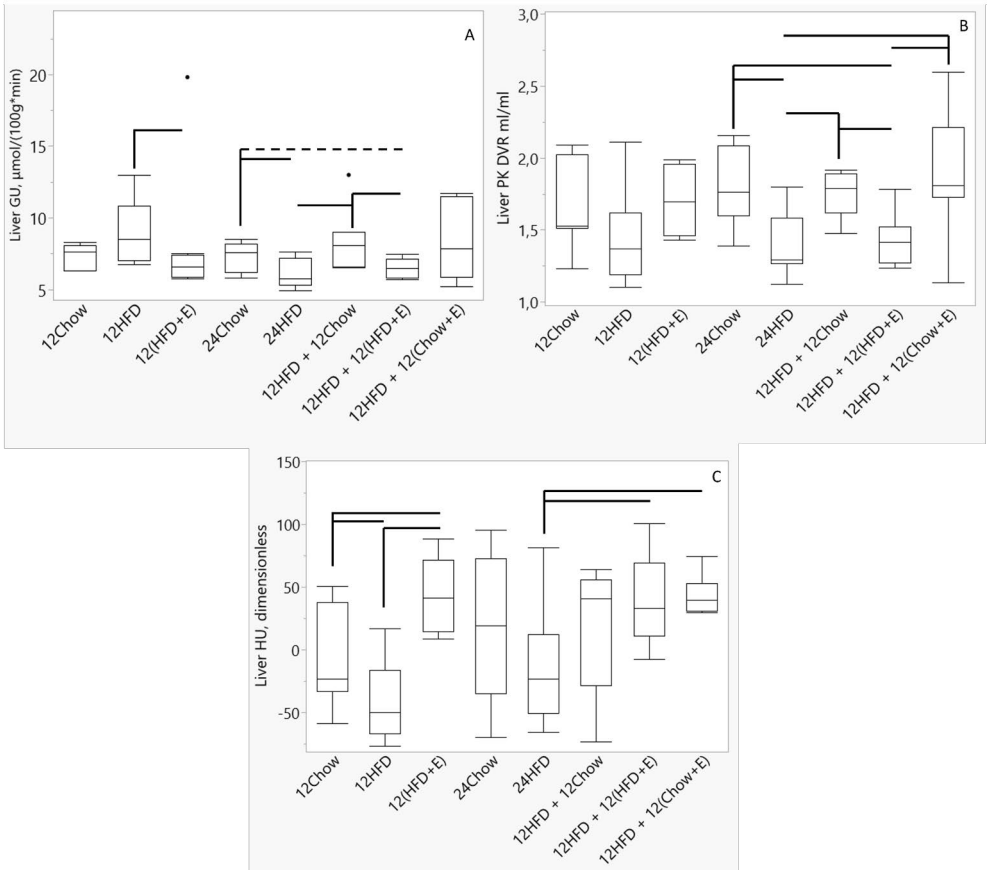

Figure 8. (A) Rat liver insulin-stimulated glucose uptake (n = 7–8/group), (B) PK11195 distribution volume ratio (DVR) (n = 8/group), and (C) Hounsfield units (n = 10–16/group). Data is presented as boxes representing quartiles and whiskers representing the 10th and 90th percentiles. Median is marked with a single line. Wilcoxon rank sum test was used for both. The black line indicates a significant difference ($p<0.05$) between groups. The dotted line indicates a tendency ($p<0.10$). Reprinted with permission from study III.

PFC was higher at baseline in the heavier twins compared to the leaner co-twins ($p = 0.035$) (Figure 5); however, after training, no changes were observed in the PFC of either group. Basal and mean blood insulin levels were higher in the heavier twins compared to the leaner co-twins at baseline ($p = 0.016$ and $p = 0.021$, respectively). ISR early and total ISR were higher in the heavier twins compared to the leaner co-twins at baseline ($p = 0.004$ and $p = 0.021$, respectively), while ISR late only tended to be higher in the heavier twins compared with their leaner co-twins ($p = 0.07$) (Table 9). There was a statistically significant difference in training response between the twins in glucose sensitivity (Time*group $p = 0.049$) (Table 9), with the heavier twins showing no change ($p = 0.36$) and the leaner twins showing a decrease ($p = 0.049$) after the intervention.

Table 9. OGTT and β-cell function (95% CI) of the leaner and heavier twin groups before and after exercise intervention.

	Heavier		**Leaner**		***p*-Value**		
	Pre	Post	Pre	Post	Baseline	Time	Time*group
n	12	11	12	10			
Basal glucose, mmol/L	5.7 (5.4;6.0)	5.8 (5.6;6.1)	5.5 (5.2;5.7)	5.5 (5.2;5.7)	0.39	0.37	0.42
Mean glucose, mmol/L	7.5 (6.7;8.2)	7.7 (7.0;8.3)	6.9 (6.1;7.8)	7.0 (6.1;7.9)	0.17	0.68	0.78
2 h glucose, mmol/L	6.5 (5.7;7.3)	6.6 (5.7;7.4)	6.1 (4.9;7.2)	5.8 (4.3;7.4)	0.32	0.84	0.52
HbA1c, mmol/mol	36.5 (35.1;37.9)	36.0 (34.2;37.7)	34.9 (32.8;37.0)	34.7 (32.2;37.1)	0.047 *†	0.58	0.68
Basal ins, pmol/L	70.5 (54.4;86.6)	63.5 (32.0;95.0)	44.0 (28.5;59.5)	49.0 (26.2;71.9)	0.006 *†	0.50 †	0.71 †
Mean insulin, pmol/L	371.6 (229.9;513.3)	339.4 (214.2;464.6)	235.8 (163.3;308.4)	258.2 (169.4;347.0)	0.01 *†	0.88 †	0.66 †
Basal insulin secretion rate, pmol·min−1·m−2	111.4 (97.5;125.2)	111.0 (95.4;126.5)	87.4 (69.4;105.4)	86.2 (69.6;102.7)	0.030 *	0.80	0.88
Glucose sensitivity, pmol·min−1·m−2·mM−1	92.5 (69.4;115.6)	103.4 (75.3;131.5)	98.5 (77.5;119.5)	75.2 (48.6;101.9)	0.66	0.44	0.049 *
	p = 0.36		*p* = 0.049 *				
Rate sensitivity, pmol·m−2 mM−1	1366.6 (906;1827)	1169.9 (680;1660)	1028.0 (668;1388)	1107.5 (601;1614)	0.049 *	0.70	0.13
PFR, dimensionless	1.4 (1.1;1.8)	1.3 (0.9;1.6)	1.7 (1.2;2.2)	1.5 (0.9;2.1)	0.48 †	0.30 †	0.52 †
ISR early, nmol/m2	13.1 (9.7;16.6)	12.3 (8.8;15.8)	10.0 (7.1;12.9)	9.3 (6.3;12.3)	0.004 *	0.50	0.92
ISR late, nmol/m2	31.9 (28.5;35.4)	29.1 (25.7;32.6)	26.9 (20.9;32.9)	25.7 (20.2;31.3)	0.07	0.24	0.50
Total ISR, nmol/m2	45.1 (39.2;50.9)	41.5 (35.8;47.2)	36.9 (29.6;44.2)	35.1 (27.9;42.2)	0.021 *	0.23	0.52
2 h OGIS, mL·min−1·m−2	375.0 (354.1;395.8)	369.0 (349.8;388.2)	414.7 (384.3;445.1)	415.8 (389.9;441.6)	0.037 *	0.75	0.63

p-value (linear mixed model) for a baseline: within-pair difference before the intervention, time: pre- and post-difference in the whole group, Time*group: did the training response differ within twin pairs. Abbreviations: HbA1c, glycosylated hemoglobin; rate sensitivity, a parameter characterizing early insulin secretion; PFR, potentiation factor ratio; ISR early, insulin secretion rate at time 0–30 min; ISR late, insulin secretion rate at time 30–120 min; 2 h OGIS, oral glucose insulin sensitivity from 0–120 min. * Statistically significant p-value ($p \leq 0.05$). † Logarithmic transformation. Reprinted with permission from study I.

5.3 Obesity-associated liver fat accumulation and metabolic impairments can be alleviated with exercise training (I and III)

In humans (study I), the effect of exercise on liver fat tended to differ between the twins (Time*group p=0.09). In the heavier twins, the LFC tended to decrease with exercise (p = 0.11), while it was unchanged in the leaner twins (p = 0.69) without weight loss. (Figure 5). In the rat studies (study III), the group that combined exercise with diet change (^{12}HFD+^{12}Chow+E) had lower total steatosis (Figure 6A) when compared to ^{24}HFD ($p < 0.01$). Both exercise training groups (^{12}HFD+^{12}(Chow+E)) and (^{12}HFD +^{12}(HFD+E)) had higher HU compared to ^{24}HFD ($p < 0.001$ in both) (Figure 8C).

In insulin-stimulated liver GU, the twin groups responded differently to training (study I) (Time*group p = 0.04), with a tendency toward a reduction in liver GU in heavier twins (p = 0.13), and no change in leaner twins (p = 0.56). (Figure 7). In the rat studies (study III), the group that combined exercise with diet change (12HFD+12(Chow+E)) had increased PK11195 uptake (Figure 8B) ($p<0.01$).

5.4 Obesity is associated with liver inflammation, which can be mitigated through exercise training (I and III)

GT was higher at baseline in the heavier twins than the leaner co-twins (study I) (p = 0.02) (Figure 9). In the rat study (study III), both the 12-week-old and 24-week-old HFD rats had higher total liver steatosis (Figure 6A), lower HU (Figure 8C), higher liver lipogranuloma numbers (Figure 10A), higher foci size scores (Figure 10B), and higher portal inflammation grade (Figure 10C) compared to the same-aged Chow rats ($p<0.05$ in all).

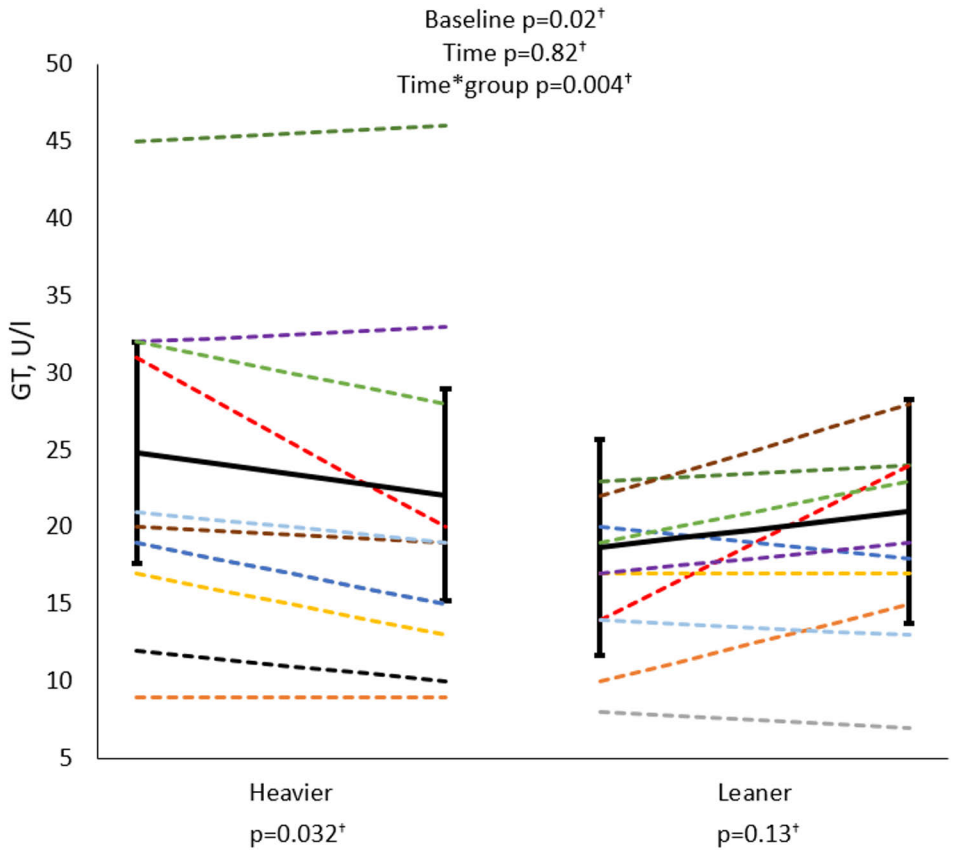

Figure 9. Gamma-glutamyl transferase (GT) was higher at baseline in the heavier twins, and the effect of training differed between the twins; for the heavier twins, a decrease in GT was observed, while an increase was seen for the leaner twins. Linear mixed model used for analysis. A single color represents a twin pair. The black line with confidence intervals represents the group average. Units per liter (U/l) Leaner twins: pre n = 12, post n = 11, and heavier twins: pre n = 12, post n = 10, † Logarithmic transformation. Reprinted with permission from study I.

The training response differed between twin groups (study I) (Time*group p = 0.004), with a significant GT reduction in the heavier twins (p = 0.032) and a tendency toward an increase in the leaner twins (p = 0.13) (Figure 9). In the rats, the group that combined exercise with a diet change (12HFD+12(Chow+E)) had lower lipogranuloma number, foci size score, and portal inflammation grade when compared to [24]HFD ($p<0.05$ in all) (Figure 10).

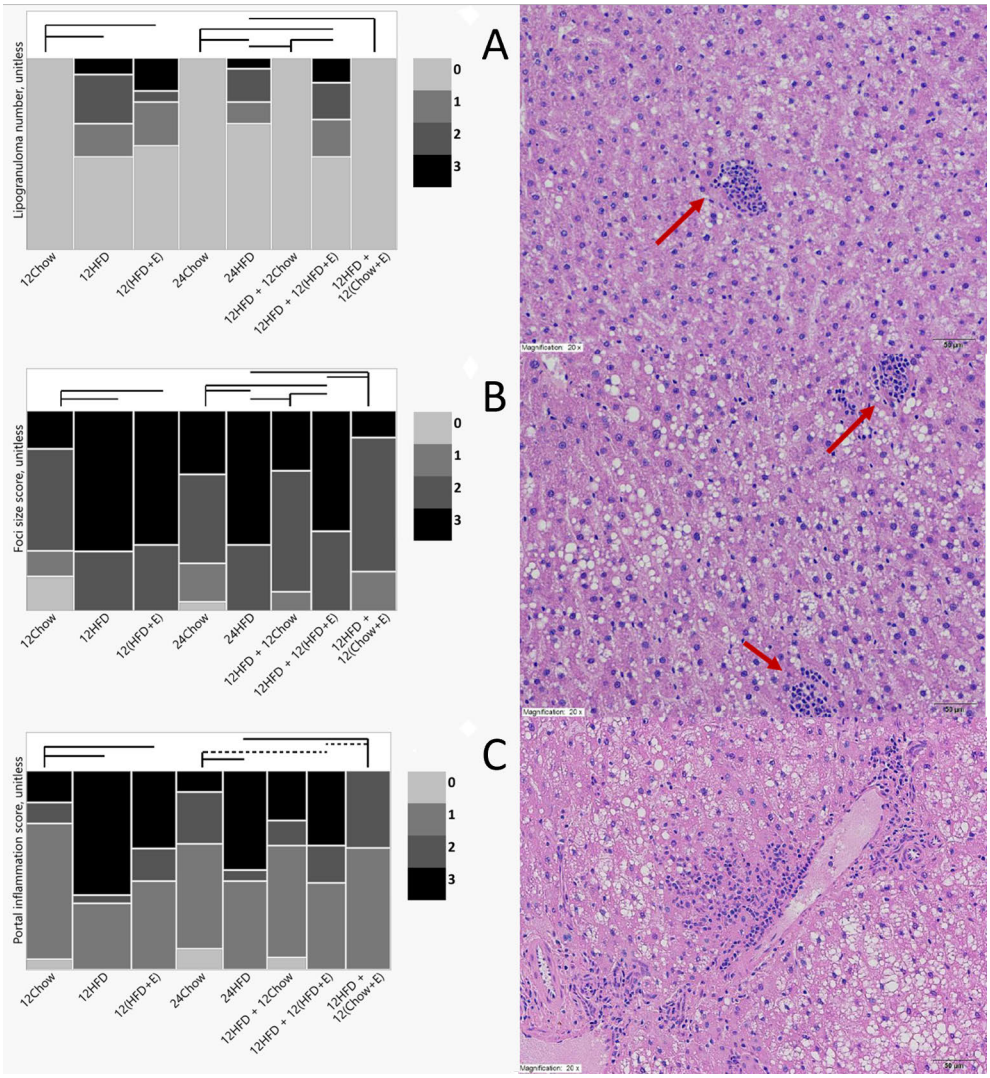

Figure 10. Rat liver lipogranuloma number (B) (*n* = 16–24/group), Foci size score (C) (*n* = 16–24/group), and portal inflammation grade (D) (*n* = 16–24/group). Data is presented as boxes representing the percentage of all individuals in the group. Wilcoxon rank sum test was used for all (A). The black line indicates a significant difference ($p<0.05$) between groups. The dotted line indicates a tendency ($p<0.10$). Modified from study III.

5.5 Exercise training improves impaired intestinal insulin-stimulated glucose uptake in leaner twins and modulates gut microbiota (II)

In study II, the heavier twins had lower small intestine and colon insulin-stimulated GU at baseline (p = 0.041 and p = 0.005, respectively) (Figures 11 and 12). At baseline, BMI had a significant inverse correlation with the small intestine GU and colon GU ($p < 0.01$, $R < -0.68$ in both) (study II supplemental material. Not shown).

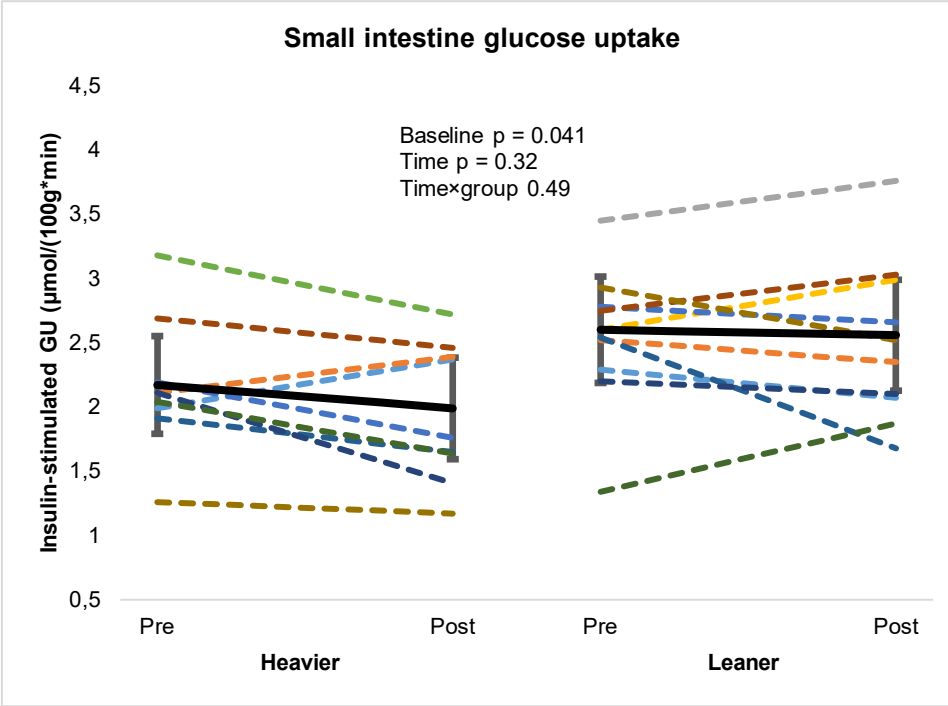

Figure 11. Heavier twins had lower small intestine GU at baseline, but no changes between the groups were seen after the intervention. Linear mixed model used for analysis. Heavier twins pre n = 11, post n = 9, and leaner twins pre n = 11, post n = 10. Twins from the same pair are coloured with the same colour. Reprinted with permission from study II.

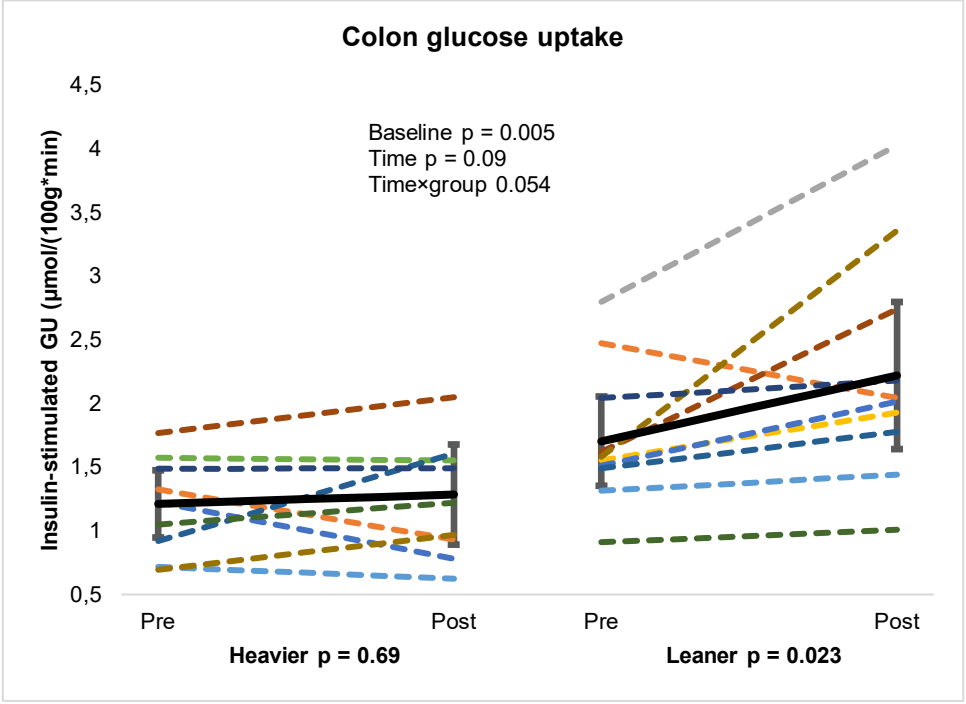

Figure 12. Lower colon GU was seen in heavier twins compared to leaner twins at baseline, and after the intervention. When the groups were analysed separately, colon GU only increased in the leaner twins. Linear mixed model used for analysis. Heavier twins pre n = 11, post n = 9, and leaner twins pre n = 11, post n = 10. Separate p-values represent the time effect when twin groups were analysed separately. Twins from the same pair are coloured with the same colour. Reprinted with permission from study II.

The training response was observed only in colon GU, and the response differed between groups (time × group $p = 0.05$). When the groups were analysed separately, colon GU only increased in the leaner twins after the intervention ($p = 0.023$) (Figure 12).

Gut microbiota composition was analysed at baseline, at mid-point 16.6 (SD 2.7) weeks after the start of the intervention, and at the end of the intervention. At baseline, there were no differences in alpha diversity between the twins. After the intervention, only Pielou's evenness (measurement of how similar or dissimilar the relative abundances of the species in a set are) decreased significantly ($p = 0.02$) in the whole population (Table 10).

Table 10. Alpha diversity of the leaner and the heavier twin groups before, mid, and after exercise intervention [mean (95% CI)].

	Heavier			Leaner			*p*-Value		
	Pre	**Mid**	**Post**	**Pre**	**Mid**	**Post**	**Baseline**	**Time**	**Time× group**
n	10	9	10	10	9	9			
Male/ female	4/8	4/7	4/7	4/8	4/6	4/6			
Pielou Evenness	0.73 (0.70; 0.76)	0.73 (0.70; 0.76)	0.69 (0.65; 0.73)	0.75 (0.72; 0.78)	0.76 (0.74; 0.78)	0.72 (0.69; 0.75)	0.33	0.019 *	0.78
Chao 1	353.8 (312.3; 395.4)	350.0 (311.3; 388.6)	357.0 (301.7; 412.3)	339.1 (277.8; 400.4)	394.3 (358.3; 430.4)	414.3 (361.7; 466.9)	0.60	0.40	0.36
Dominance	0.04 (0.03; 0.06)	0.04 (0.03; 0.05)	0.05 (0.03; 0.08)	0.03 (0.02; 0.04)	0.03 (0.02; 0.03)	0.04 (0.02; 0.05)	0.25	0.14	1.00
Observed otus	347.9 (307.4; 388.4)	343.4 (306.4; 380.4)	345.0 (290.9; 399.1)	334.5 (273.2; 395.8)	387.1 (352.0; 422.3)	401.6 (349.3; 453.8)	0.63	0.53	0.37
Shannon	6.1 (5.8; 6.4)	6.1 (5.8; 6.4)	5.8 (5.3; 6.2)	6.2 (5.8; 6.7)	6.5 (6.3; 6.8)	6.2 (5.9; 6.6)	0.64	0.07	0.58
Simpson	1.0 (0.9; 1.0)	1.0 (1.0; 1.0)	1.0 (0.9; 1.0)	1.0 (1.0; 1.0)	1.0 (1.0; 1.0)	1.0 (1.0; 1.0)	0.31	0.23	0.83

p-value (linear mixed model) for baseline: within-pair difference before intervention, time: pre, mid, and post difference in whole sample, time*group: did the training response differ within twin pairs. Heavier co-twins pre n = 12, mid n = 10, post n = 10, leaner co-twins pre n = 12, mid n = 10, post n = 9. * Statistically significant p value ($p \leq 0.05$). † Logarithmic transformation. Reprinted with permission from study II.

No difference was observed in the beta-diversity between the twins at baseline, but beta-diversity changed significantly after the training intervention in the whole population. Indeed, PCoA of inter-sample variation based on the Bray–Curtis index, Jensen–Shannon Divergence, and Jaccard index showed significant segregation at all the analysed taxonomic levels ($p = 0.001$ for all distance metrics at phylum level, at genus and ASV levels, *p*-value below 0.05 for Jaccard Index only. Between the three time points, with the main change observed at mid-point, which was significantly different from both baseline and post-intervention time points ($p < 0.05$ in all distance metrics, at phylum, genus, and ASV levels) (Figure 13).

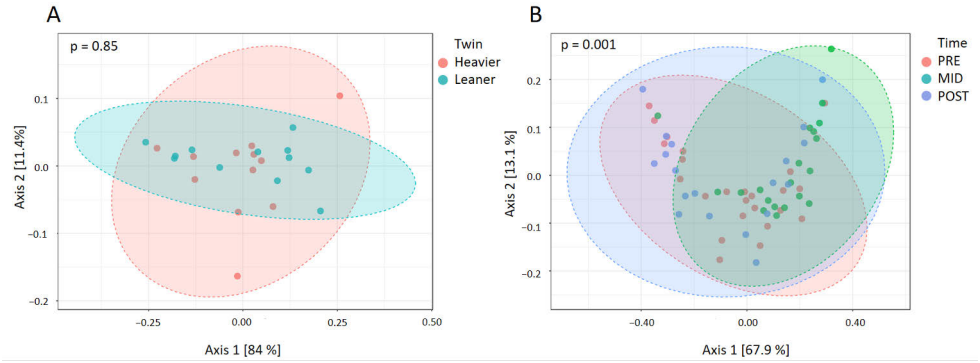

Figure 13. At baseline, beta-diversity computed as based on Bray–Curtis index, Jensen–Shannon Divergence, and Jaccard index dissimilarity indices was no difference between the twins (A), but exercise training intervention caused a significant change (according to the three distance metrics) in beta diversity (B). Figures report PCoA plots based on Jaccard index at the phylum level. Reprinted with permission from study II.

When the twin groups were analysed separately, beta diversity over time was significantly different in the leaner twins ($p < 0.05$ for all dissimilarity indexes) but not in the heavier twins ($p > 0.05$ for all), suggesting that the training-induced changes in relative taxon abundances were mostly driven by the leaner twins (Figure 14).

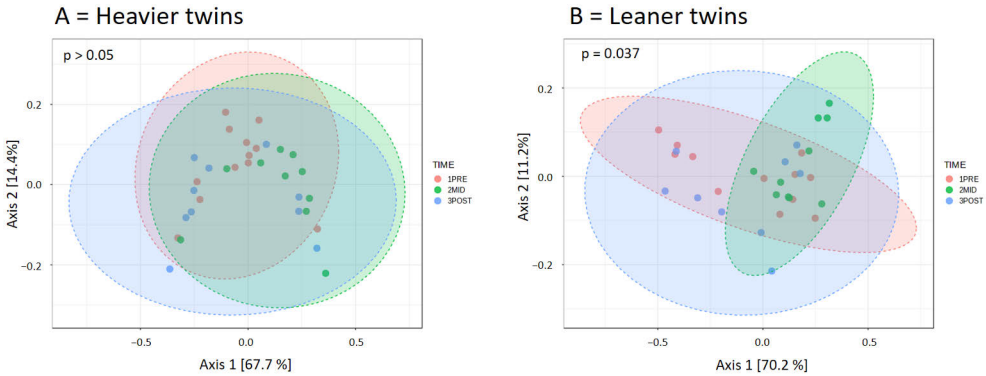

Figure 14. When the twin groups are analysed separately, beta diversity computed based on Bray–Curtis index, Jensen–Shannon Divergence, and Jaccard index distance metrics over time changed significantly only in leaner twins. Figures report PCoA plots based on Jaccard index, at the phylum level. (A) = heavier twins, (B) = leaner twins. Reprinted with permission from study II.

Then the taxonomic composition of the heavier and leaner twins and their change over time was investigated. In accordance with the diversity results, the relative

taxon abundances were similar between the twin groups at baseline. In the whole population, the intervention led, at the mid-point, to a reduction in *Bacteroidota* and *Proteobacteria* phyla and an increment in *Firmicutes* phylum (pFDR < 0.05). However, at the end of the intervention, all three phyla (*Bacteroidota*, *Proteobacteria*, and *Firmicutes*) were back to baseline levels. At the end of the intervention, only *Campylobacterota*, a bacterial phylum of low relative abundance, showed a significant increase compared to baseline. At the genus level, the intervention led to the increment of *Megamonas*, *Helicobacter*, *Sellimonas*, *Lactobacillus*, *CHKCL001*, *Cutibacterium*, *Xanthomonas*, and *Enorma* (pFDR < 0.05 for all) (Figure 15).

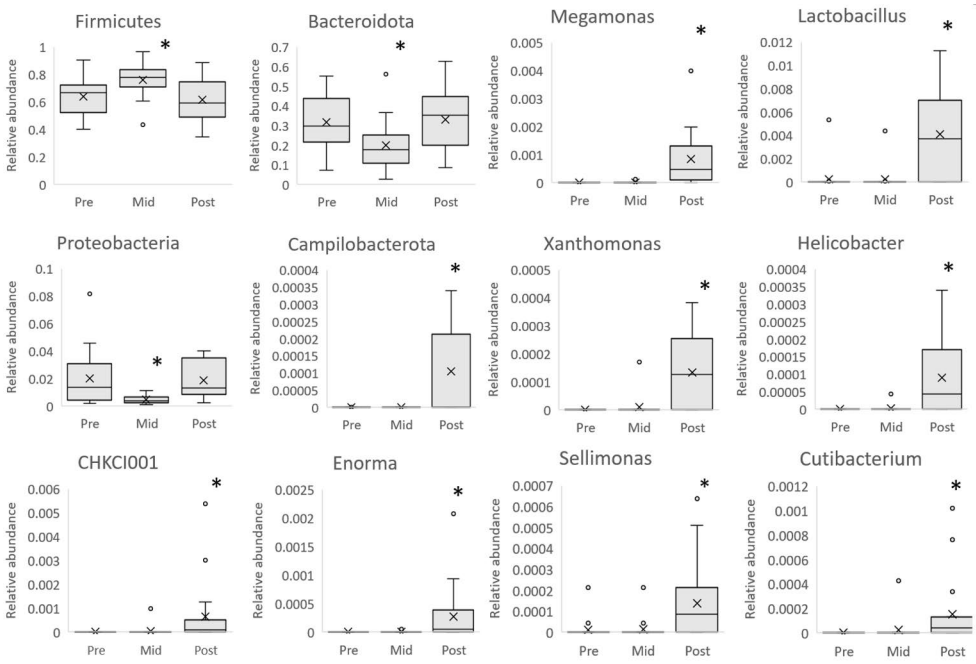

Figure 15. Bacteroidota and Proteobacteria levels decreased in the whole sample at mid-intervention but increased to baseline levels at the end of the intervention. The opposite change was observed for Firmicutes, where an increase was observed at mid-intervention, but levels fell back to baseline at the end of the intervention. After the intervention, there was an increase at the phylum level in *Campylobacterota* and at the genus level in *Megamonas, Helicobacter, Sellimonas, Lactobacillus, CHKCL001, Cutibacterium, Xanthomonas,* and *Enorma* compared to baseline in the whole sample. Linear mixed model used for analysis. *Statistically significant pFDR value (pFDR≤0.05). Pre heavier n = 12, Leaner n = 12. Mid heavier n = 10, Leaner n = 10. Post heavier n = 10, Leaner n = 9. The boxplots represent relative abundances. The box plot whisker represents the maximum and minimum, excluding outliers. Modified from study II.

The analysis of taxonomic composition in the two twin groups showed that the transient (at mid-point only) increment of Firmicutes and reduction of *Bacteroidota* and *Proteobacteria* (trend, pFDR = 0.09) phyla were similar between twins but reached statistical significance only in the leaner group, with the exception of the reduction of *Proteobacteria* (Figure 16).

Similarly, the increment in *Campylobacterota* at the end of the intervention was statistically significant in the leaner but not the heavier twins.

At the genus level, *Megamonas* abundance was significantly increased in the whole population, whereas the increment of *Lactobacillus* genera, although showing a similar trend in both the heavier and the leaner twins, only reached statistical significance in the leaner twins (Figure 16).

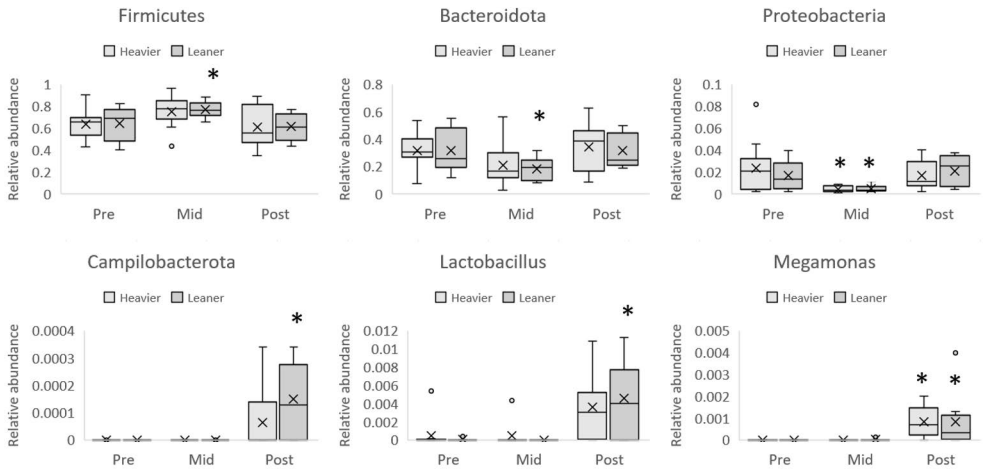

Figure 16. The transient (at mid-point only) increment of Firmicutes and reduction of *Bacteroidota* and *Proteobacteria* phyla were similar between twin groups but reached statistical significance in the leaner group only, with the exception of the reduction of *Proteobacteria*. Similarly, the increment of *Campylobacterota* at the end of the intervention was statistically significant in leaner but not in heavier twins. The increment of *Lactobacillus* genera reached statistical significance in the leaner twins only. Linear mixed model used for analysis. *Statistically significant pFDR value (pFDR≤0.05). Pre heavier n = 12, Leaner n = 12. Mid heavier n = 10, Leaner n = 10. Post heavier n = 10, Leaner n = 9. The box plots represent relative abundances. The box plot whisker represents the maximum and minimum, excluding outliers. Reprinted with permission from study II.

6 Discussion

Obesity is a condition that affects individuals worldwide, and its prevalence has increased yearly (S. K. Ahmed and Mohammed 2025). Obesity is associated with both systemic and organ-specific comorbidities such as T2D, insulin resistance, and ectopic fat accumulation (Iozzo, Hallsten, et al. 2003; Fabbrini et al. 2008; Chih-Yuan Wang et al. 2014; Motiani et al. 2017; Brauer et al. 2024).

Exercise offers many benefits to overall health and well-being (Qiu et al. 2023) and may ameliorate obesity driven metabolic changes as a medicine-free alternative or by supporting medical interventions (Motiani et al. 2017; Heiskanen et al. 2018; Motiani et al. 2019).

This thesis aimed to assess the effects of obesity in the pancreas, liver, intestine, and intestinal microbiota and whether these can be ameliorated with a six-month-long exercise intervention (studies I and II). To minimise the confounding effects of genetics, monozygotic twins discordant for BMI were recruited as participants. This thesis also aimed to gain a more in-depth understanding of obesity-induced liver steatosis and inflammation, and the relationship between them, with a complementary rat study setting enabling histological evaluation of the liver with and without exercise (Study III).

6.1 Liver steatosis, the role of inflammation and exercise.

At baseline, the heavier twins in the human trial (study I) had a higher fat percentage than their leaner co-twins. In a similar vein, all the HFD-treated groups in the rat trial (study III) had considerably more histologically evaluated overall steatosis than the non-HFD groups. HFD groups had lower liver HU and higher total liver steatosis across all age categories. Similarly, the heavier twins in study I had higher LFC at baseline compared to their leaner co-twins. The results of studies I and III were in line with previous research, showing that obesity is one of the main components leading to an increase in LFC (Viljanen et al. 2009; Pár and Pár 2017).

The twin groups (study I) tended to respond differently to the training intervention, as the LFC tended to decrease (31%) only in the heavier twins. The effects of exercise were more widely observed in rats (study III), since the inclusion

of exercise resulted in considerably higher HU values in all age groups. Unexpectedly, compared to HFD (^{24}HFD) animals, the chow diet (^{24}Chow) per se did not lead to a greater average HU of the liver. This may be due to the large heterogeneity in the Chow group results. In the histological findings, both diet change (^{12}HFD+^{12}Chow) and diet change with exercise (^{12}HFD+^{12}Chow+E) lowered total steatosis compared to the ^{24}HFD group, with the combined intervention being the most effective.

Previous human studies have shown that exercise training decreases LFC and increases HU, independent of weight loss (Johnson et al. 2009; Hallsworth et al. 2011; Slentz et al. 2011; Keating et al. 2012). However, there are also studies where the changes in LFC have been attributed to weight loss or a higher baseline LFC (Motiani et al. 2019; H.-J. Zhang et al. 2016). Additionally, it has been demonstrated that altering one's diet alone can effectively reduce (Thoma et al. 2012) and increase (Luukkonen et al. 2018) the amount of fat in the liver. The usage of HU has been seen as a potential non-invasive method to evaluate the degree of low-grade liver steatosis in humans with biopsy-proven MAFLD (H. N. Kim et al. 2023). Liver HU measured in rats (study III) was lower both after exercise (^{12}HFD+(^{12}HFD+E)) and with the change in both diet and exercise (^{12}HFD+(^{12}Chow+E)), while total steatosis was lower only with the diet and exercise (^{12}HFD+(^{12}Chow+E)) when compared to the 24HFD group. This discrepancy in the results may be due to the methodological difference that total steatosis reflects the percentage of cells with visible fat droplets in the liver samples, and HU the total volume of fat within the liver.

Together, studies I and III show that exercise and diet are ways to decrease LFC. Our findings in twins agree with previous data (Johnson et al. 2009; Hallsworth et al. 2011; Keating et al. 2012) showing that exercise training can decrease liver fat content even without concomitant weight loss, especially in heavier individuals. However, based on the rat studies, the combination of a diet change and exercise may offer a more effective way to reduce LFC when compared to exercise only.

In contrast to our original hypothesis, the heavier twins' baseline insulin-stimulated liver GU was substantially higher than that of their leaner co-twins. (study I). In the rat study (study III), similar findings were seen only in the 12-week-old HFD group, which had the highest liver GU, while the ^{24}HFD group had a relatively low liver GU.

The finding of higher liver glucose uptake in heavier twins at baseline (study I) was interesting, as liver GU has been previously shown to be decreased in obesity (Immonen et al. 2014) and T2D (Borra et al. 2008) when compared to lean controls during euglycemic-hyperinsulinemia. This is believed to be a result of decreased glucokinase activity, which is the liver glycogen synthesis rate-limiting step. (Nozaki et al. 2020). In both fasting and glucose-loaded states, leptin-receptor-defective pre-obese and obese rats have higher liver GU than controls under free-living (real-life)

settings, which may reflect the level of liver inflammation (Guzzardi et al. 2022). Liver glucose uptake has also been shown to be increased in liver steatosis, when normalized to the metabolically active liver tissue, i.e., excluding the inert fat volume (Keramida et al. 2014), and correlates positively with BMI (Batallés et al. 2013). Thus, the results of study I could suggest that increased liver insulin-stimulated GU, simultaneously with obesity, increased LFC, and a sedentary lifestyle, may be an indicator of liver inflammation.

The effect of exercise training differed between the twin groups, and training seemed to decrease liver glucose uptake in the heavier twins, while increasing it in the leaner co-twins. In rats, exercise alone was not enough to cause significant changes in liver GU, but diet change (^{12}HFD+^{12}Chow) increased liver GU compared to ^{24}HFD. In previous studies, exercise has been shown to improve liver GU (Motiani et al. 2019). In study III, given that the hyperinsulinemic euglycemic clamp was employed to measure liver GU, the increase in liver GU in the diet change group ^{12}HFD+^{12}Chow may indicate improved liver insulin sensitivity brought on by diet-induced reductions in LFC and inflammation. Similar findings of improved liver insulin sensitivity and reduction of LFC have been seen in humans with ketogenic diet interventions (Luukkonen et al. 2020).

In study III, liver PK11195 uptake was evaluated as a possible proxy for inflammation. The 24-week-old HFD groups (^{24}HFD and ^{24}HFD+E) had lower PK11195 uptakes when compared to other groups. The result was surprising, as liver TSPO expression has been shown to be increased in MAFLD and correlates closely with MAFLD progression when assessed with [^{18}F]FEDAC, a more liver-specific TSPO ligand (L. Xie et al. 2012).

The impact of TSPO on liver steatosis is unclear because, although its expression is associated with the advancement of the disease, its absence is complex and may be interpreted differently based on the stage of the disease. In fact, TSPO deficiency has also been thought to exacerbate the advancement of MAFLD (Y. Li et al. 2021, 2024, 2025). By using Atriol, a cholesterol-binding disrupting TSPO ligand, metabolic-associated steatohepatitis can be ameliorated (Y. Li et al. 2024). The proposed mechanism behind the amelioration is reduced lipid accumulation, diminished liver lobular inflammation and fibrosis, and decreased cell death. In advanced MAFLD stages, TSPO downregulation leads to bile acid synthesis, which ameliorates liver fibrosis (Y. Li et al. 2021).

Additionally, some preclinical research indicates that the downregulation of TSPO in the liver is linked to obesity (Dimitrova-Shumkovska et al. 2010; Thompson et al. 2013). Rats placed on a high-fat, high-carbohydrate diet have decreased TSPO expression in the liver, which correlates with increased oxidative stress in these tissues and systemic hypercholesterolemia (Dimitrova-Shumkovska et al. 2010). Also, high liver short fatty chain levels have been associated with several

unique methylation genes that correlated negatively with TSPO mRNA expression (Sehgal et al. 2023). In study III, groups with control diet (^{24}Chow), diet change (^{12}HFD+^{12}Chow), and especially diet change combined with exercise (^{12}HFD+(^{12}Chow+E)) had higher PK11195 uptake when compared to HFD groups (^{12}HFD and ^{12}HFD+(^{12}HFD+E)), which could suggest TSPO downregulation as a compensatory mechanism for elevated inflammation and fat content. The histology data, which demonstrate more severe inflammatory signs in the livers of HFD rats, support this. In study I, the heavier twins showed greater GT levels at baseline, and a significant GT reduction after exercise training, consistent with previous evidence (Motiani et al. 2019). GT is an oxidative stress marker, which is attributed to liver inflammation (Fentiman 2012), correlating with body weight in study I and other studies (Wiegand et al. 2011). GT also correlated positively with LFC at baseline, and a significant positive correlation was observed between both the decrease in LFC and the decrease in GT, as observed in the heavier twins. Together with the GT decline, a dichotomic liver GU response was seen in the twin pairs, with a liver GU decrease in the heavier twins, and a small increase in the leaner co-twins. The decrease in GT of the heavier twins may be due to the concomitant decrease in LFC. The increase in the leaner co-twins may be associated with the improved liver insulin sensitivity caused by exercise.

In study III, lipogranulomas (aggregates of lipids containing histiocytes), foci size score (representing the size of localized lobular inflammatory spots in the liver), and portal inflammation grades (representing the presence of inflammatory cells) within portal tracts were all more prevalent in all HFD groups. The results are in line with previous studies, as lipogranulomas (Hübscher 2006; Zhu et al. 2010), increased foci size scores (Terayama et al. 2022; Z.-J. Xu et al. 2010) and increased portal inflammation grades (Rakha et al. 2010) have all been associated with increased liver steatosis. In our study, exercise training combined with a chow diet was the most effective at preventing the HFD-induced liver inflammation, compared to exercise alone.

According to the findings of studies I and III, the heavier twins' higher liver GU and LFC may indicate low-grade liver inflammation because infiltrating inflammatory cells typically increase GU (Keramida et al. 2014). The suggestion of inflammation-driven liver hypermetabolism is further strengthened in study III, as PK11195 uptake in the liver was negatively correlated with total steatosis of the liver ($r=-0.41$, $p<0.01$), and as the PK11195 intercept (inverse of residence time) and portal inflammation score ($r=0.34$, $p<0.01$) correlated positively. Exercise training may ameliorate this inflammation (Fredrickson et al. 2021).

When combined, studies I and III imply that liver GU reflects a balance between insulin stimulation of hepatocytes (which may prevail during insulin clamps in the longer HFD term) and inflammatory cell infiltration (which may prevail in GU

uptake in the early HFD phase). The downregulation of liver TSPO in the HFD groups appeared to be linked to liver steatosis and low-grade liver inflammation, which may indicate an effort to shield the organ from the advancement of MAFLD. This is an essential finding, indicating that PET imaging of PK11195 could possibly be a tool for early detection of the switch between steatosis and inflammatory damage. Both regular exercise training and diet change are effective ways to improve liver metabolism and liver inflammation. The benefits of exercise training are particularly evident in the reduction of liver fat content. However, more studies are needed to differentiate the two different drivers of liver metabolism.

6.2 Exercise and pancreatic β-cell function.

In study I, the baseline PFC surpassed the upper normal limit of 6.2% (Rossi et al. 2011) in both groups, although the heavier twins had a significantly higher PFC compared to the leaner twins. Both groups were, on average, overweight due to the fact that the inclusion criteria were based on the BMI difference between twins within the pair, and not absolute BMI ranges. The results of study I on PFC are consistent with earlier research, demonstrating a gradual relationship between rising obesity and the buildup of PFC. (Y et al. 2007).

In study I, regular exercise training did not reduce PFC in either group. The lack of difference may be due to the small number of twins and due to measuring PFC with MRS being difficult. When assessed individually, one of the heavier twins and one of the leaner twins were going against the average trend. The outlier heavier twin had decreases in visceral fat, fat mass, and LFC. The outlier leaner twin had increases in the same variables. While the leaner twin's increased PFC could be explained by an increase in total fat mass, the heavier twin's increased PFC could be the result of poor voxel placement during the MRS examination. In MRS, a voxel is placed into the target organ during the study while the subject is lying in the scanner. The MRS measurements are taken during breath holds to avoid organ movements; however, the small pancreas size and inaccurate voxel positioning might lead to detection errors, e.g., part of the voxel overlapping with intra-abdominal fat tissue. Also, PFC accumulation is usually not evenly distributed, which increases the importance of positioning the voxel in the same anatomical location before and after an intervention (C.-L. Zhang et al. 2021). Thus, in study I, the challenges in voxel placement may explain the increase in PFC in the heavier twin, as no increases in other fat parameters were observed. In the future, other methods for evaluating pancreatic fat percentage should also be considered, such as Q-Dixon-WIP, although it may be less sensitive at detecting small changes in pancreatic fat content (Yi et al. 2023).

Studies on the effects of exercise training on PFC are sparse. Previous research has demonstrated that short-term training can already result in a decline in PFC,

independent of baseline glucose tolerance (Heiskanen et al. 2018); while in a cross-sectional study in healthy MZ twins with discordant physical activity and fitness, no difference was observed between the groups in PFC (Hannukainen et al. 2011). The exact role of ectopic PFC on β-cell function is also unclear, although PFC is more commonly increased in individuals with obesity and glucose tolerance impairment (Guglielmi and Sbraccia 2018; Tushuizen et al. 2007) than in lean normally-tolerant people. In rats, an increase in beta-cell triglyceride content has been shown to cause lipotoxicity and lipoapoptosis, impairing β-cell function, which may contribute to T2D development (Y. Lee et al. 2010). However, the severity of organ steatosis induced in rodent models is usually not comparable to the levels occurring in humans.

According to the basal and mean insulin levels as well as the early and total insulin secretion rates in study I, the OGTT data demonstrated that the heavier twins had considerably higher insulin secretion at baseline. This was anticipated as the twins were divided into leaner and heavier twins by BMI, and compensatory hyperinsulinemia is known to occur in obesity (Reaven 1988). Moreover, total ISR was strongly and inversely related to the M-value, suggesting that the greater insulin secretion observed in the heavier twins compared to the leaner co-twins is explained by insulin resistance. After the exercise intervention, there were no changes in any of the above-mentioned parameters. Acute insulin secretion during an intravenous glucose tolerance test has been shown to decrease after eight months of intense exercise. (Slentz et al. 2009). In study I, the M-value improvement was significant, but training did not affect insulin secretion, and the changes in M-value and insulin secretion were not significantly correlated to those in the total ISR. This may indicate that to see changes in insulin secretion, a worse baseline insulin sensitivity, a longer period of regular exercise, or concomitant weight loss may be required.

Therefore, the findings in study I do not contradict the known link between insulin secretion and insulin resistance but show that the significant variability and the small group prevent precise assessment of the potential differences between the twin groups. However, study I indicates that obesity raises insulin secretion compared to leaner people, a characteristic associated with the onset of T2D, regardless of genetics.

Glucose sensitivity derived from OGTT data reflects the slope of the dose-response relating insulin secretion to glucose concentration. Namely, it indicates the amount of insulin produced by β-cells in response to different plasma glucose concentrations. At baseline, the twins did not differ in glucose sensitivity. The heavier twins' glucose sensitivity remained unchanged after training, consistent with previous studies with healthy and prediabetic/T2D individuals (Heiskanen et al. 2018). There were no individuals with T2D in study I, and neither group's baseline glucose sensitivity was low.

Considering that the M-value was improved similarly in both groups, the above observations suggest that the M-value and glucose sensitivity are not necessarily correlated, as supported by previous observations (E. Ferrannini et al. 2003). Using peripherally injected glucose during a standard hyperinsulinemic-euglycemic clamp study protocol, the M-value is an estimate of peripheral glucose absorption. On the other hand, as glucose is absorbed from the gut during OGTT, glucose sensitivity represents the insulin reaction to blood glucose exposure. Therefore, results from study I indicate that participants in our study have insulin resistance but no β-cell dysfunction. Overall, results from study I further strengthen the notion that independent of genetics, obesity increases PFC and insulin secretion. However, the effect of PFC accumulation on pancreatic endocrine function needs further studies.

6.3 Exercise and intestinal glucose metabolism

Intestinal insulin-stimulated GU was lower in both the small intestine and the colon in the heavier than their leaner co-twins at baseline (study II), which is consistent with earlier research demonstrating impaired intestinal GU in obesity (Mäkinen et al. 2015; Franquet et al. 2019). In addition, there was a strong inverse correlation between BMI and intestinal GU, confirming that intestinal insulin sensitivity is closely related to obesity. Interestingly, exercise training improved the colonic GU only in the leaner twins, disagreeing with our hypothesis. It is also noteworthy that both groups had comparable increases in whole-body insulin sensitivity (M-value), while colonic GU only considerably improved in the leaner twins.

It has previously been demonstrated that morbid obesity significantly impairs insulin-stimulated GU in the small intestine and that GU improves following bariatric surgery, resulting in weight loss. (Mäkinen et al. 2015). In the present study, no change was observed in the whole-body mass, fat percentage, or FFA-levels and the visceral fat mass only tended to decrease, suggesting that the observed improvement in colonic GU was independent of weight loss.

Training enhanced GU in the colon but not in the small intestine in study II. Glucose transportation from blood to enterocytes has been shown to occur via GLUT2 (Kellett and Brot-Laroche 2005). Prior research has demonstrated that short-term exercise increases GLUT2 expression in enterocytes and improves colonic GU while leaving small intestine GU unaltered. (Motiani et al. 2017). Moreover, similar findings have been observed after bariatric surgery (Mäkinen et al. 2015). It has been suggested that the discrepancy in GU in different parts of the intestine might be due to the differences in the location of GLUT2 receptor prevalence in the enterocytes, as GLUT2 has been observed in the basolateral membrane of an enterocyte in the small intestine (jejunum) (Ait-Omar et al. 2011); instead, in the colon, GLUT2 is only present in short epithelial portions, involving a limited number of cells (Merigo

et al. 2018). In addition, different digestive tasks between the small and large intestines may play a role in how exercise training strains these mechanisms.

Honka and colleagues showed that insulin was able to increase GU by 2.5- and 2.9-fold in the duodenum and jejunum, respectively, when studied in healthy humans during fasting and insulin stimulation (H. Honka et al. 2013). They and others further showed in pigs that ^{18}F-derived intestinal radioactivity was located in the mucosal layer during fasting and hyperinsulinaemic euglycemia (Mäkinen et al. 2015; H. Honka et al. 2013). Insulin has been shown to affect GLUT2 receptor location in the enterocyte, as insulin administration leads to internalization of GLUT2, increasing intestinal GU (Tobin et al. 2008). Metformin and other insulin-sensitizing drugs have been demonstrated to increase intestinal basolateral GU (Gontier et al. 2008), suggesting that insulin plays a major role in GU from blood to enterocyte. While GLUT2 has a major role in the unidirectional delivery of glucose across the intestine together with SGLT1, it seems to contribute to GU into the enterocytes, especially during hyperglycemia (Ait-Omar et al. 2011; Klip et al. 2024). However, more studies on the mechanisms behind insulin-mediated GU from blood to enterocytes are needed.

The results of study II, when paired with earlier research, show that colon GU is more susceptible to training-induced adaptations than small intestine, and that small intestine insulin sensitivity is strongly linked to obesity. Our study's findings demonstrate the advantages of consistent, long-term exercise for colon GU in slimmer twins, regardless of genetics, since there were no appreciable changes in body composition.

6.4 Effects of obesity and exercise training on gut microbiota.

Previously, the gut microbiome has been shown to be influenced by host genetics (Goodrich et al. 2014, 2016), body composition (Allen et al. 2018; Y. Yang et al. 2017), and metabolic disorder status (Munukka et al. 2012). Nonetheless, some research indicates that nutrition, aging, and shared housing are the primary environmental factors influencing human gut microbiota. (Vilchez-Vargas et al. 2022; Rothschild et al. 2018). In study II, there was no difference in alpha and beta diversity between the twin groups at baseline. After the intervention, Pielou´s evenness decreased significantly, and a transient change was seen in pre vs. mid and mid vs. post comparisons in the beta diversity of the leaner twins. The notable shifts in three prevalent phyla, *Firmicutes*, *Bacteroidota*, and *Proteobacteria,* are mostly responsible for the mid-point shift in beta diversity itself. Proteobacteria and B*acteroidota* decreased, whereas Firmicutes increased from pre to mid in the whole study population. Because obese individuals often have proportionately more

Firmicutes to *Bacteroidota* than lean people, and because a low-calorie diet and weight loss reduce *Firmicutes* and increase *Bacteroidota*, *Firmicutes* have been thought to be linked with obesity (Ley et al. 2006; Pekkala et al. 2015) and obesity related conditions such as MAFLD (Jian et al. 2021). Additionally, it has been demonstrated that host bacterial composition is influenced by food; those with diets higher in fat and protein have more *Firmicutes* than those with diets higher in fiber and vegetables (De Filippo et al. 2010). Even in the absence of changes in body weight, the diet itself affects the host's bacterial composition; mice fed a high-fat diet showed an increase in *Firmicutes* both with and without contemporaneous obesity (Hildebrandt et al. 2009). However, studies with humans where no difference in the relative abundance of *Firmicutes* after short-term overfeeding with fat exist (Jian et al. 2021). Nevertheless, based on this, *Firmicutes* have been proposed as more effective in extracting energy from food than *Bacteroidota* (Krajmalnik-Brown et al. 2012).

Although *Proteobacteria* are a natural component of the human gut microbial community, their relative abundance differs across healthy, ill, lean, and obese people. Increases in *Proteobacteria's* relative abundance have been linked to metabolic diseases and obesity. (Shin et al. 2015; Bai et al. 2019). Exercise has been demonstrated to alter the composition of the gut microbiota by reducing *Proteobacteria* in obese women and children (Quiroga et al. 2020; Munukka et al. 2018). *Proteobacteria* in our study showed a clear decline from pre to mid and a return to baseline from mid to post time points for the entire group. The transient decline in the midpoint is an unexpected finding. When the training logs were checked for a possible explanation for the finding, the average heart rate during the second endurance training workout decreased by 3.6 beats per minute in the second half of the intervention, most likely as a result of increased aerobic fitness, but neither body weight nor exercise duration changed between the first and second halves of the intervention in our study. As the change in *Proteobacteria* was transient at the mid-point, the slight decrease in average heart rate did not affect the result most likely. The drop in *Proteobacteria* in the entire group from pre to mid remains unexplained. It's unclear if this was caused by a lifestyle change at the start of the intervention or by long-term exercise training stabilizing the composition of the microbiota later.

A statistically significant increase in *Firmicutes* was only seen in the leaner twins, who also had a significant increase in daily sugar consumption, particularly at mid-point, which may explain the finding and highlight the sensitivity to nutritional changes, even though both twin groups showed similar changes in the increase of Firmicutes and decrease in Bacteroidota at mid-point.

Unlike the three other major phyla, *Campylobacterota* increased from pre- to post-intervention. There are few studies on *Campylobacterota* in the human

microbiome. It has been observed that people infected with the SARS CoV-2 who have severe respiratory symptoms had higher relative abundances of *Campylobacterota*. (Mazzarelli et al. 2022) and Campylobacterota phyla have been associated with heme B synthesis pathways (E. A. Jensen et al. 2020). Heme is necessary for red blood cells to bind oxygen and transport it to organs and tissues, therefore an increase in *Campylobacterota* may indicate better oxygenation and aerobic capacity. (Bizjak et al. 2020). When twins were analyzed separately, the increase in *Campylobacterota* was only significant in the leaner twins, who also had higher aerobic capacity (VO_{2peak}). Thus, the increase in Campylobacterota after the exercise intervention may reflect an increased demand and turnover of heme B.

Firmicutes, Bacteroidota, Proteobacterota, and *Campylobacterota* appear to be sensitive to dietary and exercise changes when the data from study II are combined. The hypothesis suggested by Oliver et al., that there is an inverse relationship between dietary fiber intake and alpha diversity (Oliver et al. 2021) is supported by study II, and the results of study II highlight the adaptability of microbiota at a phylum level to nutritional changes such as sugar consumption. The results of study II lend more credence to the idea that *Firmicutes* can flourish in surroundings with higher energy requirements because they are more adept at absorbing energy (Turnbaugh et al. 2006).

Although *Firmicutes* decreased from mid to post-intervention, the relative abundance of *Lactobacillus*, *Megamonas*, and *CHKCL001* genus (all belonging to the *Firmicutes* phyla) increased in the present study. It has previously been demonstrated that members of the phylum *Firmicutes* are more prevalent in elite athletes (Y. Xu et al. 2022) and that aerobic exercise training with weight loss increases *Lactobacillus* (Mahdieh et al. 2023). In healthy people without a history of professional athletic training, probiotics containing members of the *Lactobacillus* genus have been demonstrated to reduce upper respiratory tract infections (Gleeson et al. 2011) and improve endurance performance (W.-C. Huang et al. 2019).

Megamonas was strongly associated with exercise alone, while both *CHKCL001* and *Lactobacillus* were associated with both exercise and nutritional variables such as sugar or its more specific sub-types, glucose and sucrose. *Lactobacillus*, however, was associated with exercise to a much greater degree than *CHKCL001*.

Our study shows that within the Firmicutes phylum, *Lactobacillus*, *Megamonas*, and *CHKCL001* are sensitive to exercise to a varying degree, but *Lactobacillus* and *Megamonas* also react to changes in nutritional habits, especially regarding sugar consumption. The exercise-induced benefits occur even in the absence of a simultaneous decrease in body weight. However, when examined independently, only the leaner twins showed statistically significant increases in the relative abundance of *Lactobacillus*, indicating that body weight might affect how the body reacts to exercise. *Helicobacter* (*Proteobacteria* phyla), *Sellimonas* (*Firmicutes*

phyla), *Enorma* (*Actinobacteria* phyla), and *Rikenella* (Bacteroidota phyla) increased in both groups after training, showing a strong association with exercise alone. Previously, *Helicobacter*, *Sellimonas*, and *Rikenella* have been suggested to be related to positive changes in host health. *Helicobacter* is widely known for one of its subspecies, namely *Helicobacter pylori*, which is known for gastrointestinal infections (Hołubiuk and Imiela 2016). However, in rat studies, transplanted faecal matter to non-exercising mice from exercising mice fed with either a normal diet or HFD caused increases in the abundance of *Helicobacter*, which indicates that exercise has a role in *Helicobacter* abundance (Lai et al. 2018). *Sellimonas* has been thought to be a biomarker reflecting recovery of intestinal homeostasis (Muñoz et al. 2020). It is, however, worth noting that increases in the relative abundance of *Sellimonas* have also been shown in chronic kidney disease patients (Lun et al. 2018). The role of *Enorma* in health is unclear, but increased abundances of *Enorma* have been observed in morbidly obese patients with cholecystectomy, and lower abundances have been observed in patients with Blastocystis (Caudet et al. 2022). *Rikenella* has been shown to increase its relative abundance from an exercise intervention conducted on ApoE knockout mice with additional net positive health changes, such as decreased obesity (W.-C. Huang et al. 2022). Study II indicates that *Helicobacter*, *Sellimonas*, *Enorma*, and *Rikenella* are malleable with exercise and may represent net positive changes in human health.

In our study, the relative abundance of *Cutibacterium* (*Actinobacteria* phyla) increased in both twins. *Cutibacterium* was associated with nutrition and exercise. *Cutibacterium* is a commensal bacteria that is most commonly found on the skin (Corvec 2018). The relationship between *Cutibacterium* and exercise is unclear, as the studies of exercise and *Cutibacterium* are sparse.

Interestingly, the microbiota and colonic or small intestine GU did not correlate at baseline. Certain bacterial genera have been connected to intestinal GU as measured by FDG-PET during fasting, despite the fact that the precise relationship between intestinal glucose absorption and microbiota remains unknown. (Kang et al. 2017). The outcome might suggest that exercise and obesity have a more direct impact on intestinal GU (glucose uptake from the circulation). It is known that intestinal microbiota taken from different sections of the gastrointestinal tract differ significantly (K. Yang et al. 2025). The microbiota data in study II came from faecal samples. Thus, intestinal GU may also be correlated with microbiota obtained directly from the colon or small intestine. However, because of the study's methodology, this is still unknown and could be a topic for additional research.

The twins in study II were all from Finland, and although their body compositions varied greatly, the twins' intake of soluble polysaccharides and insoluble fiber was the only notable nutritional variation between them at baseline, according to food diaries. The body composition of the twin groups did not change

significantly between the pre-intervention and mid-intervention periods, nor did training length or adherence. These findings would suggest that exercise has more of an impact at the genus level than at the phylum level. Overall, the findings in study II provide support to the notion that, independent of genetics or weight loss, the host gut microbiota is a dynamic organism that responds to environmental changes.

Study II indicates that obesity impairs insulin-stimulated intestinal GU (intestinal uptake of circulating glucose from blood) independent of genetics. Long-term regular exercise training improved aerobic fitness and whole-body insulin sensitivity in both the leaner and the heavier co-twins. Though both twin groups exhibited some microbiota changes at the genus level, most changes in insulin-stimulated colon GU and microbiota composition were significant in the leaner twins.

6.5 Strengths and limitations

The unique setting in studies I and II employing MZ twins discordant for BMI is one of the thesis's key advantages since it provides a means of assessing the benefits of exercise with the least amount of genetic confounding. The setting utilized in research III also made it possible to assess the liver parameters in vivo and provided the opportunity to integrate PET imaging data with morphological histology.

The use of dynamic PET, a cutting-edge imaging technique that makes it possible to assess substrate uptake into tissues, is an additional strength of this thesis. The PET imaging was also conducted during insulin-stimulated conditions to assess whole-body insulin sensitivity (M-value) in humans in studies I and II. M-value has long been regarded as the "gold standard" for assessing human insulin sensitivity (DeFronzo et al. 1979).

While microbiota studies on twins and the effects of exercise on microbiota are plenty, interventional studies combining these two to our knowledge have not been made before, which is a unique strength of this study.

Limitations, as always, also exist in this thesis. In studies I and II, the inclusion criteria were based on the BMI difference between twins within the pair, and not absolute BMI ranges. MZ pairs with a significant difference in body fat mass, and leaner twins with a normal fat percentage would be ideal for our research. As no measures of fat mass were available in the cohorts, BMI was used as the proxy to identify pairs with sufficient intrapair fat difference. The effects of this can be seen in study I, where both groups at baseline had an average LFC and PFC above the upper normal limit of (LFC 5.56% and PFC 6.2%) (Szczepaniak et al. 2005; Rossi et al. 2011).

The small number of participants in studies I and II is one of their main limitations. Power calculations were made when planning the project CROSSYS.

While power calculations were not possible for all parameters due to non-existing twin data, Calculations were made for VO_{2peak}, M-value, and liver fat content. In VO_{2peak} and M-value, 6 twin pairs were enough, but in liver fat content, the calculations recommended 22 twin pairs. The small number of participants is partially due to the COVID-19 pandemic during the study period, as some potential participants declined to participate. In the older cohorts, surprisingly many pairs were not willing to participate, and those who were willing were not eligible based on the inclusion and exclusion criteria.

In study I, MRS was used to evaluate both pancreatic and liver fat content. The manual placement of the voxel used in the MRS must be accurate to avoid detection errors from nearby tissues such as intra-abdominal fat. Due to the small size of the pancreas, there may have been detection errors in the pancreatic fat content results of study I.

Only the microbiota and no other data were collected at mid-intervention, which makes the microbiota data interpretation challenging in study II. The food diaries were completed by the participants and not by the researchers. When using food diaries, there is always the possibility of under-reporting. In our microbiota sensitivity analyses with additive calculation methods, not all assumptions of the model were fulfilled due to the much-skewed distributions, as several genera showed frequent zero abundance.

Intestinal GU was calculated, standardized, and normalized to the unitary volume of the gut segment (study II). It was not possible to measure the entire intestinal GU because of the intestine's difficult structure, which could provide further insight into how overall intestinal metabolism affects glycaemic control.

In study III, the rats were fed ad libitum without limitations, which may cause over- or underfeeding between individuals based on differences in hunger or hierarchical behaviour between the rats. Another limitation is that the running of the rats was voluntary, and the older rat groups ran significantly less than the younger rats, which may affect the interpretation of the results. The animals were invasively catheterized, FDG-PET studies were done during anaesthesia, and the rats were sacrificed after the imaging studies, which is a limitation, as it only allowed a cross-sectional design. The catheterization was done on the same day as the clamp and imaging studies were done, which may affect results due to systemic stress caused by the catheterization. However, all rats were catheterized similarly on the study day, so the effect of acute catheterization should cause minimal variance between rats.

7 Conclusion

The main findings of the thesis can be summarised as:

1. Independent of genetic factors in monozygotic twins discordant for BMI, obesity is associated with increased pancreatic and liver fat content and disrupted liver metabolism. Liver insulin-stimulated glucose uptake may be upregulated due to liver fat-induced liver inflammation, which may be ameliorated by long-term exercise training.
2. Independent of genetic factors in monozygotic twins discordant for BMI, obesity is associated with decreased intestinal insulin-stimulated glucose uptake, but the degree of obesity does not seem to affect intestinal microbiota composition. Different parts of the intestine may respond differently to exercise, as a significant increase in insulin-stimulated glucose uptake was observed only in the colon. Most changes in colon glucose uptake and microbiota were significant only in the leaner twins, while both twin groups showed training-induced changes in genus-level gut microbiota composition.
3. Obesity induced liver fat accumulation is associated with liver inflammation visible at enzymatic and histological levels. Liver TSPO downregulation may be linked to liver fat accumulation and low-grade liver inflammation, which may indicate an attempt by the organ to shield itself from the advancement of metabolic dysfunction-associated fatty liver disease. Exercise is associated with decreased liver fat content and inflammation, especially when combined with dietary changes.

In conclusion, the effects of exercise on splanchnic organs, independent of genetics, seem to depend on the level of obesity. In leaner individuals, benefits are associated with improved colon glucose metabolism and microbiota, while heavier individuals may benefit by decreasing liver fat content and liver inflammation.

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