Does sex influence the effect of mixed mode exercise training on glycemic control, insulin sensitivity and inflammatory markers in overweight/obese, sedentary males and females?

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Introduction: Type 2 diabetes mellitus (T2D) is prevalent within Canada, with a prediction of 5 million people living with this condition by 2025. Exercise reduces the risk of T2D by improving insulin sensitivity. However, recent trials have suggested that exercise training may be less efficacious at improving insulin sensitivity in females compared with males, which could have implications for the prevention and management of T2D in females. The purpose of this research was to examine whether sex influenced the effectiveness of mixed-mode training on glycemic control, insulin sensitivity and inflammation in overweight/obese individuals. **Methods:** Twenty-seven overweight/obese, sedentary males (n=12) and females (n=15) were recruited for a 12-week mixed-mode, exercise intervention. Prior to training, participants underwent anthropometric, aerobic fitness ($\dot{V}O_{2max}$ test), strength (3-5 RM test) and oral glucose tolerance test (OGTT) assessments. Training consisted of 3 weekly sessions involving 30 minutes of aerobic and 30 minutes of resistance training. **Results:** There was no sex difference in glucose AUC ($p=0.22$, $\eta_p^2=0.03$) or C_{max} ($p=0.14$, $\eta_p^2=0.03$); however, when adjusted for the glucose dose relative to LBM, males had a higher glucose AUC ($p=0.002$, $\eta_p^2=0.18$) and C_{max} ($p=0.001$, $\eta_p^2=0.19$) than females. TNF-α, ($p=0.04$, $\eta_p^2=0.13$) and MIP-1β ($p=0.006$, $\eta_p^2=0.20$) were higher in males than females. There was no effect of training on glycemic control, insulin resistance/sensitivity indices, pancreatic β-cell function or inflammatory markers. However, the absolute change in glucose AUC (males: -99.8 mmol/L·120min, females +58.3 mmol/L·120min, $p=0.01$, $d=1.06$), C_{max} (males: -0.60 mmol/L, females +0.7 mmol/L, $p=0.04$, $d=0.87$) and IL-1ra (males: -18.2 pg/mL, females +28.9 pg/mL, $p=0.02$, $d=1.20$) differed between the sexes. . **Conclusion:** Changes in glycemic control and inflammation following training differed between males and females. A sex difference was seen in inflammatory markers; however, further

research is required. Finally, females had lower glucose AUC and C_{max} relative to LBM compared to males, which questions the use of a standard 75g glucose dose during an OGTT as a measure of impaired glucose tolerance.

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Table of Contents

Author's Declaration ... ii
Abstract ... iii
Acknowledgements ... v
Table of Contents ... vi
List of Figures ... ix
List of Tables ... x
List of Abbreviations ... xi
Chapter 1: Introduction and Literature Review ... 1
1.0 Literature review ... 1
1.1 Type 2 diabetes mellitus ... 1
1.2 Development of T2D ... 2
1.2.1 Diagnostic criteria for T2D, impaired fasting glucose and impaired glucose tolerance ... *2*
1.2.2 Development of insulin resistance and β-cell dysfunction in obesity ... *2*
1.3 Role of insulin in glucose uptake and metabolism in liver and skeletal muscle ... 3
1.3.1 Insulin secretion and clearance ... *3*
1.3.2 Glucose is taken up and stored as glycogen in the liver and skeletal muscle ... *4*
1.3.3 The role of insulin in glucose metabolism in the liver ... *5*
1.3.4 Insulin resistance in the liver ... *6*
1.3.5 The role of insulin in glucose metabolism in skeletal muscle ... *6*
1.3.6 Insulin resistance in skeletal muscle ... *9*
1.4 Measuring insulin resistance and sensitivity ... 9
1.4.1 Hyperinsulinemic-euglycemic clamp (HEC) ... *9*
1.4.2 Oral glucose tolerance test (OGTT) ... *10*
1.4.3 Glycated hemoglobin (HbA1C) ... *11*
1.4.4 Indices of insulin resistance/insulin sensitivity ... *12*
1.5 Sex differences in T2D ... 14
1.5.1 Prevalence ... *14*
1.5.2 Glucose uptake and insulin sensitivity ... *14*
1.6 Effects of sex hormones on insulin sensitivity ... 15
1.6.1 Estrogens ... *15*

1.6.2 Progesterone ... *17*
1.6.3 Testosterone ... *18*
1.7 Inflammation ... **18**
1.7.1 Overview ... *18*
1.7.2 Effects of inflammation on insulin resistance ... *20*
1.7.3 Effects of acute exercise on inflammation ... *21*
1.7.4 Sex differences in inflammation ... *23*
1.8 Effects of exercise training ... **24**
1.8.1 Exercise and risk of T2D ... *24*
1.8.2 Aerobic training ... *25*
1.8.3 Resistance training ... *30*
1.8.4 Mixed training as an ideal intervention ... *33*
1.9 Current literature on sex differences in insulin sensitivity and exercise ... **41**
Chapter 2: Rationale, Purpose, Objectives and Hypotheses ... 45
2.0 Rationale ... **45**
2.1 Purpose ... **49**
2.2 Objectives ... **49**
2.3 Hypotheses ... **49**
Chapter 3: Methods ... 50
3.1 Participants ... **50**
3.2 Study design ... **51**
3.3 Sample analysis ... **59**
3.4 Calculations ... **59**
3.5 Statistical analysis ... **61**
Chapter 4: Results ... 63
4.1 Timeline ... **63**
4.2 Participant characteristics ... **65**
4.3 Training compliance ... **66**
4.4 Body composition ... **67**
4.5 Fitness outcomes ... **69**
4.6 Glycemic control ... **71**
4.7 Indices of insulin sensitivity/resistance ... **79**

4.8 β-cell function 81
4.9 Plasma inflammatory markers 86
Chapter 5: Discussion 89
References 103
Appendices 125
Appendix 1: 125
Appendix 2: 127
Appendix 3: 129
Appendix 4: 130
Appendix 5: 132

List of Figures

Figure 3.1……..…….....**52**

Figure 4.1……..…….....**64**

Figure 4.2……..…….....**75**

Figure 4.3……..…….....**75**

Figure 4.4……..…….....**76**

Figure 4.5……..…….....**80**

Figure 4.6……..…….....**88**

Figure 6.1……..……....**126**

Figure 6.2……..……....**126**

Figure 6.3……..……....**133**

Figure 6.4……..……....**133**

List of Tables

Table 1.1……...…….……...**13**

Table 1.2……...…….……...**37**

Table 1.3……...…….……...**43**

Table 3.1……...…….……...**57**

Table 3.2……...…….……...**60**

Table 4.1……...…….……...**65**

Table 4.2……...…….……...**66**

Table 4.3……...…….……...**68**

Table 4.4……...…….……...**69**

Table 4.5……...…….……...**69**

Table 4.6……...…….……...**70**

Table 4.7……...…….……...**71**

Table 4.8……...…….……...**71**

Table 4.9……...…….……...**74**

Table 4.10……...…….…….**78**

Table 4.11……...…….…….**79**

Table 4.12……...…….…….**81**

Table 4.13……...…….…….**81**

Table 4.14……...…….…….**83**

Table 4.15……...…….…….**85**

Table 4.16……...…….…….**85**

Table 4.17……...…….…….**86**

Table 4.18……...…….…….**87**

Table 4.19……...…….…….**87**

Table 6.1……...…….…….**125**

Table 6.2……...…….…….**127**

Table 6.3……...…….…….**130**

Table 6.4……...…….…….**131**

Table 6.5……...…….…….**131**

Table 6.6……...…….…….**132**

List of Abbreviations

Akt	Protein kinase B
AMPK	AMP-activated protein kinase
ATP	Adenosine triphosphate
AUC	Area under the curve
BF%	Body fast %
BMI	Body mass index
BW	Body weight
C_{max}	Highest observed glucose concentration during an OGTT
CaMK II	Ca^{2+}/calmodulin-dependent protein kinase II
CK-2	Casein kinase-2
CRP	C-reactive protein
CVD	Cardiovascular disease
DAG	Diacylglycerols
DOC2B	Double C2-like domain-containing protein
ELISA	Enzyme-linked immunoassay
eNOS	Endothelial nitric oxide synthase
ER	Estrogen receptor
E2	Estradiol-17β
FBG	Fasting blood glucose
FEV_1	Forced expiratory volume in one second
FFA	Free fatty acid
FoxO1	Forkhead box protein I
FPG	Fasting plasma glucose
FPI	Fasting plasma insulin
FVC	Forced vital capacity
GCK	Glucokinase
GLUT	Glucose transporter type
GPx	Glutathione perioxidase
GTP	Guanosine triphosphate
G6Pase	Glucose 6-phosphatase
HEC	Hyperinsulinemic-euglycemic glucose clamp
HC	Hyperglycemic glucose clamp
HIIT	High intensity interval training
HISI	Hepatic insulin sensitivity index
HOMA-B	Homeostatic model assessment for β-cell dysfunction
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
H_2O_2	Hydrogen peroxide
HbA1C	Glycated hemoglobin
IFG	Impaired glucose tolerance
IGT	Impaired fasting glucose
IL	Interleukin
IRS	Insulin receptor substrates
IVGTT	Intravenous glucose tolerance test
LBM	Lean body mass

MAPK	Mitogen-activated protein kinase
MICT	Moderate intensity continuous training
Mn-SOD	Manganese superoxide dismutase
MPI	Mean plasma insulin
MPG	Mean plasma glucose
MRT	Medical X-ray technologist
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NF-κB	Nuclear factor κB
NOX4	NADPH oxidase 4
OGTT	Oral glucose tolerance test
PTEN	Phosphatase and tensin homolog
PI3P	Phosphatidylinositol (3,4,5)-trisphosphate
PEPCK	Phosphoenolpyruvate carboxykinase
PDPK1	phosphoinositide-dependent protein kinase 1
PI3K	Phosphoinositide 3-kinase
PKC	Protein kinase C
PGC-1α	Proliferator-activated receptor γ co-activator 1α
QUICKI	Quantitative insulin sensitivity check index
REHIT	Reduced exertion high intensity interval protocol
RIA	Radioactive immunoassay
ROS	Reactive oxygen species
SNARE	soluble N-ethylmaleimide-sensitive factor attached protein receptor
SIT	Sprint interval training
T_{max}	Time at which the highest observed glucose concentration during an OGTT occurs
TBC1D1	TBC1 domain family member 1
TBC1D4	TBC1 domain family member 4
TNF-α	Tumor necrosis factor alpha
T2D	Type II diabetes mellitus
WC	Waist circumference

Chapter 1: Introduction and Literature Review

1.0 Literature review

1.1 Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2D) is a metabolic disorder which results from the impairment of insulin production and/or action, primarily due to the development of insulin resistance at the cellular level in response to chronic hyperglycemia (LeBlanc et al., 2019; Olokoba et al., 2012). Diabetes Canada indicated that in 2015 there was an estimated 3.4 million Canadians living with T2D (Houlden, 2022). It is predicted that by the year 2025, there will be 5 million Canadians with T2D, indicative of a 44% increase in T2D prevalence over a 10-year period (Houlden, 2022). As with many chronic diseases, T2D can be linked to a variety of modifiable risk factors including smoking, obesity, poor diet and physical inactivity (Centers for Disease Control and Prevention, 2004; Hu et al., 2001). One of the primary risk factors for T2D is obesity, which additionally contributes to the development of insulin resistance (Al-Goblan et al., 2014; Kahn et al., 2006). Obesity is a critical risk factor due to its ability to desensitize the tissue response to insulin. The incorporation of healthy lifestyle habits including a healthy diet and physical activity can be useful for preventing T2D as well as mitigating any further progression of the disease (Colberg et al., 2010). Improvements include weight loss, reduced risk of cardiovascular disease (CVD) and mortality, and improved blood glucose levels due to increases in insulin sensitivity (Colberg et al., 2010). Considering the incidence of T2D has drastically increased in the past decade, steps should be taken to help reduce to the risk wherever possible (Olokoba et al., 2012).

1.2 Development of T2D

1.2.1 Diagnostic criteria for T2D, impaired fasting glucose and impaired glucose tolerance

T2D is a chronic disease which is defined by consistently elevated blood glucose levels (Punthakee et al., 2020). T2D is diagnosed when fasting blood glucose level is ≥ 7.0 mmol/L, glucose concentration following a 2 h oral glucose tolerance test (OGTT) is ≥ 11.1 mmol/L, or glycated hemoglobin (HbA1C) is ≥ 6.5% (Punthakee et al., 2020). Abnormalities in blood glucose concentrations are observed up to 5 years before (Siu, 2015) a frank diagnosis of T2D is made and are typically characterized as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). An individual is considered to have IFG when fasting glucose concentration is ≥ 6.1, but < 7.0 mmol/L and IGT when glucose concentration at the 120 min time point following a 2h OGTT is ≥ 7.8, but < 11.1 mmol/L (Punthakee et al., 2020). Presence of either IGF, IGT or an HbA1C between 6.0 – 6.4% is indicative of pre-diabetes (Punthakee et al., 2020). The development of IFG, IGT and frank T2D result from the development of insulin resistance and β-cell dysfunction (DeFronzo et al., 2015).

1.2.2 Development of insulin resistance and β-cell dysfunction in obesity

Insulin resistance is defined as the inability of tissues to respond to the insulin signal, which attenuates the uptake of glucose into cells (primarily skeletal muscle and adipose tissue) and prevents the suppression of endogenous glucose production and release by the liver leading to sustained hyperglycemia (DeFronzo et al., 2015). With obesity, it is common for hyperinsulinemia to be present, however, whether this is due to hypersecretion of insulin or decreased insulin clearance is controversial (Erdmann et al., 2008; Koh et al., 2022). In obesity, hyperinsulinemia develops prior to hyperglycemia as a compensatory mechanism to promote glucose uptake and maintain normal blood glucose levels (Thomas et al., 2019). Sustained

elevated insulin concentrations will cause insulin responsive tissues to decrease their sensitivity to the insulin signal, triggering the accumulation of glucose in the blood and further insulin release, which in turn will worsen hyperinsulinemia (Thomas et al., 2019).

Obesity is associated with increased inflammation, hyperglycemia, and insulin resistance, all of which can lead to β-cell damage and dysfunction (Cerf, 2013). Impaired β-cell function results in impaired insulin secretion, which leads to worsened glycemic control (Cerf, 2013). Chronically high blood glucose levels, which result from insulin resistance, impact the regenerative properties of β-cells causing a greater level of apoptosis compared to cell growth (Marchetti et al., 2007), ultimately leading to decreased β-cell functional mass (DeFronzo et al., 2015; Saisho, 2015) and decreased insulin secretion, resulting in sustained hyperglycemia and furthering β-cell dysfunction (Cerf, 2013). Hyperglycemia also induces a pro-inflammatory state, which can lead to mitochondrial stress and subsequent β-cell death (Cerf, 2013). The interplay between insulin resistance and β-cell dysfunction is not fully understood; however, both can exacerbate each other, resulting in further elevations in glucose concentrations and leading to progression of IFG/IGT to T2D (Cerf, 2013).

1.3 Role of insulin in glucose uptake and metabolism in liver and skeletal muscle

1.3.1 Insulin secretion and clearance

Following a meal, the carbohydrates in food are broken down into glucose and absorbed into the blood stream, which increases blood glucose levels (Chadt & Al-Hasani, 2020). The increase in blood glucose concentration will trigger the release of insulin from the β-cells of the pancreas, which occurs in a biphasic pattern (Henquin et al., 2002). In humans, the first phase of insulin secretion occurs as a rapid burst within 10 minutes after the increase in blood glucose concentration and serves to inhibit endogenous glucose production within the liver (Huang &

Joseph, 2014). Alternatively, the second phase of insulin secretion occurs as a progressively slow sustained increase in insulin concentration and serves to continue to suppress endogenous glucose production, but more importantly, increase muscle glucose uptake to reduce blood glucose concentrations (Huang & Joseph, 2014). Insulin will continue to be secreted so long as blood glucose concentrations remain elevated and will stop once blood glucose levels have dropped back to homeostatic levels (Huang & Joseph, 2014). Upon release from the β-cell, insulin travels via the hepatic portal vein to the liver where upwards of 50-80% is cleared during first passage (Koh et al., 2022; Najjar & Perdomo, 2019) with the remaining 20-50% entering the systemic circulation where it facilitates glucose uptake into various tissues, most notably at the muscle (Chadt & Al-Hasani, 2020; Najjar & Perdomo, 2019). Some of the circulating insulin (~45-50%) is cleared during its first pass by the kidneys and skeletal muscle with the remaining insulin being cleared by the liver, kidneys and skeletal muscle during subsequent passes (Najjar & Perdomo, 2019). Insulin clearance is a continuous process with mean time of insulin within the circulation being < 10 min (Najjar & Perdomo, 2019).

1.3.2 Glucose is taken up and stored as glycogen in the liver and skeletal muscle

Glucose is taken up into skeletal muscle and liver and stored as glycogen to serve as a reserve for when energy production is required (Jensen et al., 2011). About 80% of glycogen is found in skeletal muscle and the remainder being found in the liver (Jensen et al., 2011). Glucose is taken up via the glucose transporter type (GLUT) protein family (Chadt & Al-Hasani, 2020; Najjar & Perdomo, 2019). Within skeletal muscle, GLUT4 is the primary transporter into the tissue and its incorporation into the membrane of skeletal myocytes is regulated by insulin (Chadt & Al-Hasani, 2020) and contraction (Lauritzen, 2013). This differs from the liver where GLUT2 is the main protein for glucose transport however, this isoform does not require insulin

and remains on the surface of hepatocytes to allow for continuous glucose uptake (Chadt & Al-Hasani, 2020). GLUT1 transporters can be found on all cell types within the body and provide low level of glucose uptake for basal function (Huang & Joseph, 2014).

1.3.3 The role of insulin in glucose metabolism in the liver

Insulin has a multitude of sites where it can bind and trigger downstream events, however within the liver, there are certain differences that are not found in other tissues. With respect to glucose uptake, GLUT2 proteins permit passive transport of glucose molecules into hepatocytes (Adeva-Andany et al., 2016). This facilitative transport allows for bidirectional movement of glucose both into and out of the cell with the assistance of sodium-glucose co-transporters (Adeva-Andany et al., 2016). Unlike skeletal muscle, the rate of movement via GLUT2 transporters is directly proportional to the concentration of glucose in the blood stream and does not rely on insulin to stimulate transportation (Adeva-Andany et al., 2016). In the fasted state, the liver will undergo both glycogenolysis, the breakdown of glycogen stores, and gluconeogenesis, the synthesis of glucose molecules, to ensure blood glucose levels remain within acceptable ranges (Adeva-Andany et al., 2016). Insulin plays a role in regulating these processes as it suppresses both glycogenolysis and gluconeogenesis in the fed state by inhibiting phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6-phosphatase (G6Pase) enzymes (Meshkani & Adeli, 2009). A study by Adkins et al. (2003) found that a higher concentration of insulin is required to suppress gluconeogenesis compared to glycogenolysis, indicating that glycogen break down is the process that is suppressed first. Furthermore, insulin can also act through insulin receptor substrates (IRS) proteins on hepatocytes to activate hepatic insulin release through glucokinase (GCK) and glycogen synthase (Petersen et al., 2017).

1.3.4 Insulin resistance in the liver

As the GLUT2 transporters allow for passive diffusion of glucose, insulin resistance will affect other aspects of the liver's involvement in glucose regulation, most notably gluconeogenesis and glycogenolysis (Meshkani & Adeli, 2009). Insulin is responsible for inhibiting both gluconeogenesis and glycogenolysis, thus insulin resistance attenuates the suppression of these processes resulting in excess production and release of glucose into the circulation (Hatting et al., 2018; Meshkani & Adeli, 2009). Normally, insulin results in the activation of protein kinase B (Akt), which in turn promotes lipogenesis and glycogen synthesis, as well as inhibits Forkhead box protein I (FoxO1), which suppresses gluconeogenesis (Titchenell et al., 2015); however, in the insulin resistant state, insulin signaling via Akt to FoxO1 is blunted and thus so is the suppression of gluconeogenesis (Titchenell et al., 2015). Hyperglycemia alone is enough to suppress hepatic glycogenolysis; however, insulin is required to stimulate glycogen synthesis (K. F. Petersen et al., 1998), thus in the insulin resistant state increased hepatic glucose production is due to increased hepatic gluconeogenesis, not increased hepatic glycogenolysis (Shulman, 1999). In addition, circulating free fatty acid (FFA) levels are increased in obesity/insulin resistance and can cause accumulation of diacylglycerols (DAG), which can activate atypical protein kinase C [aPKC, (Jornayvaz & Shulman, 2012)]. Increased aPKC has been found to inhibit IRS phosphorylation, further advancing the development of hepatic insulin resistance (Jornayvaz & Shulman, 2012).

1.3.5 The role of insulin in glucose metabolism in skeletal muscle

In skeletal muscle glucose uptake is mediated predominately by GLUT 1 and GLUT 4 (Chadt & Al-Hasani, 2020). At rest in the fasted state basal skeletal muscle glucose uptake occurs via GLUT 1 (Chadt & Al-Hasani, 2020). However, in response to both insulin and muscle

contraction, GLUT4 is translocated to the sarcolemma and t-tubules in order to increase glucose uptake (Chadt & Al-Hasani, 2020). Importantly, insulin and contraction act via different signaling pathways that converge at TBC1 domain family member 1 (TBC1D1) and TBC1 domain family member 4 (TBC1D4) to promote GLUT4 translocation (Chadt & Al-Hasani, 2020). Furthermore, these two pathways act synergistically with one another to enhance glucose uptake (Chadt & Al-Hasani, 2020). Unlike the liver where glucose is released to help maintain blood glucose levels, in skeletal muscle, once glycogen has been formed it will remain within that tissue as skeletal muscle lacks G6Pase, which prevents the release of glucose into the blood stream (Jensen et al., 2011). As such, muscle glycogen acts as a local pool of energy and does not contribute to the regulation of blood glucose levels in a fasted state (Jensen et al., 2011).

1.3.5.1 Insulin-stimulated glucose uptake

When glucose levels rise following a meal, glucose is taken up by skeletal muscle from the blood stream via GLUT4 through activation of the insulin-signaling cascade (Ferrari et al., 2019). Upon release from the pancreas, insulin travels to skeletal muscle and binds to the insulin receptor which is a receptor tyrosine kinase (Ferrari et al., 2019). The insulin receptor will self-phosphorylate to activate itself and will act on a family of IRS proteins (Ferrari et al., 2019). The most common subtypes that are activated are IRS-1 and IRS-2 which will activate phosphoinositide 3-kinase (PI3K) (Ferrari et al., 2019). PI3K will drive the synthesis of phosphatidylinositol (3,4,5)-trisphosphate (PI3P), a molecule that activates phosphoinositide-dependent protein kinase 1 (PDPK1) (Ferrari et al., 2019). PDPK1 will then go on to activate Akt and aPKC (Ferrari et al., 2019). These two proteins will act on separate pathways to activate GLUT4 translocation (Ferrari et al., 2019). Akt phosphorylates TBC1D1 and TBC1D4, which permits the dissociation of the Rab protein from guanosine triphosphate (GTP), which in turn

allows GLUT4 to translocate to the sarcolemma and t tubules (Ferrari et al., 2019). Simultaneously, aPKC will phosphorylate the double C2-like domain-containing protein (DOC2B) (Ferrari et al., 2019). The phosphorylated DOC2B can activate the soluble N-ethylmaleimide-sensitive factor attached protein receptor (SNARE) which works synergistically with syntaxin-4 to trigger the translocation of the GLUT4-containing vesicles to the membrane.

1.3.5.2 Contraction-mediated glucose uptake

Independent of insulin release, exercise can stimulate glucose uptake via a different pathway that converges at TBC1D1 and TBC1D4 (Ferrari et al., 2019). While exact mechanisms remain incompletely understood, activation of AMP-activated protein kinase (AMPK), Rac1/actin and Ca^{2+}/calmodulin-dependent protein kinase II (CaMK II) have all been found to be involved in exercise-induced GLUT4 translocation to the sarcolemma and T-tubules (Ferrari et al., 2019; Richter & Hargreaves, 2013; Yue et al., 2021). AMPK phosphorylates and inactivates TBC1D1 and TBC1D4 which removes inhibition on Rab GTPases allowing GLUT4 to translocate to the membrane (Richter & Hargreaves, 2013). Muscle glucose uptake during exercise can increase up to 100x compared with rest, depending on exercise intensity and duration (Richter, 2020); however, GLUT4 content at the membrane only increases 2x with exercise (Richter, 2020) The greater increase in glucose uptake relative to GLUT4 translocation suggests that exercise also increases the intrinsic activity of GLUT4; however, this is controversial, and this discrepancy may be due to methodological limitations associated with measurement of GLUT4 translocation (Richter, 2020).

1.3.6 Insulin resistance in skeletal muscle

The development of insulin resistance in skeletal muscle affects insulin signaling, glucose transport and glucose metabolism (Abdul-Ghani & DeFronzo, 2010) and is due to both receptor and post-receptor defects (M. C. Petersen & Shulman, 2018). The content and activation of the insulin receptor and subsequent phosphorylation of IRS-1 at the tyrosine site is reduced in the skeletal muscle of obese individuals and severely reduced in T2D patients (Cusi et al., 2000; M. C. Petersen & Shulman, 2018r). The phosphorylation at the serine site of IRS-1 impairs its ability to be phosphorylated at the tyrosine site and thus interrupts the signaling cascade (Cusi et al., 2000). Additionally, blunted activation of PI3K and Akt in response to insulin has also been found in insulin resistance (Cusi et al., 2000; M. C. Petersen & Shulman, 2018). Together the blunting of multiple points in the insulin signaling cascade leads to decreased TBC1D1/TBC1D4 phosphorylation, which reduces GLUT4 translocation and decreases glucose uptake into the myocyte. Within the myocyte there are several mechanisms that have been proposed to be involved in the development of insulin resistance through the interruption of the IRS/PI3K pathway including accumulation of intracellular fatty acids and/or their metabolites, increased inflammation and oxidative stress (Martins et al., 2012; Saini, 2010).

1.4 Measuring insulin resistance and sensitivity

1.4.1 Hyperinsulinemic-euglycemic clamp (HEC)

The hyperinsulinemic-euglycemic clamp is the “gold standard” method used to measure how well tissues within the body respond to insulin, also known as insulin sensitivity (J. K. Kim, 2009). The clamp is performed following an overnight fast (Krentz et al., 2015). During the test insulin is administered intravenously at a constant rate to maintain insulin levels above the normal range [hyperinsulinemia (J. K. Kim, 2009)]. Insulin is usually administered at 6

pmol/kg/min or 0.24 nmol/min/m^2 body surface area, with the value relative to body surface area being more appropriate for obese individuals (Krentz et al., 2015). Simultaneously, a glucose infusion of 20% glucose v/v is also administered to maintain a euglycemic state where blood glucose levels are consistent over the period of the test (J. K. Kim, 2009). In order to maintain euglycemia, the rate of glucose administration changes depending on the quantity of glucose metabolized within the body (J. K. Kim, 2009). The high concentration of insulin in the body will suppress endogenous hepatic glucose production, ensuring that any changes in glucose concentrations can be associated with the utilization of exogenous glucose by skeletal muscle (80%) and adipose tissue (20%) with the respective proportions (Krentz et al., 2015). The test takes 120 minutes with the last 30 minutes of the test being considered steady state (Krentz et al., 2015). The quantity of glucose metabolized is directly measured through the glucose disposal rate (J. K. Kim, 2009). The glucose disposal rate is calculated every 20 minutes using the glucose infusion rates for four, 5-minute intervals and then adjusted for lean body mass (Singal et al., 2010). The higher the glucose disposal rate the more insulin sensitive the individual (Stern et al., 2005). A glucose disposal rate lower than 28 μmol/min/kg lean body mass is indicative of insulin resistance (Stern et al., 2005). Since this value is used to measure insulin sensitivity *in vivo*, these tests are highly valued as they provide accurate information regarding the insulin response within an individual; however, since the glucose is infused into the individual, bypassing the gut, it is not reflective of what happens when glucose is consumed orally as it prevents the incretin effect (Holst et al., 2021).

1.4.2 Oral glucose tolerance test (OGTT)

The oral glucose tolerance test (OGTT) is an indirect measure of an individual's insulin sensitivity (Muniyappa et al., 2021). Clinically, while the participant is in a fasted state, they

consume a 75 g glucose beverage and blood draws are taken at 0, 30, 60, 90 and 120 minutes and analyzed for glucose and insulin concentration (Muniyappa et al., 2021). Taking blood throughout the test allows for visualization of glucose handling capabilities, specifically in relation to their insulin response (Muniyappa et al., 2021). Reference values for blood glucose at the 2-hour mark can be used for diagnostic purposes to diagnose impaired glucose tolerance and T2D as detailed above (Sakaguchi et al., 2015). Furthermore, fasting values and/or values throughout the 2-hours can be used to calculate varying indices of insulin resistance/insulin sensitivity as discussed in more detail below (Gutch et al., 2015). Data from the OGTT provides information related to the body's ability to dispose of glucose after consuming a glucose load, and thus is an indicator of glucose tolerance; however, as other factors such as insulin secretion and incretins also contribute to glucose tolerance, the OGTT does not provide a direct measure of insulin sensitivity (Muniyappa et al., 2008).

1.4.3 Glycated hemoglobin (HbA1C)

HbA1C is a measure that can be done in blood samples to determine the average blood glucose levels of an individual over a period of time, approximately 3 months (Sherwani et al., 2016). As blood glucose levels can vary greatly throughout the day, glucose analysis on spot blood draws might not capture a full picture of the individual's glycemic control (Sherwani et al., 2016). In the presence of glucose, the hemoglobin protein found within red blood cells undergo reactions to covalently bond the glucose molecule to the hemoglobin protein (Sherwani et al., 2016). Red blood cells turn over approximately every 120 days allowing changes in blood glucose levels to be seen around the 3-month mark (Sherwani et al., 2016). According to Diabetes Canada, an A1C between 6.0 and 6.4% is indicative of pre-diabetes and an A1C $\geq$ 6.5% is indicative of T2D (Punthakee et al., 2020). HbA1C levels have been positively correlated with

incidence of diabetes and can be used alongside fasting blood glucose (FBG) and OGTTs for risk assessment (Sherwani et al., 2016). Another advantage of the HbA1C test is that it does not have to be performed in the fasted state, making it easier for sample collection (Jagannathan et al., 2020). Currently, the American Diabetes Association uses HbA1C levels in its screening and diagnosis guidelines however, it should be noted that this should be used in conjunction with other measures for determining insulin resistance and potential metabolic syndromes (Jagannathan et al., 2020). It is assumed that the level of HbA1C is proportional to the blood glucose levels, however, there can be some individual differences in glycation reactions that can result in an HbA1C measure that is higher or lower than the corresponding blood glucose levels (Jagannathan et al., 2020). A study done by Marini et al. compared the relationship between HbA1C and HEC with respect to insulin sensitivity and β cell function in non-diabetic offspring of T2D patients and found that patients with an A1C $\geq$ 5.7% were insulin resistant and had β-cell dysfunction, both hallmarks of T2D (Marini et al., 2014).

1.4.4 Indices of insulin resistance/insulin sensitivity

There are numerous indices that have been developed that use data from blood samples taken in the fasted state and/or during an oral glucose tolerance test. These indices, what they measure and their correlation with the HEC are reported in Table 1.1.

Table 1.1: Summary of indices of insulin resistance/insulin sensitivity

Index	Equation	What it measures	Correlation with HEC	Cut-off criteria
Homeostasis model assessment for insulin resistance (HOMA-IR)	$= \frac{FPI \times FPG}{22.5}$	Peripheral insulin resistance	0.88 (Matthews et al., 1985)	Varies based on age, sex, ethnicity >2.5 (Gutch et al., 2015)
HOMA for β-cell dysfunction (HOMA-B)	$= \frac{FPI \times 20}{FPG \times 3.5}$	β cell dysfunction	0.69 (Matthews et al., 1985)	N/A
Quantitative Insulin Sensitivity Check Index (QUICKI)	$= \frac{1}{\log FBG + \log FBI}$	Peripheral insulin sensitivity	0.61 (Otten et al., 2014)	Non-obese: 0.382±0.007 Obese: 0.331±0.010 (Gutch et al., 2015)
Matsuda	$= \frac{10000}{\sqrt{FPI \times FPG \times MPI \times MPG}}$	Whole-body insulin sensitivity	0.67 (Otten et al., 2014)	$\geq$ 4.3 indicates insulin resistance (Gutch et al., 2015)
Stumvoll	Various linear regression analysis that uses multiple time point throughout the OGTT in addition to demographic parameters such as age, BMI and sex	Peripheral insulin sensitivity and β cell dysfunction	0.62-0.79 depending on the equation used (Gutch et al., 2015).	N/A
2h Oral Glucose Insulin Sensitivity (OGIS)	$= f(G_0, G_{90}, G_{120}, I_0, I_{90}, I_{120}, D_0)$	Peripheral insulin sensitivity	Lean: 0.73, Obese: 0.53, T2D: 0.57 (Mari et al., 2001)	> 9.8 (Mari et al., 2001)
Cederholm	$= \frac{75000 + (G_0 - G_{120}) \times 1.15 \times 180 \times 0.19 \times m}{120 \times G_{mean} \times \log I_{mean}}$	Peripheral insulin sensitivity	0.533 (Soonthornpun et al., 2003)	$\geq$ 79 ± 14 mg I^2/mmol/mIU/min (Cederholm & Wibell, 1990)
McAuley	$\left(\frac{Mffm}{I}\right) = e^{2.63 - 0.28 \ln(I_0) - 0.31 \ln(TAG_0)}$	Peripheral insulin sensitivity	0.317 (Sarafidis et al., 2007)	$\geq$ 5.8 (McAuley et al., 2001)

This table shows the various indices used to calculate insulin sensitivity and resistance, how they are calculated, their correlation with the gold-standard hyperinsulinemic, euglycemic clamp and their diagnostic cutoffs. *FPG - fasting plasma glucose, FPI - fasting plasma insulin, HEC - hyperinsulinemic, euglycemic clamp. Matsuda: MPI - mean plasma insulin concentration during the OGTT (mIU/l) and MPG mean glucose concentration during OGTT. 2h OGIS: G – plasma glucose concentrations, I – plasma insulin concentrations with the specific time point indicated in the subscript and D_0 – oral glucose dose relative to body surface area (g/m^2). Cederholm: 75,000 – glucose load in an OGTT (mg), G_0 – fasting plasma glucose concentration (mmol/l),*

G_{120} – plasma glucose concentration at 120 min of OGTT (mmol/l), 1.15 – factor transforming whole venous blood glucose to plasma values (not needed is plasma is used), 180 – conversion factor for transformation of glucose concentration from mmol/l into mg/dl, 0.19 – glucose space in liter per kg of body weight, m – body weight (kg)120 – length of OGTT (min), G_{mean} – mean plasma glucose concentration throughout OGTT (mmol/l) and I_{mean} -mean plasma insulin concentration throughout OGTT (mmol/l). McAuley: I_0 – fasting plasma insulin concentration (mIU/l) and TAG_0 – fasting plasma triglycerides concentration (mmol/l).

1.5 Sex differences in T2D

1.5.1 Prevalence

The prevalence of T2D varies between males and females across the lifespan. Worldwide in 2017, 12.3 million more males have T2D than females, equating to a lower worldwide prevalence for females (8.4%) than males [8.9%, (Cho et al., 2018)]. Various studies have found that males have a slightly higher prevalence of T2D when compared to females in populations from Asian or European decent (Jia et al., 2007; Tracey et al., 2016; Wild et al., 2004; H. Zhang et al., 2019). Moreover, prevalence can change over a life course with females having a higher prevalence in the youth stage and males having an increased prevalence during midlife (Lipscombe & Hux, 2007; Schober et al., 2005). Furthermore, T2D prevalence peaks earlier in males (65-69 y) than females [70-79 y, (Cho et al., 2018)], which is in line with the fact that T2D risk increases following menopause (Li et al., 2019).

1.5.2 Glucose uptake and insulin sensitivity

The analysis of sex differences in insulin sensitivity has shown the potential for dysglycemia to present differently in males and females (Lundsgaard & Kiens, 2014). Various studies have suggested that males are more prone to developing insulin resistance compared to females (Lundsgaard & Kiens, 2014). In the Kuhl study, when comparing glucose handling of 8000 males and females using an OGTT, it was determined that males were 2 times more likely to have IFG and T2D (Kuhl et al., 2005). Another study found that females had a 15% higher rate

of glucose clearance compared to males during an intravenous glucose tolerance test (IVGTT) (Clausen et al., 1996). When multiple studies that performed HEC were analyzed, the majority of the studies showed that females have higher insulin sensitivity compared to males (Lundsgaard & Kiens, 2014). These sex differences in insulin sensitivity only seem to be present prior to the development of T2D as similar levels of insulin resistance can be found in both sexes as the disease progresses (Tramunt et al., 2020a).

IGT and IFG are two additional measures that are related to an increased risk of T2D and CVD and have been found to differ between the sexes (Unwin et al., 2002). Unwin et al. (2002) found that males had a higher risk of IFG compared to females however, females had a higher risk of IGT compared to males. These differences are speculated to be due to sex differences in body composition. Since females typically have a smaller stature and less muscle mass, they would inherently have a higher blood glucose concentration 2-hours after consuming 75g of glucose as they have less muscle tissue and overall muscle mass to clear the glucose load (Unwin et al., 2002). Indeed, differences in height and body surface area have been found to be negatively related to 2-h blood glucose concentration and likely explain the sex-based difference in IGT (Palmu et al., 2021; Sicree et al., 2008). Thus, when comparing glucose tolerance between males and females, consideration must be made to the relative dose of glucose administered.

1.6 Effects of sex hormones on insulin sensitivity

1.6.1 Estrogens

Estrogens are a series of steroid hormones mainly produced by the ovaries that act on tissues to help develop the female reproductive system and regulate secondary sex characteristics (Wise et al., 2009). The most biologically active estrogen is 17β-estradiol [E2, (Wise et al.,

2009)]. Throughout the menstrual cycle, levels of estrogen fluctuate between 10-300 pg/mL for proper signaling of ovulation and to prepare the uterus for pregnancy (Reed & Carr, 2021). Following the start of menses, the first ~10 days of the follicular phase consist of the lowest estrogen levels, making it the time when estrogen level are most comparable to males who have a normal adult range of 40-50 pg/mL (Lundsgaard & Kiens, 2014; Reed & Carr, 2021). Estrogen concentrations spike and peak ~12-14 days after the start of menses in order to trigger ovulation (Reed & Carr, 2021). Estrogen then declines and then slowly rises and remain high throughout the luteal phase and then declines just prior to menses onset (Reed & Carr, 2021).

Estrogen influences muscle metabolism, physiology and disease risk (Beaudry & Devries, 2019; Devries et al., 2005; Horstman et al., 2012). Research has shown that premenopausal females have a greater insulin sensitivity than age matched males (Geer & Shen, 2009) and thus are at a decreased risk for metabolic syndrome and T2D (Lundsgaard & Kiens, 2014). However, the risk increases to the same level as males at menopause (Lindheim et al., 1994). Furthermore, post-menopausal females who were given intravenous estrogen were seen to have an increase in insulin action by 20% (Greising et al., 2009). A study by Moreno et al. (2010) found that 17β-estradiol treatment in rats improved insulin sensitivity at the level of GLUT4 transporter localization. Another study by Matute et al. (1973) found that estradiol has the ability to suppress hepatic gluconeogenesis, decreasing the contribution of the liver to elevated glucose levels. A study in postmenopausal diabetic women found a significant decrease in HOMA-IR values following 12 months of estrogen hormone replacement therapy comparing to those who did not receive the therapy (Ryan et al., 2002). Taken together, these studies suggest that estrogen has a direct effect on insulin sensitivity and glycemic control.

1.6.2 Progesterone

Progesterone is another sex steroid molecule that is produced for the development of secondary sex characteristics (Kim et al., 2016). Normal values in females can range from 2 ng/mL to 20 ng/mL, with the lowest concentration being found at the beginning of menses in the follicular phase and peak concentrations occurring during the luteal phase (Henderson, 2018). Progesterone has been found to influence insulin sensitivity through the increase of ROS or caspase activity, triggering the death of the pancreatic β-cells that release insulin (Nunes et al., 2014). As well, a study by Picard et al. found that female mice developed hyperglycemia when progesterone levels were increased above normal (Picard et al., 2002). Furthermore, progesterone has been found to interrupt the PI3K pathway by degrading IRS-1 and inhibiting Akt phosphorylation which stops GLUT4 translocation and decreases glucose uptake (Wada et al., 2010). The exact mechanism remains unclear and requires further research. Unsurprisingly given the negative effect of progesterone on insulin sensitivity, insulin sensitivity is lowest during the luteal phase of the menstrual cycle when progesterone concentrations are at its highest (Pulido & Salazar, 1999). A study done in in ovariectomized rhesus monkeys found an increase in fasting insulin and insulin during an OGTT following treatment of progesterone and in combination with estrogen (Kemnitz et al., 1989). The addition of progesterone to these ovariectomized monkeys indicates the potential for the hormone to decrease insulin sensitivity as seen with higher levels of fasting insulin and insulin during the OGTT. As these values are used for various indices of insulin resistance/sensitivity, this research indicated that progesterone has negative effects on insulin sensitivity.

1.6.3 Testosterone

Testosterone is a sex hormone that assists with the development of secondary sex characteristics in males (Kim et al., 2016). Normal ranges in males are from 300-1000 ng/dL and in females are between 15-50 ng/dL (Bhasin et al., 2011; Braunstein et al., 2011). This particular hormone acts in an anabolic fashion on skeletal muscle to increase gene expression and increase size of muscle fibers (Kim et al., 2016). With respect to insulin sensitivity, Chen et al. (2006) demonstrated that testosterone concentrations were related to GLUT4 expression, permitting the improvement of glucose uptake. Moreover, there seems to be a direct positive correlation between serum testosterone levels and insulin sensitivity when specifically looking at a population of males (Pitteloud et al., 2005). As well, low testosterone levels have been found to increase visceral body fat, which would trigger an increase in the size of adipocytes and further the development of insulin resistance (Ottarsdottir et al., 2018). Obesity has been found to cause an increase in aromatase activity, causing testosterone to be converted to E2 in adipose tissue which would then act in a negative feedback look to further decrease testosterone levels (Ottarsdottir et al., 2018). Low testosterone is an independent risk factor for the development of T2D (Rao et al., 2013).

1.7 Inflammation

1.7.1 Overview

The inflammatory response is a defense mechanism initiated by the immune system in response to harmful stimuli including pathogens, toxic compounds and cell damage (Medzhitov, 2010). The inflammation response is modulated by cytokines, a family of intracellular signaling molecules (Pedersen, 2000; Zhang & An, 2007). Aside from immune cells, cytokines can be also be released from various tissues including hepatocytes (hepatokines), skeletal muscle

(myokines), and adipose tissue (adipokines) and act in an autocrine, paracrine and/or endocrine fashion to alter metabolic processes to adjust for the state of inflammation (Zhang & An, 2007).

The inflammatory response involves counteracting signals that will increase the inflammatory response and those that will bring the body back to homeostasis (Zhang & An, 2007). There are cytokines that are pro-inflammatory such as tumor necrosis factor alpha (TNF-α) and interleukin-12 (IL-12) and others that are anti-inflammatory such as IL-10 and IL-15 which help to return the body to homeostasis (Pedersen, 2000; Zhang & An, 2007). Interestingly, IL-6 can act in both a pro- and anti-inflammatory manner depending on its site of release. IL-6 released from adipose acts in a pro-inflammatory manner, whereas IL-6 released from muscle acts in an anti-inflammatory manner (Pedersen et al., 2001; Wueest & Konrad, 2018). Typically, pro-inflammatory cytokines are released in a fixed area to cause local inflammation, however if the response is elevated, these factors can leach into the circulation causing damage throughout the body if levels remain high, a state known as chronic inflammation (Zhang & An, 2007).

Obesity is characterized by chronic systemic inflammation and results from over production and release of cytokines from adipose tissue (Schmidt et al., 2015). Obese individuals have been found to have increased levels of inflammatory markers, particularly IL-6 (Ellulu et al., 2017). Adipose tissue has been determined to contribute 1/3 of the total concentration of circulating IL-6, clearly correlating obesity as a risk factor to chronic inflammation (Ellulu et al., 2017). This is also true for TNF-α as adipocytes largely contribute to the production of this pro-inflammatory cytokine (Ellulu et al., 2017). IL-6 triggers the production of C-reactive protein (CRP) from hepatocytes, which serves as an indication of systemic inflammation (Ellulu et al., 2017). In addition to TNF-α and IL-6, other pro-inflammatory cytokines reported to be elevated in obesity include pro-inflammatory IL-5, IL-12 and IFNγ (Schmidt et al., 2015). Importantly,

the chronic inflammation observed in obesity has been linked to the development of numerous chronic health conditions including T2D (Burhans et al., 2018; Esser et al., 2014; Zatterale et al., 2020).

1.7.2 Effects of inflammation on insulin resistance

There has been a link between low-grade chronic inflammation and an increased risk of developing cardiometabolic diseases, such as insulin resistance (de Rooij et al., 2009). Within the liver, TNF-α and IL-6 are able to phosphorylate the serine site of IRS-1, rendering it incapable of downstream signaling and leading to insulin resistance (Fasshauer & Paschke, 2003; Senn et al., 2002). Moreover, activation of hepatic Akt was found to be inhibited by increased IL-6 concentrations (Senn et al., 2002). These impedances would impair the suppression of glycogenolysis and gluconeogenesis via downstream enzymes such as PEPCK, G6Pase and GCK enzymes (Meshkani & Adeli, 2009; M. C. Petersen et al., 2017). In skeletal muscle, increased TNF-α concentrations have been linked to insulin resistance via an inhibition of IRS-1 (Akash et al., 2018). The interruption in this pathway would stop the translocation of GLUT4 to the plasma membrane, reducing the capability of skeletal muscle to take in glucose (de Alvaro et al., 2004; Fasshauer & Paschke, 2003). A study by Kim et al. (2013) found that increased IL-6 concentrations contributed to insulin resistance in skeletal muscle via increased toll-like receptor 4 (TLR-4), which will trigger a larger inflammatory response further inhibiting IRS-1 on serine residues (Kim & Sears, 2010). IL-6 also increases skeletal muscle lipolysis and fatty acid oxidation (Pedersen, 2017; van Hall et al., 2003; Wolsk et al., 2010), which is important acutely to increase fat utilization for energy production, but can further enhance IR development if IL-6 is chronically elevated, as it will result in dysregulation of fatty acid oxidation and accumulation of lipid intermediates (Pedersen, 2017; van Hall et al., 2003; Wolsk et al., 2010).

Importantly, as noted above, IL-6 can also act in an anti-inflammatory manner when released from skeletal muscle (typically in response to acute bouts of exercise). When IL-6 is elevated acutely for short periods of time it can increase insulin sensitivity by increasing AMPK activity in adipose tissue and skeletal muscle, subsequently enhancing insulin signal transduction and increasing glucose uptake (Pedersen, 2017). Furthermore, IL-6 has also been shown to stimulate β-cell proliferation, increasing the number of insulin releasing cells and effectively counteracting the effects of apoptosis on β-cell dysfunction (Pedersen, 2017). Thus, IL-6 acts in both a positive and negative manner when it comes to insulin resistance depending on its site of secretion and whether it is elevated acutely or chronically elevated.

1.7.3 Effects of acute exercise on inflammation

In terms of exercise, particular cytokines have been found to increase in response to acute exercise to induce specific physiological responses (Rehman & Akash, 2016; Zhang & An, 2007). For example, even though the release of IL-6 increases neutrophil recruitment and causes inflammation, it also helps the individual to better utilize specific substrates such as FFA (Rehman & Akash, 2016; Zhang & An, 2007). IL-6 is one if the first cytokines to be released from contracting skeletal muscle during an acute exercise bout and levels increase exponentially depending on exercise intensity and duration with the latter being the most important factor affecting the magnitude of its release (Pedersen, 2017; Pedersen & Febbraio, 2008). IL-6 acts in an autocrine fashion to increase fat oxidation and glucose uptake within skeletal muscle but will also act on the liver to increase gluconeogenesis and on adipose tissue to increase lipolysis (Pedersen & Febbraio, 2008). As previously mentioned, the acute increase in IL-6 following exercise will be beneficial for substrate utilization, increasing insulin sensitivity at the muscle and increasing lipolysis within adipose tissue (Pedersen & Febbraio, 2008). Following an acute

bout of exercise, IL-6 levels return to baseline approximately 48 hours after the stimulus is removed (Niemelä et al., 2016).

The release of IL-6 during an acute bout of exercise triggers the release of IL-1ra and IL-10 systemically which have anti-inflammatory actions (Pedersen & Febbraio, 2008). IL-1ra is an antagonist molecule that competitively inhibits IL-1α and IL-1β from acting in a pro inflammatory pathway (Pedersen & Febbraio, 2008). This differs from IL-10 that is involved in regulating cytokine activity by promotion the degradation of cytokine mRNA in addition to inhibiting IL-8 in neutrophils (Bogdan et al., 1992; Wang et al., 1994). A study by Dorneles et al. (2016) found that levels of IL-8 were found to be lower following a bout of high intensity interval exercise and as this molecule is responsible for immune cell recruitment, this would trigger an anti-inflammatory effect. Similarly, with macrophage inflammatory protein 1 beta (MIP-1β), exercise has been found to decrease its activity, effectively lowering the inflammatory response post exercise (Dorneles et al., 2016). TNF-α has also been shown to increase following an acute bout of exercise (Rahman et al., 2010) but has also been shown to decrease following a training regimen over a longer period of time (Jiménez-Maldonado et al., 2019). In addition, there appears to be an interaction between IL-6 and TNF-α indicating that IL-6 exerts an anti-inflammatory response by inhibiting further TNF-α secretion following acute exercise (Petersen & Pedersen, 2005). Overall, acute exercise bouts trigger the release of anti-inflammatory cytokines, which will aid in lowering basal levels of pro-inflammatory cytokines and reduce the chance of chronic systemic low-grade inflammation [see ‘section 1.8.2.2 - effects of exercise training on inflammation’, (Pedersen & Febbraio, 2008)].

1.7.4 Sex differences in inflammation

Biological sex has been found to impact various aspects of the inflammatory response. Whether inflammatory status inherently differs between healthy males and females is not well studied; however, several trials have reported sex-based differences in inflammatory markers. In a trial of 104 participants, levels of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) were higher in males compared with females (Bernardi et al., 2020; Ershler & Keller, 2000), which may be due to a protective effect of estrogen (Ershler & Keller, 2000). However, another trial found no difference in IL-6 concentration between males and females but did report that TNF-α was higher in males (Cartier et al., 2009). Interestingly, CRP is frequently reported to be higher in females than males (Cartier et al., 2009; Khera et al., 2005; Lakoski et al., 2006; Wener et al., 2000). Additionally, in overweight/obese individuals with metabolic syndrome, males had higher IL-6 and leptin, whereas females had lower adiponectin (ter Horst et al., 2020). Together these findings suggest that sex influences pro- and anti-inflammatory status and warrants further investigation given the role of inflammation in the development of T2D.

Sex differences in inflammation can potentially be mediated by sex hormones. Androgens have been found to have mainly anti-inflammatory properties whereas estrogens have been found to be either pro- or anti-inflammatory depending on the estrogen receptor (ER) isoform as well as the type of immune response (Gilliver, 2010; Straub, 2007). Testosterone specifically has been found to decrease levels of cytokines, specifically TNF-α and IL-6, which in turn decreases the chance that tissues become insulin resistance (Ottarsdottir et al., 2018). Another study by Liva & Voskuhl found that testosterone was able to increase the production of IL-10, further promoting an anti-inflammatory environment (Liva & Voskuhl, 2001). Estrogens have been found to activate various cells related to the inflammation pathway, including

macrophage and monocytes (De Paoli et al., 2021), while also directly inhibiting the expression of pro-inflammatory cytokines, TNF-α and IL-6 (Straub, 2007). This coincides with the upregulation of cytokines that are anti-inflammatory, specifically IL-10 and IL-4 (Straub, 2007). A study by Pratap et al. found that estrogens are able to upregulate inflammatory signaling through nitric oxide (NO) and nuclear factor κB (NF-κB) pathways via Akt (Pratap et al., 2015).

Adiposity levels are well known to be different between males and females in addition to the knowledge that adipocytes are involved in the systemic inflammation response (Bloor & Symonds, 2014). Females store the majority of their adipose tissue in the lower trunk of the body as subcutaneous and white adipose tissue [AT (Bloor & Symonds, 2014)]. Males store most of their fat in the upper trunk of the body as subcutaneous and visceral white AT (Bloor & Symonds, 2014). This poses an issue as visceral white AT has been shown to be more metabolically active in the inflammatory response compared to subcutaneous white AT (Ellulu et al., 2017). A study by ter Horst et al. (2020) found that in males, adipose tissue inflammation was positively correlated with systemic IL-6 and leptin levels, both pro-inflammatory markers. This differs from females, which have a negative correlation between inflammation and adiponectin, an anti-inflammatory marker (ter Horst et al., 2020). This demonstrates the whole-body metabolic differences between males and females with respect to inflammation. (ter Horst et al., 2020).

1.8 Effects of exercise training

1.8.1 Exercise and risk of T2D

The importance of regular physical activity has become increasingly more evident as it has been shown to decrease the risk of various chronic conditions, specifically the development of T2D (Colberg et al., 2010). The American Diabetes Association released statements regarding

the impacts of exercise on T2D which include research supporting that 2.5 hours of moderate to vigorous physical activity a week is recommended for high risk adults to prevent the development of T2D (Colberg et al., 2010). In addition to this statement, they have determine other effects such as acute effects of an increase in glucose uptake into skeletal muscle and acute improvements in the effectiveness of insulin from 2 to 72 hours following an acute training bout (Colberg et al., 2010). With respect to chronic effects, it has been reported that both aerobic and resistance exercise improve insulin action and blood glucose regulation and that resistance exercise can enhance skeletal muscle mass (Colberg et al., 2010). The increase in skeletal muscle content following resistance training effectively increases the storage capacity for glucose. This in conjunction with the increase in insulin action would permit an individual to better regulate blood glucose levels and prevent any pathological deterioration that could lead to T2D. Overall, the data from many randomized controlled trials supports the conclusion that the main mechanism by which exercise is able to improve the risk of T2D is through improvements of glycemic control and insulin sensitivity.

1.8.2 Aerobic training

1.8.2.1 Effects on insulin sensitivity and glucose control in liver and skeletal muscle

Numerous trials have found that aerobic exercise training improves both hepatic and peripheral insulin sensitivity (Gregory et al., 2019; van der Heijden et al., 2009; Winnick, Sherman, et al., 2008). Specifically, aerobic training for at least 6 weeks with at least three 30-minute sessions per week has been found to improve glucose handling and decrease insulin resistance, determined by improvements in HOMA-IR and blood glucose levels (Damirchi et al., 2014; Prior et al., 2014; Trachta et al., 2014). Furthermore, a meta-analysis performed by Way et al. (2016) found that regular aerobic exercise consisting of at least 3 x 60-minute sessions a week

at moderate-to-vigorous intensity (55 – 70% $\dot{V}O_{2peak}$) for at least 8 weeks has positive effects on insulin sensitivity beyond 72 hours post-exercise in adults with T2D. When looking at glycemic control, one must consider the impact of how exercise affects both hepatic and peripheral insulin sensitivity.

The liver is capable of contributing to insulin resistance through the inability to suppress endogenous glucose production and studies have examined how exercise impacts this process. A study done by van der Heijden et al. (2009) put sedentary adolescents through an aerobic training protocol for 12 weeks consisting of 4 x 30 minutes a week at ≥70% of $\dot{V}O_{2peak}$. The trial found significant decreases in Hepatic Insulin Sensitivity Index (HISI) for both lean and obese participants following the training intervention (van der Heijden et al., 2009). Shojaee-Moradie et al. (2007) found that 6 weeks of aerobic exercise consisting of 3 x 20-minute sessions at 60-80% of$\dot{V}O_{2max}$ improved the ability of insulin to suppress endogenous glucose production; however, did not affect fasting glucose or insulin. It has also been found that aerobic training induces AMPK activity via an increase in TLR-4 expression in mice, triggering an improvement in hepatic insulin sensitivity (M. Wang et al., 2018). The main signaling molecules that are upregulated within the liver include IRS-1 via tyrosine phosphorylation and Akt, two critical molecules that can be affected by other factors like inflammation (da Cruz Rodrigues et al., 2021). These findings show that aerobic training improves the ability for insulin to transduce its signal within hepatocytes, allowing for better control over endogenous glucose production.

Aerobic exercise training has also been found to improve peripheral insulin sensitivity and/or indices of insulin resistance/sensitivity such as HOMA-IR, QUICKI, Matsuda index, etc. A study by Motahari-Tabari (2015) looked at the effects of 8 weeks of aerobic exercise on insulin resistance in women with T2D. The exercise group performed 3 x 30 minutes of walking

at 60% of HR_{max} a week and saw significant decreases in plasma glucose, insulin levels and HOMA-IR values (Motahari-Tabari et al., 2015). Moreover, 6 months of aerobic training (3 sessions/week, starting at 15 min/session at 60% HR_{max} and progressing to 45 min/session at 75% HR_{max}) has been found to improve HbA1C levels (-0.51% vs. control), which is indicative of improvements in overall glycemic control and subsequently T2D management/prevention (Sigal et al., 2007). Furthermore, a meta-analysis looking at the impacts of aerobic, resistance or combined training on the impacts of reducing cardiovascular risks in adults with metabolic syndrome found that aerobic training of at least 3 x 30 minute sessions at 60-80% HR_{max} for 12 weeks significantly decreased fasting insulin levels (Wewege et al., 2018).

The effects of aerobic training on peripheral insulin sensitivity are mediated by effects on insulin signaling within skeletal muscle. Acute bouts of aerobic exercise have been found to influence the insulin signaling cascade in various ways including through the upregulation GLUT4 translocation to the cell membrane, increased angiogenesis in skeletal muscle to improve glucose uptake and increased IRS-1 phosphorylation to improve the insulin signaling cascade (Yaribeygi et al., 2019). However, exercise training can further enhance these adaptations. A study by Hood et al. (2011) found an increase in GLUT4 protein content and insulin sensitivity following 3 x 20 minute sessions (10 x 1 minute intervals at 60% peak power with 1 minute of rest) for 2 weeks in older adults. Furthermore, Gillen et al. (2014) found that GLUT4 protein concentration increased following 6 weeks of sprint interval training (SIT) protocol with 3 x 10 minute sessions (3 x 10 sec all out sprints with 2 minute low intensity periods in between) in overweight or obese individuals. A much longer study was done in middle age and older adults by Ryan et al. (2021) where they did aerobic exercise once a week for 30-50 minutes at an intensity of 50-80% $HR_{reserve}$ for a 6 month period. Following training there was an increase in

the ratio of phosphorylated/total protein for Akt, IRS-1 and insulin receptor expression (Ryan et al., 2021). These findings suggest that aerobic training improves insulin sensitivity through increased activation of key insulin signaling molecules. A meta analysis done by Richter et al. (Richter et al., 2021) suggests a variety of mechansism for the impact of exercise training on insulin action including increased expression of GLUT4 and protein hexokinase II, increased mitochondria function and volume, and increased activity of TBC1D4 through site specific phosphorylation (S704). Cumulatively, these studies demonstrate that aerobic training of at least 3 x 30 minute sessions a week for 6 weeks at an intensity of 60% $\dot{V}O_{2max}$ is required to improve peripheral insulin sensitivity and improvements are mediated through adaptations in the insulin signaling cascade.

1.8.2.2 Effects on inflammation

Throughout the literature there are some discrepancies regarding the impact of aerobic training on inflammation with some studies reporting significant improvements (El-Kader & Al-Shreef, 2018; Ordonez et al., 2014; Samjoo et al., 2013) while others have not found any improvement (Devries et al., 2008; Donges et al., 2010). However, overall several meta-analyses have reported that aerobic training improves inflammatory status in various populations (García-Hermoso et al., 2023; Hayashino et al., 2014; Xing et al., 2022; Zheng et al., 2019). A meta-analysis by Hayashino et al. found that aerobic exercise 3-4 times a week, for a total of at least 120 minutes, for 3 months improves inflammation in patients with T2D, specifically by reducing IL-6 and CRP levels (Hayashino et al., 2014). Elevated levels of CRP have been associated with increased insulin resistance and is correlated with the development of T2D (Gelaye et al., 2010; Tabák et al., 2010). Furthermore, a 2019 meta-analysis determine that $\geq$ 12 weeks of aerobic training, 3 x 20–60-minute sessions at 55-70% of HR_{max} tends to decrease resting concentrations

of CRP, TNFα, and IL-6 levels (Zheng et al., 2019). An additional meta-analysis from Xing et al. (2022) found that aerobic exercise of at least 3 x 30 minute/sessions/week for 12 weeks at of any intensity was sufficient to decrease levels of IL-6, CRP and TNF-α. García-Hermoso (2023) conducted a meta-analysis and found a significant association between changes in TNF-α and HbA1C, indicating the direct connection between how improvements in inflammation can affect glycemic control. This was found with aerobic protocols that included moderate intensity continuous training (MICT) and high intensity interval training (HIIT) at a moderate-vigorous intensity for at least 3 x 60 minute sessions a week for 24 weeks (García-Hermoso et al., 2023). A study done by El-Kader & Al-Shreef (2018) consisted of 3 sessions a week of training for 6 months with an aerobic group performing 40 minutes a session at 60-80% HR_{max}. Following training there was a decrease in TNF-α and IL-6 concentrations in the aerobic group (-32.7% and -31.8% change respectively) (El-Kader & Al-Shreef, 2018). There is clear evidence showing an influence of aerobic exercise on improving inflammatory markers; however, it seems that in order for aerobic exercise to decrease inflammation, longer sessions are required (≥ 40 minutes).

In addition, the effect of aerobic training on inflammatory markers must consider sex as a factor. A study by Samjoo et al. (2013) found a trend for IL-6 to decrease 21%, despite being non-significant, following a 12-week, incremental aerobic training protocol terminating with 3 x 60 minute biking sessions at 70% $\dot{V}O_{2peak}$ by the final week of training in sedentary obese males. These findings differed from a study by Devries et al. (2008) which did not find any decrease in inflammatory markers such as IL-6 in an obese female population following a very similar protocol. Despite being a similar protocol, there were differences in training volume as participants in the Samjoo et al. trial began with double the time of aerobic exercise to those in the Devries et al. study. In addition, by week 12, participants in the Samjoo et al. trial were

training at a higher intensity at 70% of $\dot{V}O_{2peak}$ compared to 65% of $\dot{V}O_{2peak}$ in the Devries at al. This difference in training volume could have been the variable that triggered the differential response instead of the sex based differences. A meta-analysis performed by Del Rosso et al. (Del Rosso et al., 2023) looked at the influence of various exercise modalities on cytokines in individuals with overweight/obesity. With respect to aerobic exercise, the paper found that MICT at an intensity of at least 60% $\dot{V}O_{2peak}$, for an average of 3.5 days a week for at least 8 weeks influenced changes in cytokines in a sex dependent manner as CRP, Il-6 and TNF-α decreased in males, but did not change in females (Del Rosso et al., 2023). Regardless of the influence of sex, the decrease in IL-6 concentration following a training regimen has been correlated with decreased risk for chronic low-grade inflammation and subsequently metabolic disease (Pedersen & Febbraio, 2008). The influence of sex on the impact of aerobic exercise on inflammation requires further investigation in order to make concrete conclusions regarding the presence of sex-based differences and the required volume to elicit these differences. Together, the findings of these studies indicate that training at least 3 times per week at a moderate-to-vigorous intensity for at least 120 minutes per week for at least a 12 week period can improve inflammatory status.

1.8.3 Resistance training

1.8.3.1 Effects on insulin sensitivity and glucose control in liver and skeletal muscle

Resistance training has been shown to have similar effects on insulin sensitivity as aerobic training (Gordon et al., 2009). A meta-analysis from Mann et al. (2014) found that any type of resistance training above 50% of 1RM, at least 3 sessions a week for a minimum of 6 weeks improved insulin sensitivity with greater increases seen with greater training volumes. These adaptations were also predominantly seen in the muscles trained, indicating the need for

whole body resistance training (2014) Another meta-analysis by Pan et al. (Pan et al., 2018) found that resistance training of at 40-60% of 1RM for 3 sessions a week over at least 2 months is effective in lowering HbA1C values in individuals with T2D. Looking at a randomized controlled trial consisting of 16 weeks of progressive resistance training, 3 sessions a week, with 60-80% of their 1RM showed improvements in HbA1C values in older adults with T2D (Castaneda et al., 2002).

In the liver, a 12 week resistance training program that involved 2 x 1 hour sessions a week of whole body training at 50% of 3RM progressing to 80% 3RM was found to increase hepatic insulin sensitivity using the HISI along with a reduction in glycogenolysis following the intervention (van der Heijden et al., 2009). A study by Pereira et al. (2019) found that in rat models, even a short-term training protocol of 15 sessions improved hepatic insulin sensitivity, causing a decrease in hepatic glucose production and reducing liver inflammation through increased Akt phosphorylation and decreased TNF-α activity respectively. Similar to aerobic training, resistance training improves the liver's ability to respond to insulin and suppress endogenous glucose production (Pereira et al., 2019).

With respect to peripheral insulin sensitivity, resistance training also has the ability to improve the insulin response following training. A trial assessing the impact of resistance training in overweight, adolescents found an increase in peripheral insulin sensitivity through a frequenetly sampled intravenous glucose tolerance test post training (Shaibi et al., 2006). Following a 16-week resistance training program that involved 2 sessions a week progressing from 75% to 95% of baseline 1RM, the researchers found a 45% increase in insulin sensitivity in the resistance training group compared to 1% decrease in the control group (Shaibi et al., 2006). Another trial by Ibañez et al. (2005) found that a 16 week, progressive resistance training

program was effective in improving insulin sensitivity through the use of a frequent samples glucose tolerance test. This was done in older men with T2D and they performed whole body resistance training twice a week working between 50-80% of their 1RM (Ibañez et al., 2005). A meta analysis by Consitt et al. (Consitt et al., 2019) found that approximately 3 months of resistance training that targets major upper body and lower body muscle groups is effective as improving TBC1D4 activity through increased phosphorylated protein content relative to total protein content. In addition, a Overall, resistance training of at least 6 weeks at an intensity greater than 50% of 1RM targeting the whole body improves insulin sensitivity with a potential mechanism being through improved activity within the insulin signaling pathway as seen in an acute bout of resistance training.

1.8.3.2 Effects on inflammation

Resistance training has been reported to reduce chronic inflammation (de Salles et al., 2010). A systematic review that examined how resistance training affected TNF-α and CRP levels reported that the majority of papers found that CRP, but not TNF-α, decreased with resistance training, with a greater response when protocols were $\geq$ 16 weeks and/or involved training intensities $\geq$ 80% 1RM (de Salles et al., 2010). In addition, CRP decreased to a greater extent following resistance training in females compared to males (de Salles et al., 2010), which may be particularly beneficial given that numerous studies have reported that CRP is higher in females than males (Cartier et al., 2009; Khera et al., 2005; Lakoski et al., 2006; Wener et al., 2000). A meta-analysis done by Khalafi et al. (2023) found that resistance training targeting major muscle groups, for 3 sets of 10-12 reps for a duration of 8 weeks can be effective in decreasing levels of CRP. Another study by Forti et al. (2017) found that resistance training decreased concentrations of IL-6 in young adults. The study protocol consisted of 3 sessions a

week for 9 weeks of bilateral leg extension with a traditional high load protocol (one set of 10-12 reps at 80% of 1RM) and low-load protocol until maximal effort was reached (pre-fatiguing protocol of 60 reps at 20-25% of 1RM following by one set of 10-12 reps at 40% of 1RM). A study by Donges et al. (2010) looked at the effects of 10 weeks of resistance training and saw a decrease in CRP concentrations following the full body resistance intervention, once a week at 70% of 10RM (Donges et al., 2010). An additional meta-analysis done in older adults found a significant decrease in the CRP levels, but only a tendency for IL-6 levels to decrease following resistance training (Sardeli et al., 2018). This meta-analysis included studies that involved resistance training consisting of 5-8 whole body exercises at a moderate intensity, 3 sessions a week for $\geq$ 8 weeks (Sardeli et al., 2018). Another study done by Santiago et al. (2018), involved an 8-week intervention with 3 sessions a week where 8 exercises targeting the entire body were done for 1 set within the maximum repetition zone of 8-12 reps and weight was increased if participants exceed this rep range. They reported a significant decrease in both IL-6 and TNF-α following training, indicating the effectiveness of resistance training on cytokine concentrations. Overall, it appears that resistance training that is slightly longer, at least 8 weeks in duration and targets major muscle groups has the ability to decrease concentrations of pro-inflammatory cytokines.

1.8.4 Mixed training as an ideal intervention

When comparing the effects of aerobic and resistance training, there are conflicting results in the literature. Certain studies found that aerobic training was more effective at improving glucose handling measures including HbA1C and HOMA-IR (Lee et al., 2013; Motahari-Tabari et al., 2014). However, this finding differs from other studies that found that resistance training was more effective at improving these measures (Bweir et al., 2009; Eves & Plotnikoff, 2006). The

aforementioned meta-analysis by Pan et al. (2018) investigated the effects of aerobic, resistance or a combined intervention on the effects of HbA1C levels of individuals with T2D. It was determined that compared to aerobic and resistance training alone, the combined protocols were able to elicit a 0.17% and 0.23%, respectively, greater decrease in HbA1C values. A study done by Church et al. (2010) compared the effects of 9 months of aerobic, resistance and a mixed mode intervention on HbA1C levels. The aerobic group trained between 50-80% of their $\dot{V}O_{2max}$ to expend 12 kcal/kg a week and the resistance group performed 3 sessions a week of 2 x 10-12 reps of 4 upper body, 3 x 10-12 reps of 3 lower body exercises and 2 x 10-12 reps of abdominal exercises. The combined exercise group trained at the same intensity for aerobic exercise to achieve a 10 kcal/kg a week energy expenditure and performed 2 resistance sessions a week of 1 x 10-12 reps of the 9 exercises indicated above. The study found a 0.34% decrease in the absolute levels of HbA1C in the combined group, with no change in either the aerobic or resistance groups alone. One limitation of this study is they did not control for volume of exercise. One limitation of this study is that they did not report the volume of exercise completed by each group in common units making it difficult to determine if any training-induced differences were due to differences in training volume between the groups. For the aerobic training group exercise volume was reported as MET min/week whereas the resistance training volume was reported as weight lifted per week. In order to attempt to compare the volume between the mixed group and the aerobic and resistance trained group I calculated the relative volume of the mixed group to each individual group. By the final month, the combined group had expended less energy during exercise compared to the aerobic group (84.2% of what aerobic group expended) and lifted less weight than the resistance group (28.9% of what resistance group lifted). Since the volume for each modality is different, it is difficult to make concrete

conclusions, however, it does appear that the combined group performed a greater volume of training which could explain the difference in responses to the improvement in HbA1C. Studies would require a more accurate approximation of volume to ensure all groups are performing a similar volume of training.

Since both aerobic and resistance exercise modes act on similar aspects of the insulin signaling pathway, a mixed mode training intervention would be appropriate for improving overall insulin sensitivity. To recall the Sigal et al. (2007) study, researchers found a statistically significant decrease HbA1C when comparing mixed mode training to resistance training and also saw a non-significant decrease in HbA1C when comparing the mixed mode training to aerobic training. The aerobic training consisted of 3 sessions/week, from 15-45 min/session at 60-75% HR_{max} and the resistance portion consisted of 3 sets, 8-12 reps each set, 7 exercises covering the full body performed with progressive overload being maintained throughout the 6 months (Sigal et al., 2007). Similar trends for a greater improvement in fat mass following mixed mode training compared with resistance training alone were found when comparing baseline to the 6 month time point. Conversely, the mixed mode exercise was more effective at increasing lean body mass when compared to the aerobic training group, indicating the importance for resistance training in the protocol due the health benefits of increasing lean body mass (Sigal et al., 2007). The differential responses in these measures could have been due to the extra exercise volume as the combined exercise group completed both the aerobic only and resistance only training programs, which makes it difficult to discern if these changes are due to exercise modality or volume (Sigal et al., 2007). The use of a mixed mode training ensures a compounding effect on the improvement of insulin sensitivity while providing other positive fitness outcomes such as

improved cardiovascular health for aerobic training and improved muscle mass and bone mineral density with resistance training (Hong & Kim, 2018; Nystoriak & Bhatnagar, 2018).

Regardless of mode of exercise, it has been found that regular exercise has an anti-inflammatory effect by reducing inflammatory markers that contribute to a pro-inflammatory environment (Pedersen, 2017). With respect to inflammation, the previously mentioned meta-analysis by Khalafi et al. (2023) found that protocols that included a combination of aerobic and resistance exercise were able to trigger a decrease in IL-6 and CRP levels following the intervention. In addition, the decrease in IL-6 was not seen in either the aerobic or resistance only protocols; this decrease was only found in the mixed mode interventions. The meta-analysis done by Xing et al. (2022) found that combined exercise programs were more effective in reducing IL-6 concentrations compared to interventions with only aerobic exercise and no statistical difference between the combined and resistance only protocols. The meta analysis by Del Rosso el at. (2023) found that combined exercise protocols of aerobic and resistance training was more effective in reducing CRP compared to only aerobic training while seeing no difference between the mixed modes and resistance training only. A study done by Magalhães et al. (2020) compared mixed mode interventions of HIIT or MICT with resistance training and found a significant decrease in IL-6 concentrations after 1 year of training, regardless of the type of aerobic exercise employed (Table 1.2). While IL-6 was found to decrease, there were no statistically significant changes in CRP or TNF-α. As aerobic and resistance training have been found to affect slightly different markers of inflammation, it is to the benefit of the participant to be performing a mixed mode training regimen to gain optimal effects on reducing low grade inflammation and subsequently improving insulin sensitivity.

Table 1.2: Summary of exercise intervention studies

Study	Type	Intervention Details	Outcomes
Glycemic control and insulin sensitivity			
Castaneda et al., 2002	R	Older adults with T2D F: 3x/week I: 60-80% of their 1RM T: 50 min/session for 4 months T: 5 exercises, whole body resistance training	↓ HbA1C
Church et al., 2010	AE, R, AE+R	Sedentary adults with T2D **AE:** F: N/A I: 50-80% of $\dot{V}O_{2max}$ (Target was 12 kcal/kg) T: 9 months T: Treadmill **R:** F: 3x/week I: 10-12 reps for each exercise T: 9 months T: 2-3 exercise of upper body, lower body and abdominal exercises, whole body resistance training **AE+R:** AE: Target was 10 kcal/kg a week. R: 2x/week performing 1 x 10-12 reps of the 9 exercise listed in the resistance section	**AE+R:** ↓ HbA1C levels compared to either aerobic or resistance groups
Damirchi et al., 2014	AE	Middle aged men with metabolic syndrome F: 3x/week I: 50-60% of $\dot{V}O_{2peak}$ T: 25-40 min/session for 6 weeks T: Treadmill	↓ HOMA-IR ↓ Fasting blood glucose
Hood et al. 2011	AE	Sedentary older adults F: 3x/week I: 10 x 1 minute intervals at 60% peak power with 1 minute of rest T: 2 weeks T: Cycle ergometer	↑ Insulin sensitivity (HOMA)
Ibañez et al., 2005	R	Older men with T2D F: 2x/week	↑ Insulin sensitivity during a frequently sampled intravenous glucose tolerance test

		I: 50-80%, 3-5 sets for 10-15 reps from weeks 1-8 and then 5-6 reps for weeks 9-16 as loads increased T: 45-60 min/session for 4 months T: Whole body resistance training	
Matos et al., 2014	AE	Non-smoking, sedentary adults F: 1 session I: 60% $\dot{V}O_{2max}$ T: 60 min T: Cycle ergometer	↓ IRS-1 serine phosphorylation ↑ GLUT4 translocation
Motahari-Tabari, 2015	AE	Females with T2D F: 3x/week I: 60% of HR_{max} T: 30 min/session for 2 months T: Walking	↓ Plasma glucose ↓ Insulin ↓ HOMA-IR
Pereira et al., 2019	R	Obese male mice F: 5 sessions/week I: 70% of maximal voluntary carrying capacity (MVCC) T: 15 sessions over 3 weeks T: Climbing series	↑ HISI ↓ Hepatic insulin production ↑Akt phosphorylation ↓ TNF-α activity
Prior et al., 2014	AE	Sedentary, overweight-obese, older men and women with IGT F: 3x/week I: 50-85% % $HR_{reserve}$ T: 15-45 min/session for 6 months T: Treadmill	↓ HOMA-IR ↓ Fasting blood glucose
Ryan et al., 2021	AE	Overweight/obese middle age and older adults F: 1x/week I: 50-85% % $HR_{reserve}$ T: 30-50 min/session for 6 months T: Treadmill	↑ Phosphylated:total protein Akt, IRS-1ratio ↑ Insulin receptor conten
Shaibi et al., 2006	R	Obese male adolescents F: 2x/week I: 72-97% of baseline 1RM T: 60 min/session for 4 months T: Whole body resistance training	↑ Insulin sensitivity during a frequently sampled intravenous glucose tolerance test
Shojaee-Moradie et al., 2009	AE	Overweight male adults F: 3x/week I: 60-80% of $\dot{V}O_{2max}$ T: 20 min/session for 6 weeks T: N/A	↑ Suppression of endogenous glucose production from insulin ↔ fasting glucose/insulin
Sigal et al., 2007	AE, R, AE+R	Adults with T2D **AE:** F: 3x/week I: 60-75% % HR_{max}	**AE:** ↓ HbA1C **AE+R:**

		T: 15-45 min/session for 6 months T: Treadmill or cycle ergometer **R:** F: 3x/week I: N/A T: 6 months T: 7 exercises, whole body resistance training. 2 → 3 sets of each exercise at max weight for 7-9 reps **AE+R:** Performed the full AE and R protocols	↓ HbA1C (Greater decrease compared to R) ↑ Lean body mass (Greater increase compared to AE)
Sjøberg et al., 2017	R	Health male adults F: 1 session I: 80% of peak work load with 3 x 5 minute intervals at 100% peak work load T: 60 min/session T: One-legged knee extensor	↑ TBC1D4 serine phosphorylation ↑ Glycogen synthase
Trachta et al., 2014	AE	Non-diabetic, obese females with arterial hypertension F: 3x/week I: N/A T: 3 months T: N/A	↓ HOMA-IR ↓ Fasting blood glucose
Van der Heijden et al., 2009	AE	Sedentary lean and obese adolescents F: 4x/week I: ≥70% of $\dot{V}O_{2peak}$ T: 30 min/session for 3 months T: Treadmill	↑ HISI
Van der Heijden et al., 2010	R	Obese adolescent males and females F: 2x/week I: 50-80% of 3RM T: 60 min/session for 3 months T: Whole body resistance training (Biceps, triceps, chest, hamstring, quadriceps)	↑ HISI ↓ Glycogenolysis
Wang et al., 2018	AE	Male mice with T2D F: 5x/week I: 15-27 m/min at 2% grade T: 60 min/session for 10 weeks T: Treadmill	↑ TLR-4 expression
Inflammation			
Devries at al., 2008	AE	Sedentary lean and obese females F: 2-3x/week I: 50-65% $\dot{V}O_{2peak}$ T: 15-60 min/session for 3 months T: Cycling	↔ IL-6

Donges et al., 2010	AE, R	Sedentary male and females adults **AE:** F: 1x/week I: N/A T: 10 weeks T: Cycle ergometer **R:** F: 1x/week I: 75% of 10RM T: 10 weeks T: Whole body resistance training	**AE** ↔ IL-6 or CRP **R:** ↓CRP ↔ IL-6
El-Kader & Al-Shreef, 2018	AE, R	Sedentary older adults **AE:** F: 3x/week I: 60-80% HR_{max} T: 40 min/session for 6 months T: Treadmill **R:** F: 3x/week I: 8-12 reps at 60-80% of 1RM T: 40 min/session for 6 months T: 8 exercises, whole body resistance training	**AE:** ↓ IL-6 ↓ TNF-α **R:** ↔ IL-6 or TNF-α
Forti et al., 2017	R	Young healthy adults F: 3x/week I: High resistance protocol (one set of 10-12 reps at 80% of 1RM) and a low-resistance protocol (pre-fatiguing protocol of 60 reps at 20-25% of 1RM → one set of 10-12 reps at 40% of 1RM) T: 9 weeks T: Leg extension	↓ IL-6
Magalhães et al., 2020	AE+R	Adults with T2D **HIIT+R:** F: 3x/week I: 1 minute at 90% $HR_{reserve}$ interspersed with 1 minute at 40-60% $HR_{reserve}$ + 1 set of 10-12 reps T: ~30 min* T: Cycle ergometer + 8 exercises, whole body resistance training **MICT+R:** F: 3x/week I: 40-60% $HR_{reserve}$ + 1 set of 10-12 reps T: ~45 min* T: Cycle ergometer + 8 exercises, whole body resistance training	**HIIT+R and MICT+R** ↓ IL-6 ↔ CRP or TNF-α

		*Aerobic training varied between participants at a target energy expenditure was provided for each participant	
Ordonez et al, 2013	AE	Young health women with Down syndrome F: 3 sessions/week I: 55-65% % HR_{max} T: 30-40 min/session for 10 weeks T: Treadmill	↓ IL-6 ↓ CRP ↓ TNF-α
Santiago et al., 2018	R	Sedentary elderly females F: 3x/week I: 1 set, 8-12 reps at 60-80% of 1RM (Increased weights if rep range was exceeded) T: 2 months T: 8 exercises, whole body resistance training	↓ IL-6 ↓ TNF-α
Samjoo et al., 2013	AE	Sedentary lean and obese males F: 2-3x/week I: 50-70% $\dot{V}O_{2peak}$ T: 30-60 min/session for 3 months T: Cycling	↓ IL-6

This tables outlines various studies that performed exercise intervention and specifics the outcomes related to measures of insulin resistance, glycemic control and inflammation. *AE - aerobic exercise, R - resistance exercise, ↑ - statistically significant increase, ↓ - statistically significant decrease, ↔ - no change.*

1.9 Current literature on sex differences in insulin sensitivity and exercise

Few studies have specifically looked at sex differences in insulin sensitivity after an exercise training protocol. When analyzing current literature, there seems to be a pattern that insulin sensitivity and glycemic control improves to a greater extent in males compared to females response to exercise training (Gillen et al., 2014; Metcalfe et al., 2012; Potteiger et al., 2003; Rytz et al., 2020; Søgaard et al., 2018). Gillen at al. found that after a SIT protocol over 6 weeks consisting of 3 x 10 minute sessions (3 x 10 sec all out sprints with 2 minute low intensity periods in between), there were similar magnitudes in the decrease of HOMA-IR and fasting blood insulin in males and females (Gillen et al., 2014). However, it was found that the average blood glucose concentration over a 24 hour period, an indicator of glycemic control, improved in

males following training but not females, which corresponded with a greater increase in GLUT4 content in males when compared to females (Gillen et al., 2014). These findings indicate that males could have a greater improvement in insulin sensitivity compared to females when performing the same training. Similarly, Metcalfe found that the Cederholm index improved by 28% in males but did not improve in females after 6 weeks of SIT (Metcalfe et al., 2012). However, in a subsequent study they did not find a difference between the sexes in response to training, but in this study where they reduced the work rate at which the participants trained at, they did not find that insulin sensitivity improved in either sex (Metcalfe et al., 2016). In response to a longer-term (16-months), moderate intensity aerobic training Potteiger et al. (2003) saw a consistent improvement in insulin sensitivity measures such as insulin area under the curve (AUC), fasting insulin and 2 h insulin and glucose in males only. Another study from Søgaard et al. (2018) found that a training protocol of 3 sessions/week for 6 weeks of HIIT training with 5 x 1 minute intervals with 1.5 minutes of rest in between influenced insulin sensitivity and glycemic control measures. Both sexes were seen to improve in insulin sensitivity however, females saw a 1% increase whereas males saw an 11% increase (Søgaard et al., 2018). In addition, HbA1C levels improved in males but not females (Søgaard et al., 2018). Furthermore, while not a direct comparison, Samjoo et al (2013) found improvements in insulin sensitivity in sedentary obese males, but Devries et al (2013) did not find improvements in insulin sensitivity in obese females in response to 12 weeks of moderate intensity continuous exercise. All of these studies only used aerobic exercise for their training protocol, and it would be intriguing to investigate the potential effects of resistance training alone or a mixed model training protocol on insulin resistance.

One caveat to the aforementioned findings is that menstrual cycle was not controlled for. It is important that menstrual cycle is controlled for when examining the effects of training on insulin

sensitivity as insulin sensitivity changes across the menstrual cycle due to fluctuations in sex hormones. Specifically, elevated progesterone concentrations in the luteal phase of the menstrual cycle directly impacting insulin sensitivity, causing an increase in insulin resistance during this period of time. Previous trials comparing the effects of sex on insulin sensitivity and glycemic control following training have not controlled for the phase of the menstrual cycle the females were tested in, which may explain why no effect of training was found in females. Further work in this area is required to examine sex-based differences in the effects of training on insulin sensitivity, as well as examine mechanisms (i.e. inflammation) that could be mediating these differences, while controlling for the menstrual phase in which females are tested.

Table 1.3: Summary of studies looking at sex based differences in insulin sensitivity following an exercise intervention

Study	Type	Intervention Details	Outcomes	
			Male	Female
Gillen et al., 2014	AE	Overweight sedentary adults F: 3x/week I: 3 x 20 sec all-out springs at 0.05kg/kg of BW T: 6 weeks T: Cycle ergometer	↓ 24 hour blood glucose ↓ 24 hour AUC blood glucose ↑ GLUT4 protein content (greater post training compared to females)	↔ 24 hour blood glucose ↔ 24 hour AUC blood glucose ↑ GLUT4 protein content
Metcalfe et al., 2012	AE	Health sedentary young adults F: 3x/week I: 2 x 10-20 sec all-out cycling sprints at 7.5% of BW in resistance T: 10 min/session for 6 weeks T: Cycle ergometer	↑ Cederholm	↔ Cederholm
Metcalfe et al., 2016	AE	Health sedentary young adults F: 3x/week I: 2 x 10-20 sec all-out cycling sprints at 5% of BW in resistance T: 10 min/session for 6 weeks T: Cycle ergometer	↔ HOMA-IR ↔ Cederholm ↔ Fasting insulin and glucose ↔ Insulin and glucose AUC	↔ HOMA-IR ↔ Cederholm ↔ Fasting insulin and glucose ↔ Insulin and glucose AUC
Potteiger et al., 2003	AE	Health sedentary young adults F: 3-5x/week	↓ Insulin AUC (16 month)	↔ Insulin AUC (16 month)

		I: 60-75% HR reserve T: 20-45 min/session for 16 months T: Treadmill	↓ Fasting insulin (9 and 16 month) ↓ 2 h insulin and glucose (9 and 16 month)	↔ Fasting insulin (9 and 16 month) ↔ 2 h insulin and glucose (9 and 16 month)
Rytz et al., 2020	AE	Sedentary older adults with and without metabolic syndrome F: 3x/week I: 30-70% HR reserve T: 20-40 min/session for 6 months T: Treadmill	↓ HOMA-IR (w/ metabolic syndrome)	↔ HOMA-IR(w/ metabolic syndrome)
Søgaard et al., 2017	AE	Sedentary older adults F: 3x/week I: 5 x 1 min intervals with 1.5 min rest in between T: 6 weeks T: Cycle ergometer	↑ Whole body insulin sensitivity (greater post training compared to females) ↓ HbA1C (sex x training effect)	↑ Whole body insulin sensitivity ↑ HbA1C (sex x training effect)

This table provides the details of studies that have included both sexes in their trial and separated the analysis in order to make sex based differences in response to exercise intervention with respect to insulin sensitivity. *AE - aerobic exercise, R - resistance exercise, ↑ - statistically significant increase, ↓ - statistically significant decrease, ↔ - no change.*

Chapter 2: Rationale, Purpose, Objectives and Hypotheses

2.0 Rationale

Type 2 Diabetes (T2D) has become a large concern in Canada as the prevalence has exponentially increased over recent years with an estimation that there will be 5 million Canadians living with T2D by 2025 (Houlden, 2022). The hallmark feature of T2D is insulin resistance, which is defined as the inability of tissues to respond to insulin signaling to 1) promote glucose uptake and 2) suppress endogenous glucose release from the liver, thus resulting in hyperglycemia (Galicia-Garcia et al., 2020). Over time, sustained hyperglycemia can induce significant damage to blood vessels, nerves and organs increasing the risk of cardiovascular disease, stroke, amputation, blindness and kidney disease (Giri et al., 2018). One of the primary risk factors for T2D is overweight and obesity, which contributes to the development of insulin resistance (Al-Goblan et al., 2014; Kahn et al., 2006). In 2018, nearly 27% of Canadians were considered obese and another 36% were considered overweight based on self-reported BW and height data (Statistics Canada, 2019), thus strategies to improve insulin sensitivity in overweight/obese individuals could have a crucial impact on reducing the risk of T2D in Canadians.

Obese individuals have higher circulating levels of inflammatory markers contributing to a chronic state of low-grade inflammation (Zatterale et al., 2020). Increased adiposity results in an increased production and release of pro-inflammatory adipokines such as IL-6 and TNF-α. These cytokines impact the insulin signaling cascade within the liver by phosphorylating the serine site of IRS-1, contributing to the development of insulin resistance (Fasshauer & Paschke, 2003; Senn et al., 2002). This is similarly seen with TNF-α in skeletal muscle (Akash et al., 2018) and the interruption in this cascade reduces the translocation of GLUT4 to the cell

membrane, reducing the ability to take up glucose (de Alvaro et al., 2004; Fasshauer & Paschke, 2003). IL-6 also contributes to the development of insulin resistance by increasing TLR-4 concentration which further inhibits IRS-1 (Kim & Sears, 2010; Kim et al., 2013). Overall, the increased levels of pro-inflammatory cytokines found in obesity lead to a state of chronic inflammation and contributes to the development of IR.

Exercise, whether aerobic or resistance, has been found to have positive effects on insulin sensitivity and is known to decrease the risk of developing T2D (Ley et al., 2016; Patel et al., 2018). Aerobic exercise and resistance training have been shown to improve glycemic control and insulin sensitivity through improvements in HbA1C, HOMA-IR and glucose AUC during an OGTT (Baum et al., 2007; Castaneda et al., 2002; Winnick, Gaillard, et al., 2008). Furthermore, both aerobic and resistance exercise improve hepatic insulin sensitivity as evidenced by an improved ability to suppress endogenous glucose release (Pereira et al., 2019). While both RT and AT are known to improve insulin sensitivity, the combination of these modes of exercise may be more effective (Church et al., 2010). A study done by Church et al. (2010) compared the effects of a 9-month aerobic, resistance and a mixed mode intervention on HbA1C levels. The study showed a -0.34% decrease in HbA1C levels for the mixed mode exercise protocol that was not seen in either the aerobic or resistance groups alone, however, the mixed mode group did a slightly higher volume of exercise than the aerobic and resistance only groups.

Exercise has a variety of effects with respect to the inflammatory response whereby inflammation increases acutely following a bout of exercise to induce repair and adaptation but decreases following a period of training (Ploeger et al., 2009). Authors of a 2019 meta-analysis determined that $\geq$ 12 weeks of aerobic training, 3 x 20–60-minute sessions at 55-70% of HR_{max} tends to decrease resting concentrations of CRP (SMD=0.53), TNF-α (SMD=0.75), and IL-6

(SMD=0.75) levels (Zheng et al., 2019). A study by Forti et al. (2017) found resistance training is effective in decreasing levels of IL-6 in young adults. Another study done by Santiago et al. (2018), an 8-week intervention with 3 sessions a week where 8 exercises targeting the entire body were done found significant decreases in both IL-6 and TNF-α following training, indicating the effectiveness of resistance training on cytokine concentrations. In addition to seeing improvements with either aerobic or resistance only protocols, a meta-analysis from Khalafi et al. (2023) found that mixed mode training was able to elicit a decrease in IL-6 and CRP concentrations. Importantly, the decrease in IL-6 was only seen in the combined exercise programs and not in the aerobic or resistance only protocols. An important consideration here is that the mixed mode exercise programs appeared to have a slightly higher volume of exercise. As sucha more in depth analysis is required to determine if a combined exercise program is more effective at improving chronic inflammation compared to the use of either aerobic or resistance training alone.

Exercise is known to prevent the development of T2D in both males and females (Ley et al., 2016; Patel et al., 2018). However, the effects of exercise training on insulin sensitivity and glycemic control are blunted in females (Gillen et al., 2014; Metcalfe et al., 2012; Potteiger et al., 2003; Rytz et al., 2020; Søgaard et al., 2018). Specifically, while HOMA-IR was reported to improve similarly in males and females in response to 6-weeks of HIIT, 24-h glycemic control only improved in males, which was accompanied by a greater increase in GLUT4 content (Gillen et al., 2014). Similarly, a study by Metcalfe et al. (2012) found that insulin sensitivity as determined with the Cederholm index improved in males, not females, following 6 weeks of SIT (3 x 10 min sessions/week, consisting of 2 x 10-20 sec all-out cycling sprints at 7.5% of BW in resistance) It is not just following interval training that blunted improvements in insulin

sensitivity are found. Potteiger el at. (2003) found that males showed improvements in insulin sensitivity following 16 months of supervised moderate intensity aerobic exercise (3-5 x 20-45 min sessions/week at 60-75% HR reserve) whereas females showed no improvement. To the best of our knowledge no one has compared the effects of resistance training or mixed-mode training on insulin sensitivity between males and females and thus this requires further examination.

If inflammation is involved in the development of insulin resistance in overweight/obese individuals, then perhaps sex-based differences in the effects of training on inflammatory markers may help explain differences in the effects of training on insulin sensitivity in males and females. Similar to insulin resistance and glycemic control, there have been sex-based differences in inflammation found in the literature. A study by Samjoo et al. (2013) found a trend for IL-6 to decrease (-21%) with a 12-week aerobic training protocol including 3 x 60 minute biking sessions from 50% $\dot{V}O_{2peak}$and increasing to 70% $\dot{V}O_{2peak}$ by the final week of training in obese males. While not a direct comparison, these findings differed from a study by Devries et al. (2008) which did not find any decrease in inflammatory markers such as IL-6 (-0.30 pg/mL) in an obese female population (n= 24, p=0.11) following a very similar protocol. The exercise protocol in the Samjoo et al. paper was slightly higher in volume and intensity compared to that of Devries et al., which could have contributed to the differential results. On the other hand, a systematic review by de Salles et al. (2010) saw a greater decrease in CRP levels in females when compared to males following resistance training. Research such as these studies suggest that the effects of training may differ between the sexes and between exercise modes and thus highlights the importance of including both males and females when conducting trials investigating the effects of exercise interventions on insulin sensitivity and inflammation.

2.1 Purpose

To determine if sex influences the effects of a mixed mode exercise training regimen on insulin sensitivity and inflammation in overweight/obese males and females

2.2 Objectives

To compare the effects of mixed mode exercise training between overweight/obese males and females on:

1) Insulin sensitivity and glycemic control
2) Pancreatic β-cell function
3) Pro- and anti-inflammatory cytokines

2.3 Hypotheses

1) Females will be more insulin sensitive and have lower levels of inflammation compared to males prior to training
2) Insulin sensitivity and glycemic control during an OGTT will improve following training in both sexes, but to a greater extent in males
3) β-Cell function will improve following training in both sexes, but to a greater extent in males
4) Training will decrease pro-inflammatory and increase anti-inflammatory cytokines in both sexes, but to a greater extent in males

Chapter 3: Methods

3.1 Participants

A total of 27 participants between the ages of 18-45 were recruited (12 males and 15 females). These individuals had a BMI $\geq$25 kg/m^2 and were sedentary (exercised less than once a week). Participants were excluded due to the presence of the following: the loss of significant weight 3 months prior to the start of the study (classified as >10% of total BW), cardiovascular disease (hypertension that required >2 medications and/or a recent myocardial infarction less than 6 months), uncontrolled hypertension (>140/90 mmHg), congestive heart failure that required >1 medication for angina, arrhythmia or general control, T2D, history of a stroke with residual hemiparesis, presence of renal disorder with a creatinine >140, GI disorders (ex. Crohns, Colitis), individuals who had bariatric surgery, liver disorders (ex. previous liver transplant, diagnosed non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) or cirrhosis), muscular dystrophy, severe osteoarthritis or osteoporosis, severe peripheral neuropathy, orthopedic problems, respiratory conditions (ex. Chronic obstructive pulmonary disease with forced vital capacity (FVC) or forced expiratory volume in one second (FEV_1) <70% of predicted mean value for their age), asthma that required >2 medications. Females were excluded if they had a dysregulated menstrual cycle, amenorrhea, were menopausal or peri-menopausal, pregnant or seeking to become pregnant or were nursing. Participants were also excluded for the use of anti-inflammatory medications, insulin administration, >1 medication for lowering glucose, anti-coagulants, platelet inhibitors, simvastatin (zocor), weight loss medication (Contrave, Orlistat, Saxenda), all beta-blockers or any medication that had been recorded to affect protein metabolism (ex. corticosteroids). Individuals who had undertaken a barium infusion or any infusion consisting of a contrast agent <3 weeks previously or those with an

implantable electronic device were excluded. The Get Active Questionnaire (GAQ) was used to exclude participants unable to participate in exercise. In addition, males who consumed >15 drinks a week (or >3 drinks a day) or females who consumed >10 drinks a week (or >2 drinks a day) or individuals who smoked were excluded. The use of volitional dietary supplementation use was analyzed on a case-by-case basis, but those individuals were required to stop taking the supplement 2 weeks prior to study intake. Groups were matched for age, BMI, protein intake relative to BW and $\dot{V}O_{2peak}$ relative to LBM.

3.2 Study design

The study was part of a larger trial examining the effects of the addition of anabolic (MUSCLE 5, Stay Above Nutrition, Hamilton, ON, Canada) and weight loss (TRIM 7, Stay Above Nutrition, Hamilton, ON, Canada) supplements on body composition and insulin sensitivity. The study was a parallel group, controlled trial that involved 41 study visits. Consent and preliminary testing occurred in the first 3 visits, visits 4-39 consisted of in-person training sessions and visits 40-41 consisted of post-training testing. The overall study schematic is found in Figure 3.1.

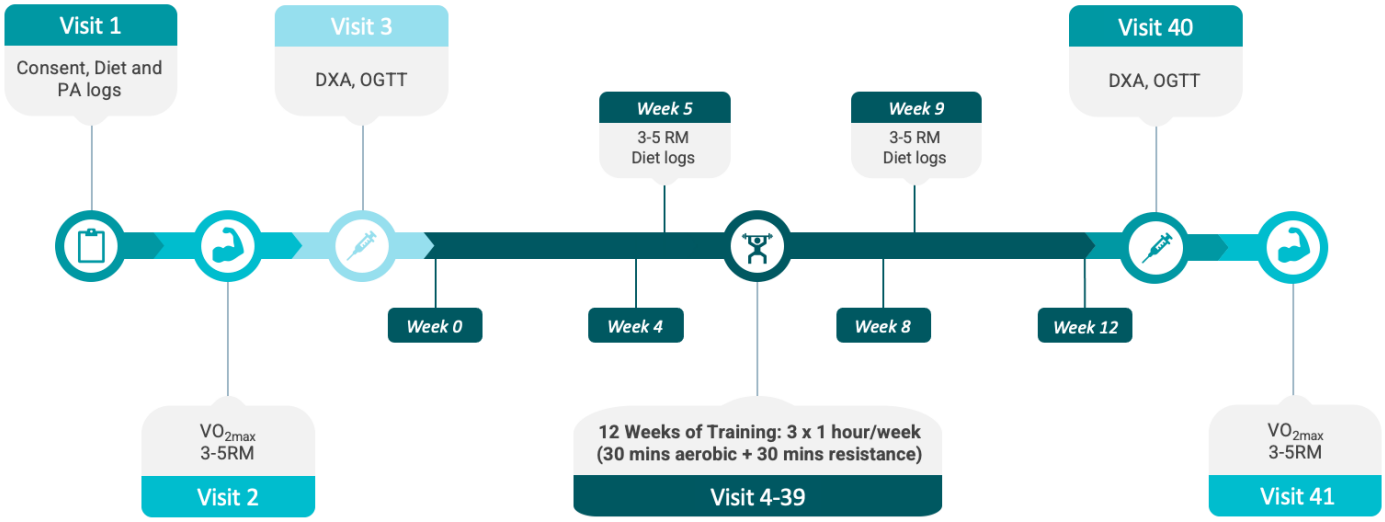

Figure 3.1: Study Schematic
PA: Physical activity, DXA: Dual X-ray absorptiometry, OGTT: Oral glucose tolerance test.

Visit 1:

The first study visit included a detailed description of the procedures and protocol of the current study as well as a discussion of the risks and benefits of participation. Participants were asked about and had the inclusion and exclusion criteria explained to them and at that point were asked to provide informed consent for participation. At this visit, participants underwent assessment of anthropometric measures (weight, height, waist circumference) and were given instructions on how to complete a 3-day food log and 7-day physical activity log. Participants were sent home with log sheets to record food intake and physical activity along with a pedometer to determine habitual daily activity level.

Visit 2:

The second study visit allowed for assessment of current aerobic fitness and strength. v̇ Participants completed a maximal oxygen uptake ($\dot{V}O_{2max}$) test on a cycle ergometer. The results from the $\dot{V}O_{2max}$ test were used to determine the target heart rate for the aerobic training sessions.

$\dot{V}O_{2max}$ was determined using a progressive exercise test on a cycle ergometer (Sport Excalibur, Lode, The Netherlands) using a computerized open-circuit gas collection system (TrueOne 2400, Parvo Medics, Utah). Male participants cycled at 50 watts for 2 min and thereafter the intensity increased in increments of 30 watts/2 min. Female participants cycled at 50 watts for 2 min and thereafter the intensity increased in increments of 20 watts/2 min. Heart rate was monitored throughout the test. $\dot{V}O_{2max}$ was established when O_2 consumption values reached a plateau or as the highest value during the incremental ergometer protocol, when pedal revolutions could not be maintained over 60 rpm despite vigorous encouragement and the respiratory exchange ratio was more than 1.15. After a brief rest, participants underwent an assessment of maximal strength (3-5RM) which was used to predict 1RM and used to determine strength training loads [Estimated 1RM = weight + (weight x # of reps x 0.033)]. Maximal muscle strength was determined for leg press (LP), leg extension [KE (Atlantis Strength, Legs PE-105, Quebec)], hamstring curl [HC (Atlantis Strength, Legs PE-106, Quebec)], shoulder press [SP (Atlantis Strength, Shoulders E-149, Quebec)], chest press (CP) and lat pulldown [LPull (Atlantis Strength, Back D-123, Quebec)]. To start, a specific warm-up of the given exercise was performed using a light weight for which the participant felt comfortable completing 10 repetitions. Load was then be progressively increased by ~10-20% for each attempt until a true 3-5RM was reached with 2 minutes rest between each attempt. Two minutes of rest was given in between each attempt to avoid muscular fatigue. A successful attempt required the participant to move the load throughout the full range of motion with correct form. Prior to leaving the laboratory, participants were instructed to record everything that they eat on the day before the next visit and informed that they repeated this exact diet prior to visit 40.

Visit 3:

The third visit occurred at least 72 h after visit 2 and participants reported to the lab following an overnight fast. Additionally, participants were instructed to refrain from moderate-to-vigorous physical activity for 72 h and alcohol for 48 h prior to this visit. This visit included an assessment of body composition by dual-energy x-ray absorptiometry (DXA). Some participants had 2 scans performed consecutively by a certified Medical X-Ray Technologist (MRT) if the line of vision of the scanner did not align appropriately with the body. Prior to the scan participants were asked to change into a hospital gown and remove all jewelry. Participants then underwent standard OGTT. Participants had a catheter inserted into the antecubital vein and a fasted blood sample was taken. Participants consumed a 75g glucose Trutol beverage (Thermo Scientific, Middletown, USA) and blood samples were drawn at 0, 10, 20, 30, 45, 60, 90 and 120-minutes post consumption. Blood was collected into serum separator (Insulin, C-peptide), and K2-EDTA (Glucose, IL-1β, IL-1ra, IL-1α, IL-6, IL-8 IL-10, IL-15, TNF-α, MIP-1β) collection tubes. HbA1C measurements were performed using blood taken from the K2-EDTA tube prior to centrifugation using the A1CNOW$^{®+}$ device (Indianapolis, USA). Plasma tubes were be spun immediately. Serum tubes were left to stand for ~30 minutes to allow blood to clot and then were spun. Separated plasma and serum sat on ice as it was pipetted into the appropriate storage tubes. Samples for C-peptide were put into cryovials and snap frozen in liquid nitrogen and stored at -80° C until analyzed. All other samples were put into Eppendorf and stored at -80° C until analyzed. Following each blood draw, the catheter was flushed with a sterile saline solution in order to prevent clotting within the catheter. The total amount of blood drawn was approximately 120 mL. Given that hormone fluctuations throughout the menstrual cycle

influence muscle metabolism, insulin sensitivity and water retention, both OGTT and DXA assessments for females were taken in the mid-follicular phase (day 3 – 10) of the menstrual cycle both prior to and following training, with the exception of 3 females. Menstrual cycles were self-tracked by female participants and they informed the research of team of each start of their next menstrual cycle. In the situation where the female could not be tested in the mid-follicular phase of the menstrual cycle at pre-testing, they were tested in the same phase of the menstrual cycle during post-testing. Training started after pre-testing such that females finished training right before the start of or during menses so that post-testing could take place during the mid-follicular phase of the menstrual cycle.

Visits 4 – 39 – Training sessions

Participants trained 3 days per week performing a combined aerobic and resistance training regime (EnduRX). Aerobic training intensity was progressed through adjustment of training work rate to achieve the appropriate target heart rate. Resistance training intensity was progressed after the completion of week 4 and 8 through 3-5RM retesting and adjusting the weights appropriately (Appendix 2). Diet was reassessed at weeks 5 and 9 by performing a 3-day diet recall.

Aerobic exercise:

Participants were able to select their machine of choice for aerobic exercise from the following: Treadmill (Excite Live Run, TechnoGym, New Jersey), elliptical (Integrity Series Elliptical, LifeFitness, California), stationary bike (M3 Indoor Bike, Keiser, California), and recumbent bike (V Series Recumbent Bike, LifeFitness, California)

Day 1: Alternating between 30 minutes moderate-intensity continuous training (MICT) session and 30 minutes Fartlek training. The 30 minutes of moderate intensity continuous training started at 55% $\dot{V}O_{2max}$ (weeks 1-4), increasing to 60% $\dot{V}O_{2max}$ (weeks 5-8) and finally 65% $\dot{V}O_{2max}$ (weeks 9-12).The 30 min Fartlek session consisted of 5 min at 50% $\dot{V}O_{2max}$, 1 min at 60% $\dot{V}O_{2max}$, 1 min at 50% $\dot{V}O_{2max}$, 1 min at 70% $\dot{V}O_{2max,}$ 1 min at 50% $\dot{V}O_{2max}$, 1 min at 80% $\dot{V}O_{2max}$, 10 min at 50% $\dot{V}O_{2max}$, 1 min at 60% $\dot{V}O2\dot{V}O2max$, 1 min at 50% $\dot{V}O_{2max}$, 1 min at 70% $\dot{V}O_{2max}$, 1 min at 50% $\dot{V}O_{2max}$, 1 min at 80% $\dot{V}O_{2max}$and 5 min at 50% $\dot{V}O_{2max}$.

Day 2: 10 x 1 min high intensity interval training (HIIT) at 90% HRmax interspersed with low intervals at 50W for male and 30W for female with a 5 min warm up and cool down at 50W for male and 30W for female.

Day 3: 30-minute moderate intensity continuous aerobic class using a variety of pre-existing cardio workout videos online (Appendix 3).

Table 3.1: Schedule for aerobic training during the exercise intervention

Week #	Type of Aerobic Training		
	Day 1	**Day 2**	**Day 3**
1	MICT (55% $\dot{V}O_{2max}$)	HIIT	Virtual Cardio
2	Fartlek	HIIT	Virtual Cardio
3	MICT (55% $\dot{V}O_{2max}$)	HIIT	Virtual Cardio
4	Fartlek	HIIT	Virtual Cardio
5	MICT (60% $\dot{V}O_{2max}$)	HIIT	Virtual Cardio
6	Fartlek	HIIT	Virtual Cardio
7	MICT (60% $\dot{V}O_{2max}$)	HIIT	Virtual Cardio
8	Fartlek	HIIT	Virtual Cardio
9	MICT (65% $\dot{V}O_{2max}$)	HIIT	Virtual Cardio
10	Fartlek	HIIT	Virtual Cardio
11	MICT (65% $\dot{V}O_{2max}$)	HIIT	Virtual Cardio
12	Fartlek	HIIT	Virtual Cardio

This table depicts the type of aerobic training that was performed on particular days throughout the trial in addition to increases in intensity for MICT.

Resistance exercise:

Day 1 and 2: Whole body circuit session at 35% 1RM consisting for three circuits of 45 seconds per exercise with 25 seconds of rest aiming for 20-25 reps for circuits 1 and 2 with the last set of each exercise to failure. The order of the circuit was as follows: leg press, chest press, hamstring curl, front to lateral raises, leg extension, lat pulldown, squat

to calf raises with a medicine ball, bicep curls, seated Russian twists with a medicine ball, tricep extension.

Day 3: Whole body elastic band circuit completed at home for three cycles of 30 seconds per exercise with 15 seconds of rest (aiming for 20-25 repetitions) per circuit with the last set of each exercise to failure. The order of the circuit is as follows: squats, chest press, leg extension, seated rows, knee flexion lateral raises, seated hip flexion, bicep curls, seated dorsiflexion, seated tricep extensions, calf raises, and seated abdominal crunches (Appendix 3).

Visit 40:

Forty-eight to 72 hours after the last training session participants returned to the lab for post-training OGTT and body composition assessments. This visit was a repeat of what occurred at visit #3. Participants were instructed to refrain from moderate to vigorous physical activity for 48-72 h and alcohol for 48 h prior to this visit and arrive to the visit after an overnight fast. Additionally, participants were reminded to eat the same food the day before this visit as they did the day before visit #3.

Visit 41:

This visit occurred 24-48 h after visit 40 and was a repeat of what occurred at visit #2 in order to determine the effects of training on muscle strength and aerobic fitness. Post training measurements of waist circumference, height and weight were also completed. Post dietary analysis was done by using a 3-day diet recall.

3.3 Sample analysis

Blood samples were analyzed for inflammatory markers (IL-1β, IL-1ra, IL-1α, IL-6, IL-8 IL-10, IL-15, TNF-α, MIP-1β) and glycemic control (glucose, insulin, C-peptide) with kits that are commercially available. IL-1β, IL-1ra, IL-1α, IL-6, IL-8 IL-10, IL-15, TNF-α, MIP-1β was analyzed using a custom Bio-Plex Pro Human Cytokine Assays (17009188, BioRad, Mississauga, Canada). Glucose was analyzed using a hexokinase assay (Infinity Glucose Hexokinase, TR15421, Thermo Fischer Scientific, Mississauga, Canada). Insulin and C-peptide were analyzed using radioactive immunoassay (RIA) kits (HI-14K and HCP-20K respectively, Millipore Sigma, Oakville, Canada). All blood samples underwent minimal freeze thaw cycles and only removed when needed for immediate analysis. The CVs for all kits are as follows: glucose hexokinase assay (2.28%), insulin radioactive immunoassay (3.22%), c-peptide radioactive immunoassay (4.29%) and inflammatory markers (7.32%).

3.4 Calculations

Insulin resistance and sensitivity was determined using several validated equations (Table 3.2). HOMA-IR and QUICKI methods were used as a measure of fasted insulin sensitivity (H. Chen et al., 2003; Matthews et al., 1985). The Matsuda, 2-h OGIS and Stumvoll indices were used as indicators of fed state insulin sensitivity. The Matsuda index was used as an indicator of whole-body sensitivity as it considers both the hepatic and skeletal muscle insulin response (Matsuda & DeFronzo, 1999). The 2-h OGIS was used to assess peripheral insulin sensitivity during an OGTT. (Patarrão et al., 2014). The Stumvoll index was used to assess peripheral insulin sensitivity during an OGTT with variations as different equations utilize different variable such as BMI, sex and age in the calculations of insulin sensitivity (Stumvoll et al., 2001). For investigation of β-cell function, glucose sensitivity was calculated which is the main

characteristic of β-cell function and is represented by the slope of the β-cell dose-response (Utzschneider et al., 2007). Rate sensitivity was analyzed which characterizes the insulin secretion in the early stages of its release (Utzschneider et al., 2007). Potentiation ratio was analyzed which charactizes the relative enhancement of insulin secretion from basal to the 2 h mark of the OGTT (Utzschneider et al., 2007). In addition, basal insulin secretion and clearance as calculated as well as mean insulin secretion and clearance throughout the OGTT will be determined. Finally, the insulin secretion at a fixed glucose load (5 and 5.5 mmol/L) adjusted for the potentiation factor at basal levels was determined and can be used to compare the insulin response in a fasted state.

Table 3.2: Indices used to calculate insulin sensitivity and insulin resistance

Index	Equation
Homeostasis model assessment for insulin resistance (HOMA-IR)	$= \frac{FPI \times FPG}{22.5}$
Quantitative Insulin Sensitivity Check Index (QUICKI)	$= \frac{1}{\log FBG + \log FBI}$
Matsuda	$= \frac{10000}{\sqrt{FPI \times FPG \times MPI \times MPG}}$
Stumvoll (No demographics)	$= 0.156 - 0.0000459 \times (I_{120}) - 0.000321 \times (I_0) - 0.00541 \times (G_{120})$
Stumvoll (Demographics)	$= 0.222 - 0.0033 \times (BMI) - 0.0000779 \times (I_{120}) - 0.000422 \times (age)$
2h Oral Glucose Insulin Sensitivity (OGIS)	$= f(G_{0,}G_{90,}G_{120,}I_{0,}I_{90,}I_{120,}D_0)$

This table shows the equations that were used to calculate insulin sensitivity and insulin resistance in the trial.
FPG - fasting plasma glucose, FPI - fasting plasma insulin, HEC - hyperinsulinemic, euglycemic clamp. Matsuda: MPI - mean plasma insulin concentration during the OGTT (mIU/l) and MPG mean glucose concentration during OGTT. Stumvoll (No demographics): I_0 – plasma insulin concentration at 0 min of OGTT(pmol/L), I_{120} – plasma insulin concentration at 120 min of

OGTT (pmol/L), G_{120} – plasma glucose concentration at 120 min of OGTT (mmol/L). Stumvoll (Demographics): BMI – body mass index (kg/m^2), I_{120} – plasma insulin concentration at 120 min of OGTT (pmol/L) and age in years. 2h OGIS: G – plasma glucose concentrations, I – plasma insulin concentrations with the specific time point indicated in the subscript and D_0 – oral glucose dose relative to body surface area (g/m^2).

3.5 Statistical analysis

Sample size was determined using ANOVA_power to run simulations based on glucose AUC and insulin sensitivity as outcomes (Appendix 1). Data from Metcalfe et al. (2012) was used to design a 2x2 sex x training smallest effect size of interest with a sample size of 15 males and 15 females, yielding 86% and 100% power, respectively, to detect the effect following n=2,000 simulations. All statistical analyses and graphs were done using R programming language (R Foundation for Statistical Computing, IN). Data was presented as "means±SEM" for n = 12 males and n = 15 females. Baseline differences between groups and absolute and percent change in outcomes between groups were analyzed using non-paired samples t-tests. Cohen's d values were calculated for t-tests to determine effect sizes (small 0.2, medium 0.5, large 0.8). Training compliance for each sex was also be analyzed using a non-paired samples t-test. A 2-way mixed model ANOVA with sex (2 levels, male/female) as the between variable and training (2 levels, pre/post training) as the within variable was used to analyze the effects of sex and exercise on fitness outcomes, HbA1C, glucose (C_{max}, T_{max}, AUC), insulin (C_{max}, T_{max}, AUC), insulin sensitivity/resistance indices, β-cell function indices and inflammatory markers. Tukey's HSD test was used for post-hoc analyses when required. Partial eta-squared (η_p^2) values were calculated to estimate effect sizes (small 0.01, medium 0.06, large 0.14) for all interactions. Significance was set at $p<0.05$. For all outcomes following the intervention, absolute and percent change was calculated between pre and post measures for each sex and analyzed using a non-paired samples t-test. Glucose AUC was also normalized to glucose dose relative to BW

[Adjusted glucose AUC = glucose AUC/(75/BW)], LBM [Adjusted glucose AUC = glucose AUC/(75/LBM)]and height[Adjusted glucose AUC = glucose AUC/(75/ht)] . Similar calculations were performed to adjust glucose Cmax for BW, LBM and height.

Chapter 4: Results

4.1 Timeline

Recruitment began in May 2022, with *n* = 191 potential participants contacted (Figure 4.1). From that sample, we did not receive replies from 86 people. From the 105 that responded, 68 were ineligible and 37 were randomized to start the trial. Cohort 1 started in July 2022 with *n* = 8 and finished in October 2022 with *n* = 6 following 2 participants who withdrew from the trial (issues with time commitment). Cohort 2 began in August 2022 with *n* = 17 and finished in December 2022 with *n* = 13 with 4 participants withdrawing from the study (issues with time commitment). Cohort 3 started in February 2023 with *n* = 12 and completed in May 2023 with *n* = 8 with 4 participants withdrawing from the study (issues with time commitment and injury sustained outside of the trial).

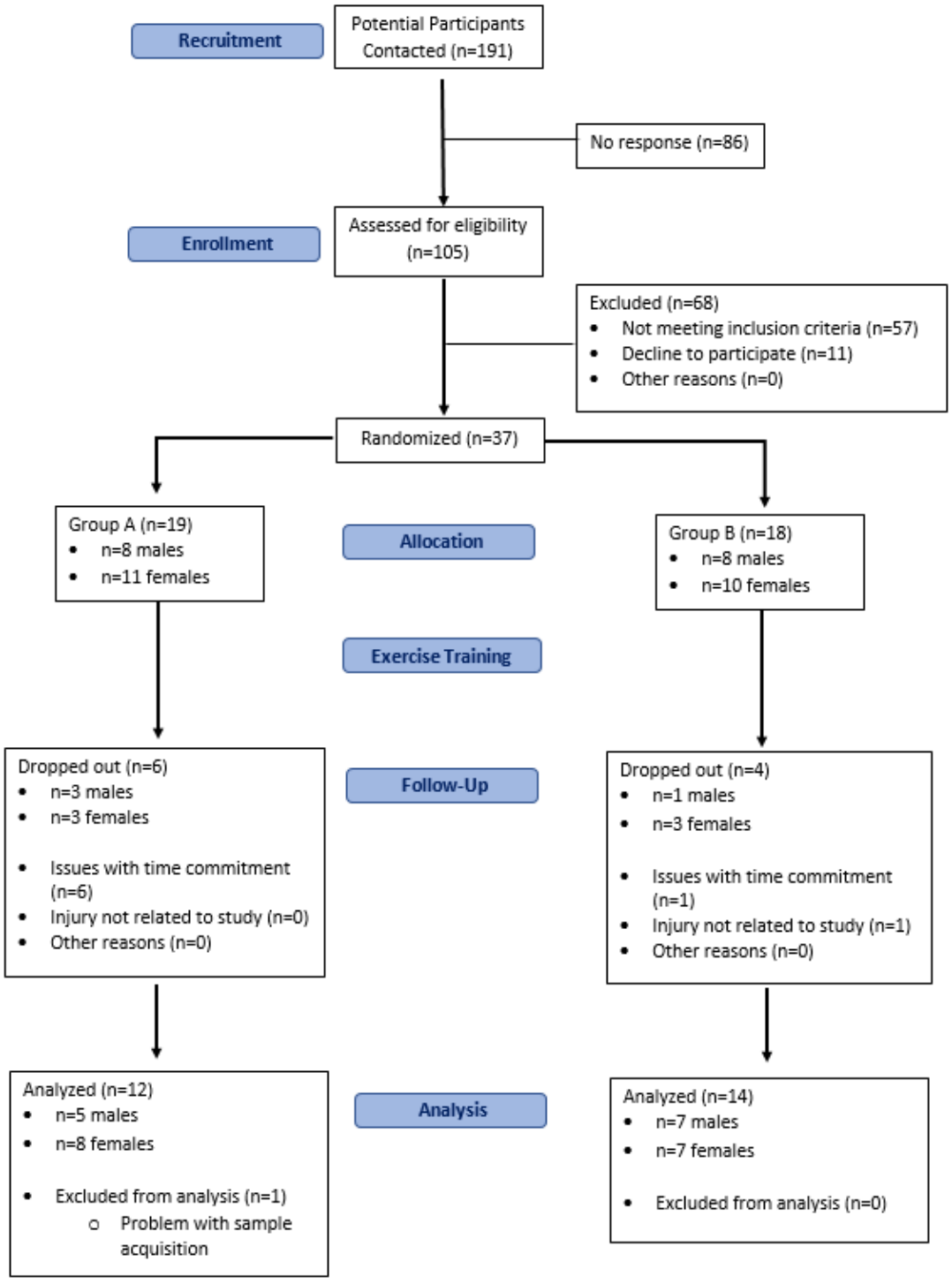

Figure 4.1: CONSORT chart for the TRIM trial recruitment.

4.2 Participant characteristics

Participant characteristics can be found in Table 4.1. There were significant differences between males and females in BW, %BF, LBM and %LBM, which were to be expected. However, there were no significant differences between groups for $\dot{V}O_{2max}$ relative to BW and FFM, indicating that groups were properly matched for aerobic fitness prior to starting the training protocol. Further, there were no differences between sexes in the 7-day average step count and relative 1 RM leg press strength. There was a significant difference in baseline strength for chest press relative to BW. With respect to baseline diet, there was no difference in total energy intake between males and females (p=0.45). There was a significant difference in absolute carbohydrate intake (p=0.04, d=0.85) and the percentage of total energy coming from carbohydrates (p=0.02, d=0.96. There were no significant differences in baseline diet for total or relative fat or protein intake (p>0.21, d<0.49). Changes in diet from pre to post training were reported in Appendix 4.

Table 4.1: Participant characteristics

	Males	**Females**	***p* value**
Age (years)	28 ± 2	30 ± 2	0.45
BW (kg)	105.8 ± 8.0	87.3 ± 4.0	0.04*
Height (cm)	1.75 ± 0.02	1.67 ± 0.01	0.0008*
Waist circumference (cm)	112.5 ± 5.4	101.2 ± 3.9	0.09
BMI (kg/m^2)	34.5 ± 2.8	31.3 ± 1.3	0.27
# of overweight	4	8	
# of obese	8	7	
Body fat (kg)	32.5 ± 4.4	35.0 ± 2.2	0.91
Body fat (%)	31.8 ± 1.7	39.9 ± 0.8	<0.0001*

LBM (kg)	71.4 ± 3.9	52.3 ± 2.0	<0.0001*
LBM (%)	68.3 ± 1.7	60.1 ± 0.8	<0.0001*
$\dot{V}O_{2max}$ (ml/kgBW/min)	26.8 ± 1.5	23.6 ± 1.5	0.15
$\dot{V}O_{2max}$ (ml/kgLBM/min)	38.2 ± 1.7	39.2 ± 2.4	0.94
Average daily step count over 7 days (# of steps)	7037 ± 770	6208 ± 484	0.35
Relative 1 RM chest press strength (kg/BW)	1.25 ± 0.10	0.70 ± 0.05	<0.0001*
Relative 1 RM leg press strength (kg/BW)	3.64 ± 0.49	3.02 ± 0.26	0.25
Total energy intake (kcal)	2238.7 ± 269.8	1843.5 ± 172.2	0.21
Carbohydrates (g)	271.2 ± 29.6	193.9 ± 20.2	0.04*
Carbohydrates (% of total kcal)	49.4 ± 1.9	41.6 ± 2.4	0.02*
Fats (g)	90.6 ± 14.4	74.7 ± 6.3	0.29
Fats (% of total kcal)	35.2 ± 1.6	38.2 ± 2.3	0.31
Protein (g)	90.0 ± 10.5	81.0 ± 11.1	0.57
Protein (% of total kcal)	16.4 ± 1.5	18.0 ± 1.5	0.47
Protein ($g/kg_{BW/d}$)	0.9 ± 0.1	1.0 ± 0.2	0.63

Results are displayed as mean ± SEM, n = 12 males and n = 15 females
* Significance from independent samples t-test, significantly different with p value <0.05.

4.3 Training compliance

Table 4.2 depicts the training compliance for males and females across the 12-week training intervention. There was no statistical difference in the training compliance between the sexes.

Table 4.2: Training compliance for the 12-week mixed mode training intervention

	Males	**Females**	***p* value**	**Cohens *d***
Training compliance (%)	89.6 ± 2.3	93.5 ± 1.5	0.14	0.57

This table shows the percent of total sessions completed for each sex out of a total of 36 sessions.

4.4 Body composition

Measures of body composition prior to and following the training intervention can be found in Table 4.3. In terms of waist circumference, there was an effect of sex ($p=0.04$, $\eta_p^2=0.08$) with a large effect size showing males had a greater waist circumference compared to females. There was no effect of training ($p=0.40$, $\eta_p^2=0.01$) and no a sex x training ($p=0.54$, $\eta_p^2=0.01$) interaction for waist circumference. For BW, there was a large effect of sex ($p=0.001$, $\eta_p^2=0.19$) indicating that males weighed more than females. There were no effects of training ($p=0.74$, $\eta_p^2>0.00$) or sex x training interaction ($p=0.81$, $\eta_p^2>0.00$). There were no effects of sex ($p=0.96$, $\eta_p^2>0.00$), training ($p=0.94$, $\eta_p^2>0.00$) or sex x training interaction ($p=0.39$, $\eta_p^2>0.00$) for absolute body fat mass. When body fat was expressed as a percentage of total BW, there was a large effect of sex ($p<0.0001$, $\eta_p^2=0.46$) such that females had a greater %BF compared to males, but no effect of training ($p=0.98$, $\eta_p^2>0.00$) or sex x training interaction ($p=0.87$, $\eta_p^2>0.00$). As for LBM, there was a large effect of sex ($p<0.0001$, $\eta_p^2=0.48$) with males having a higher absolute amount of LBM compared to females. There were no significant effects of training ($p=0.56$, $\eta_p^2=0.01$) or sex x training interaction ($p=0.76$, $\eta_p^2>0.00$). When expressed as a percentage of BW, there was a large effect of sex ($p<0.0001$, $\eta_p^2=0.46$) with males having a higher percent LBM compared to females. There were no significant effects of training ($p=0.98$, $\eta_p^2>0.00$) or sex x training interaction ($p=0.87$, $\eta_p^2>0.00$).

Table 4.3: Body composition

	Male		Female		*p* value		
	Pre	**Post**	**Pre**	**Post**	**S**	**T**	**S*T**
Waist Circumference (cm)	112.5 ± 5.4	106.1 ± 3.8	101.2 ± 3.9	99.9 ± 3.8	0.04*	0.40	0.54
BW (kg)	105.8 ± 8.0	105.5 ± 7.8	87.3 ± 4.0	84.0 ± 4.0	0.001*	0.74	0.81
Body fat (kg)	34.5 ± 4.4	34.6 ± 4.3	35.0 ± 2.2	34.4 ± 2.1	0.96	0.94	0.39
Body fat (%)	31.8 ± 1.7	32.0 ± 1.7	39.9 ± 0.8	39.8 ± 0.7	<0.0001*	0.98	0.87
LBM (kg)	71.4 ± 3.9	70.8 ± 3.7	52.3 ± 2.0	49.6 ± 2.4	<0.0001*	0.56	0.72
LBM (%)	68.3 ± 1.7	68.0 ± 1.7	60.1 ± 0.8	60.2 ± 0.7	<0.0001*	0.98	0.87

Results are displayed as mean ± SEM, n = 12 males and n = 15 females
* Significance from a 2-way mixed model ANOVA, significantly different with p value <0.05.

The absolute and percent change for body composition measures are reported in Tables 4.4 and 4.5 respectively. Waist circumference was seen to be statistically different for both the absolute and percent change (p=0.01, d=0.99 and p=0.01, d=1.03 respectfully) showing a large effect size and indicating that males had a greater decrease in waist circumference compared to females post training. The absolute and percent changes in the remaining body composition measures following training were not significantly different between the sexes ($p \geq 0.13$). However, the absolute and percent change in BW showed a medium effect size (p=0.17, d=0.57 and p=0.12, d=0.63 respectively), despite being non-significant, indicating that in females BW decreased to a greater extent compared to males. This was also seen for LBM (kg) as there were medium effect sizes for the absolute and percent change (p=0.18, d=0.55 and p=0.14, d=0.62, respectively) without reaching statistical significance showing that in females LBM decreased to a greater extent compared to males.

Table 4.4: Absolute change in body composition in response to the mixed-mode training intervention

	Males	Females	*p* value	Cohens *d*
Waist Circumference (cm)	-6.5 ± 2.0	-1.3 ± 0.6	0.01*	0.99
BW (kg)	-0.4 ± 0.9	-3.3 ± 1.7	0.17	0.57
Body fat (kg)	0.1 ± 0.5	-0.6 ± 0.6	0.37	0.36
Body fat (%)	0.3 ± 0.4	-0.2 ± 0.5	0.55	0.24
LBM (kg)	-0.5 ± 0.7	-2.7 ± 1.3	0.18	0.55
LBM (%)	-0.3 ± 0.4	0.2 ± 0.5	0.55	0.24

Results are displayed as mean ± SEM, n = 12 males and n = 15 females
* Significance from independent samples t-test, significantly different with p value <0.05.

Table 4.5: Percent change in body composition in response to the mixed-mode training intervention

	Males	Females	*p* value	Cohens *d*
Waist Circumference	-5.2 ± 1.4	-1.2 ± 0.7	0.01*	1.03
BW	-0.3 ± 0.8	-3.6 ± 1.8	0.13	0.63
Body fat	0.2 ± 0.5	-0.6 ± 0.6	0.37	0.36
Body fat	0.9 ± 1.3	-0.2 ± 1.3	0.55	0.24
LBM	-0.6 ± 0.9	-5.2 ± 2.6	0.14	0.62
LBM	-0.4 ± 0.6	0.3 ± 0.9	0.55	0.24

Results are displayed as mean ± SEM, n = 12 males and n = 15 females
* Significance from independent samples t-test, significantly different with p value <0.05.

4.5 Fitness outcomes

Fitness outcomes before and after training are presented in Table 4.6. $\dot{V}O_{2max}$relative to BW was greater in males for a main effect of sex ($p=0.03$, $\eta_p^2=0.09$) with a medium effect size and increased following training ($p=0.03$, $\eta_p^2=0.09$) with a medium effect size. There was no difference in response between males and females for the sex x training interaction ($p=0.73$, $\eta_p^2 \geq 0.00$). When expressed relative to LBM, there was no difference in $\dot{V}O_{2max}$ between the sexes ($p=0.88$, $\eta_p^2 \geq 0.00$) and $\dot{V}O_{2max}$ was higher following training ($p=0.02$, $\eta_p^2=0.11$) with a medium effect size. There were also no difference in the response to training for $\dot{V}O_{2max}$ relative to LBM between males and females ($p=0.96$, $\eta_p^2 \geq 0.00$). There were main effects of sex ($p<0.001$, $\eta_p^2 \geq 0.19$) and training ($p<0.02$, $\eta_p^2 \geq 0.10$) on absolute strength for all exercises with large effect sizes for sex and at least a medium effect size for training. There was no sex x

training interaction for absolute strength for any of the exercises ($p>0.05$, $\eta_p^2 \leq 0.02$).There was a difference in relative strength between males and females for chest press, leg extension, lat pulldown, hamstring curl and shoulder press ($p<0.02$, $\eta_p^2 \geq 0.11$) with at least a medium effect size, but no difference between the sexes for leg press ($p=0.12$, $\eta_p^2 \geq 0.05$) despite having a medium effect size. Relative strength increased following training for all exercises ($p<0.005$, $\eta_p^2 \geq 0.10$) with at least a medium effect size. There was no sex x training interaction for relative strength for any of the exercises ($p>0.05$, $\eta_p^2 \leq 0.01$).

Table 4.6: Fitness measures

	Male		**Female**		***p* value**		
	Pre	**Post**	**Pre**	**Post**	**S**	**T**	**S*T**
$\dot{V}O_{2max}$ (ml/kgBW/min)	26.8 ± 1.5	31.0 ± 1.9	23.6 ± 1.5	26.8 ± 1.7	0.03*	0.03*	0.73
$\dot{V}O_{2max}$ (ml/kgLBM/min)	38.9 ± 1.7	45.0 ± 2.0	39.2 ± 2.4	45.5 ± 3.1	0.88	0.02*	0.96
1 RM strength (kg)							
Chest press	125.8 ± 12.8	145.6 ± 13.2	60.3 ± 4.0	82.5 ± 4.8	<0.0001*	0.02*	0.8
Leg extension	158.0 ± 11.0	226.7 ± 17.4	105.2 ± 4.9	158.7 ± 11.9	<0.0001*	<0.0001	0.5
Lat pulldown	144.8 ± 10.0	177.9 ± 12.9	95.0 ± 3.5	109.8 ± 5.6	<0.0001*	0.007*	0.2
Hamstring curl	111.1 ± 7.3	144.9 ± 8.9	78.4 ± 3.9	101.7 ± 3.7	<0.0001*	<0.0001*	0.38
Shoulder press	112.5 ± 12.2	142.9 ± 11.9	64.0 ± 2.7	82.2 ± 3.8	<0.0001*	0.005*	0.4
Leg press	391.2 ± 63.8	652.7 ± 79.8	260.6 ± 23.6	429.9 ± 37.0	0.001*	0.0002*	0.38
Relative 1 RM strength (kg/BW)							
Chest press	1.21 ± 0.11	1.40 ± 0.11	0.70 ± 0.05	1.00 ± 0.07	<0.0001*	0.005*	0.54
Leg extension	1.52 ± 0.09	2.19 ± 0.16	1.22 ± 0.05	1.91 ± 0.14	0.02*	<0.0001*	0.93
Lat pulldown	1.42 ± 0.11	1.73 ± 0.13	1.10 ± 0.04	1.33 ± 0.07	0.0002*	0.004*	0.61
Hamstring curl	1.08 ± 0.07	1.41 ± 0.09	0.91 ± 0.04	1.23 ± 0.05	0.008*	<0.0001*	0.94
Shoulder press	1.08 ± 0.11	1.38 ± 0.05	0.75 ± 0.04	1.00 ± 0.05	<0.0001*	0.001*	0.73
Leg press	3.64 ± 0.49	6.13 ± 0.57	3.02 ± 0.26	5.27 ± 0.53	0.12	<0.0001*	0.80

Results are displayed as mean ± SEM, n = 12 males and n = 15 females
* Significance from a 2-way mixed model ANOVA, significantly different with p value <0.05.

Absolute and percent change for each fitness outcome is reported in Tables 4.7 and 4.8 respectively. The absolute and percent change for $\dot{V}O_{2max}$ relative to BW ($p=0.29$, $d=0.42$ and $p=0.57$, $d=0.23$) and LBM ($p=0.90$, $d=0.05$ and $p=0.99$, $d=0.002$) were both not significantly different. There was no differences in the absolute change in strength for any exercise ($p>0.14$,

d<0.56). Despite being not significant, the absolute change in chest press strength had a medium effect (d=0.56) with the increase being greater in females than males. The percent change in chest press strength was greater in females than males (p=0.02, d=0.97) with a large effect size. There was no difference in percent change in strength for any other exercise (p>0.42, d<0.32).

Table 4.7: Absolute change in fitness outcomes in response to the mixed-mode training intervention

	Males	Females	*p* value	Cohens *d*
$\dot{V}O_{2max}$ (ml/kgBW/min)	4.3 ± 0.8	3.1 ± 1.7	0.29	0.42
$\dot{V}O_{2max}$ (ml/kgLBM/min)	6.1 ± 1.2	6.4 ± 1.5	0.90	0.05
Relative strength (kg/BW)				
Chest press	0.19 ± 0.04	0.30 ± 0.06	0.17	0.56
Leg extension	0.67 ± 0.13	0.69 ± 0.14	0.92	0.04
Lat pulldown	0.31 ± 0.08	0.22 ± 0.05	0.32	0.38
Hamstring curl	0.34 ± 0.04	0.33 ± 0.04	0.87	0.06
Shoulder press	0.30 ± 0.05	0.25 ± 0.05	0.42	0.32
Leg press	2.49 ± 0.44	2.26 ± 0.36	0.68	0.16

Results are displayed as mean ± SEM, n = 12 males and n = 15 females
* Significance from independent samples t-test, significantly different with p value <0.05.

Table 4.8: Percent change in fitness outcomes in response to the mixed-mode training intervention

	Males	Females	*p* value	Cohens *d*
$\dot{V}O_{2max}$ relative to BW	16.1 ± 2.7	13.6 ± 3.2	0.57	0.23
$\dot{V}O_{2max}$ relative to LBM	16.2 ± 1.2	16.2 ± 3.7	0.99	0.002
Relative strength				
Chest press	18.64 ± 4.25	47.21 ± 10.05	0.02*	0.97
Leg extension	45.74 ± 9.24	58.29 ± 11.94	0.43	0.32
Lat pulldown	23.78 ± 5.60	20.51 ± 4.86	0.66	0.17
Hamstring curl	32.08 ± 4.96	37.18 ± 4.99	0.47	0.29
Shoulder press	31.73 ± 5.08	35.81 ± 7.08	0.66	0.18
Leg press	91.36 ± 24.09	76.14 ± 36.89	0.68	0.24

Results are displayed as mean ± SEM, n = 12 males and n = 15 females
* Significance from independent samples t-test, significantly different with p value <0.05.

4.6 Glycemic control

Glycemic control results are reported in Table 4.9. The percentage of HbA1C did not differ between males and females (p=0.40, η_p^2=0.02), was not influenced by training (p=0.45,

η_p^2=0.01) and the responses to training did not differ between males and females (sex x time interaction, p=0.94, $\eta_p^2 \geq 0.00$). Glucose concentrations during the OGTT are reported in Figure 4.4 and this data was used to calculate indices of glycemic control and insulin sensitivity as described below. Due to the fact that glycaemia during an OGTT is influenced by body anthropometrics and these body anthropometrics differ between males and female, Figure 4.4 also shows the glucose concentrations during the OGTT when the data are adjusted for the glucose dose relative to 1) BW, 2) LBM and 3) height.

Glucose AUC did not differ between males and females (p=0.22, η_p^2=0.03), did not change following the intervention (p=0.80, $\eta_p^2 \geq 0.00$) and there was no difference in how males and females responded to the training (p=0.18, η_p^2=0.04). When glucose AUC was adjusted for glucose dose relative to BW, there was no main effect of sex (p=0.12, η_p^2=0.05) or training (p=0.61, η_p^2=0.01) and no sex x training interaction (p=0.39, η_p^2=0.02). When glucose AUC was adjusted for glucose dose relative to LBM, there was a large main effect of sex (p=0.002, η_p^2=0.18) with males having a higher glucose AUC during the OGTT compared with females. There was no main effect of training (p=0.64, η_p^2=0.01) and no sex x training interaction (p=0.34, η_p^2=0.02). When glucose AUC was adjusted for dose relative to height, there was no main effect of sex (p=0.60, η_p^2=0.01) or training (p=0.77, $\eta_p^2 \geq 0.00$) and no sex x training interaction (p=0.15, η_p^2=0.04). The maximum glucose concentration during the OGTT (C_{max}) and its respective time (T_{max}) were determined for all participants. For glucose C_{max}, there was no significant effect of sex (p=0.14, η_p^2=0.03) or training (p=0.80, $\eta_p^2 \geq 0.00$) and no sex x training interaction (p=0.23, η_p^2=0.03). When glucose C_{max} was adjusted for glucose dose relative to BW, there was no effect of sex (p=0.11, η_p^2=0.05) or training (p=0.79, $\eta_p^2 \geq 0.00$) and no sex x training interaction (p=0.47, η_p^2=0.01). When glucose C_{max} was adjusted for dose relative to LBM, there

was a large main effect of sex ($p=0.001$, $\eta_p^2=0.19$) with males having higher maximal glucose concentration during an OGTT compared with females. There was no main effect of training ($p=0.65$, $\eta_p^2 \geq 0.00$) and no sex x training interaction ($p=0.44$, $\eta_p^2=0.01$). When glucose C_{max} was adjusted for dose relative to height, there was no main effect of sex ($p=0.30$, $\eta_p^2=0.02$) or training ($p=0.86$, $\eta_p^2 \geq 0.00$) and no sex x training interaction ($p=0.10$, $\eta_p^2=0.06$). While not statistically significant, there was a medium effect size for the sex x training interaction of glucose C_{max} when adjusted for dose relative to height. For glucose $T_{max,}$ there was no main effect of sex ($p=0.25$, $\eta_p^2=0.03$) or training ($p=0.11$, $\eta_p^2=0.05$) and no sex x training interaction ($p=0.77$, $\eta_p^2 \geq 0.00$).

Insulin AUC during the OGTT was not influenced by sex ($p=0.77$, $\eta_p^2 \geq 0.00$) or training ($p=0.82$, $\eta_p^2 \geq 0.00$) and there was no sex x time interaction ($p=0.51$, $\eta_p^2=0.01$). For insulin C_{max}, there was no main effect of sex ($p=0.44$, $\eta_p^2=0.01$), or training ($p=0.62$, $\eta_p^2=0.01$) and no sex x training interaction ($p=0.51$, $\eta_p^2=0.01$). For insulin $T_{max,}$ there was no main effect of sex ($p=0.82$, $\eta_p^2 \geq 0.00$) or training ($p=0.89$, $\eta_p^2 \geq 0.00$) and no sex x training interaction ($p=0.49$, $\eta_p^2=0.01$).

Table 4.9: Measures of glycemic control

	Male		Female		*p* value		
	Pre	**Post**	**Pre**	**Post**	**S**	**T**	**S*T**
HbA1C (%)	4.8 ± 0.1	4.8 ± 0.1	4.9 ± 0.1	4.8 ± 0.1	0.40	0.45	0.94
Glucose AUC (mmol/L · 120min)	931.6 ± 48.3	831.8 ± 43.3	926.0 ± 63.4	984.3 ± 68.2	0.22	0.80	0.18
Glucose AUC (mmol/L · 120min) by dose/BW	1,1339.7 ± 171.6	1,174.9 ± 126.9	1,073.0 ± 67.3	1,100.9 ± 87.2	0.12	0.61	0.39
Glucose AUC (mmol/L · 120min) by dose/LBM	894.8 ± 90.9	784.5 ± 64.6	643.2 ± 40.1	648.8 ± 51.4	0.002*	0.46	0.34
Glucose AUC (mmol/L · 120min) by dose/height	21.7 ± 1.1	19.4 ± 0.9	20.6 ± 1.4	21.9 ± 1.6	0.60	0.77	0.15
Glucose C_{max} (mmol/L)	9.6 ± 0.5	9.0 ± 0.5	9.8 ± 0.6	10.5 ± 0.6	0.14	0.82	0.23
Glucose C_{max} (mmol/L) by dose/BW	13.9 ± 1.7	12.7 ± 1.3	11.4 ± 0.6	11.80 ± 0.7	0.11	0.79	0.47
Glucose C_{max} (mmol/L) by dose/LBM	9.2 ± 0.9	8.5 ± 0.7	6.8 ± 0.4	7.0 ± 0.4	0.001*	0.65	0.44
Glucose C_{max} (mmol/L) by dose/height	0.2 ± 0.01	0.2 ± 0.01	0.2 ± 0.01	0.2 ± 0.01	0.30	0.86	0.10
Glucose T_{max} (min)	49.2 ± 6.8	35.4 ± 3.2	55.4 ± 9.6	45.7 ± 6.7	0.25	0.11	0.77
Insulin C_{max} (mmol/L)	204.2 ± 11.1	185.3 ± 13.8	180.4 ± 16.9	183.6 ± 21.0	0.44	0.62	0.51
Insulin T_{max} (min)	72.5 ± 8.6	65.0 ± 8.9	64.6 ± 8.6	69.2 ± 7.4	0.82	0.89	0.49

Results are displayed as mean ± SEM, n = 12 males and n = 14 females

* Significance from a 2-way mixed model ANOVA, significantly different with p value <0.05.

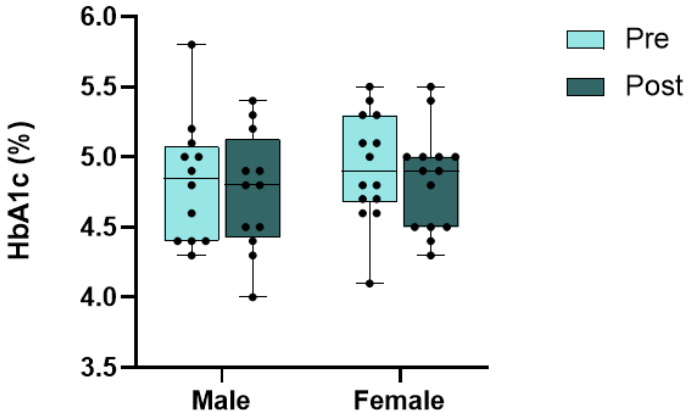

Figure 4.2: HbA1C values for males and females before and after the exercise intervention.

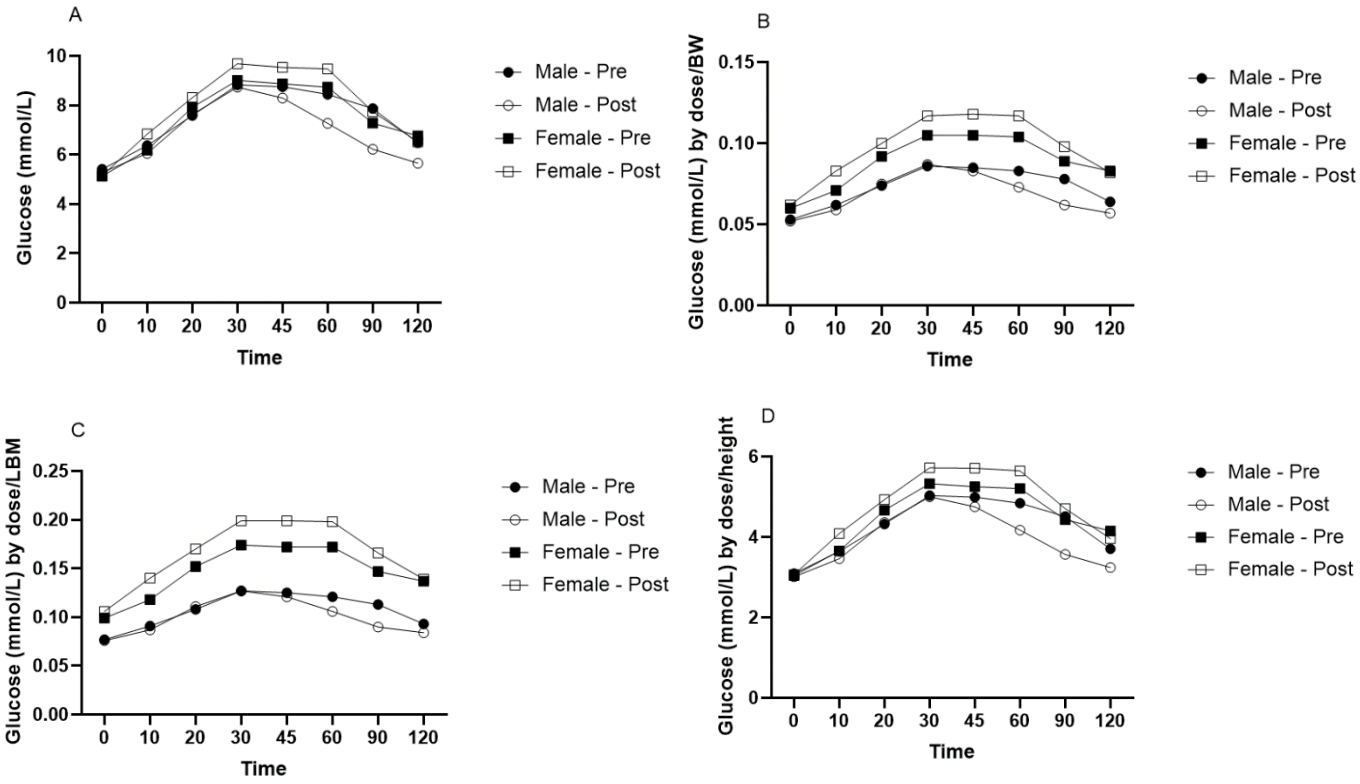

Figure 4.3: Glucose measures before and after the training intervention A) Glucose values during the OGTT, B) Glucose values during the OGTT adjusted for dose relative to BW, C) Glucose values during the OGTT adjusted for dose relative to LBM, D) Glucose values during the OGTT adjusted for dose relative to height.

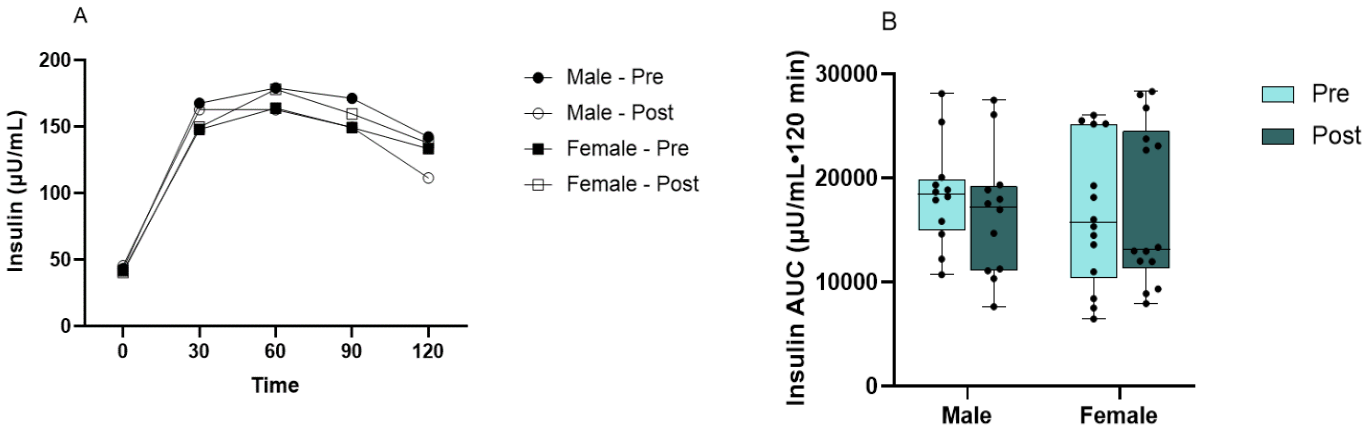

Figure 4.4: Insulin measures before and after the training intervention A) Insulin values during the OGTT, B) Insulin AUC during the OGTT.

Absolute and percent change for measures of glycemic control are reported in Tables 4.10 and 4.11 respectively. For glucose AUC, there was a significant difference in the absolute (p=0.01, d=1.06) and percent (p=0.01, d=1.10) change with a large effect size showing that glucose AUC decreased in males but increased in females following training. Similar results were found for the absolute and percent change in glucose AUC when adjusted for the glucose dose relative to BW (p=0.02, d=0.95; p=0.04, d=0.90, respectively) and the glucose dose relative to height (p=0.01, d=1.11; p=0.01, d=1.14, respectively). When adjusted for the dose relative to LBM the absolute change differed between males and females (p=0.02, d=0.96) indicating that it decreased in males and increased in females. While not significant, the percent change for glucose AUC when adjusted for the glucose dose relative to LBM there was a medium effect size (p=0.06, d=0.79) indicating that it decreased in males and increased in females.

For C_{max} there was a significant difference in the absolute (p=0.04, d=0.87) and percent (p=0.03, d=0.89) change with a large effect size indicating that C_{max} decreased in males and increased in females. Despite being not significant, when C_{max} was adjusted to the glucose dose relative to BW, there were medium effect sizes for the absolute (p=0.06, d=0.78) and percent (p=0.11, d=0.89) change showing that the value decreased for males but increased for females.

The same trend was seen when adjusted for LBM, as there were medium effect sizes for the absolute (p=0.08, d=0.73) and percent (p=0.18, d=0.57) change. When C_{max} was adjusted by dose relative to height, the absolute (p=0.001, d=1.13) and percent (p=0.001, d=1.13) changes were significantly different with a large effect size indicating that C_{max} decreased in males while it increased in females.

For insulin AUC, the results were not significant but the absolute (p=0.11, d=0.56) and percent (p=0.10, d=0.60) change had medium effect sizes indicating that insulin AUC decreased in males and increased in females. Lastly, there was a medium effect size for the percent change (p=0.18, d=0.53), but not the absolute change (p=0.41, d=0.33) in insulin C_{max} indicating that it decreased in males, but increased in females following training.

Table 4.10: Absolute change in measures of glycemic control in response to the mixed-mode training intervention

	Males	Females	*p* value	Cohens *d*
HbA1C (%)	-0.1 ± 0.2	-0.1 ± 0.1	0.92	0.07
Glucose AUC (mmol/L · 120min)	-99.8 ± 31.9	58.3 ± 52.1	0.01*	1.06
Glucose AUC (mmol/L · 120min) by dose/BW	-164.9 ± 58.0	33.9 ± 57.6	0.02*	0.95
Glucose AUC (mmol/L · 120min) by dose/LBM	-110.3 ± 34.5	9.6 ± 34.6	0.02*	0.96
Glucose AUC (mmol/L · 120min) by dose/height	-2.4 ± 0.8	1.3 ± 1.0	0.01*	1.11
Glucose C_{max} (mmol/L)	-0.60 ± 0.4	0.7 ± 0.4	0.04*	0.87
Glucose C_{max} (mmol/L) by dose/BW	-1.2 ± 0.6	0.5 ± 0.5	0.06	0.78
Glucose C_{max} (mmol/L) by dose/LBM	-0.8 ± 0.4	0.2 ± 0.3	0.08	0.73
Glucose C_{max} (mmol/L) by dose/height	-0.02 ± 0.01	0.02 ± 0.01	0.001*	1.13
Insulin AUC (mmol/L · 120min)	-1,722.3 ± 1,274.2	416.0 ± 885.7	0.11	0.56
Insulin C_{max} (mmol/L)	-18.9 ± 14.1	1.8 ± 7.1	0.18	0.53

Results are displayed as mean ± SEM, n = 12 males and n = 14 females

* Significance from independent samples t-test, significantly different with p value <0.05.

Table 4.11: Percent change in measures of glycemic control in response to the mixed-mode training intervention

	Males	Females	*p* value	Cohens *d*
HbA1C	-1.0 ± 0.2	-1.8 ± 2.3	0.88	0.08
Glucose AUC	-10.2 ± 3.1	7.9 ± 6.0	0.01*	1.10
Glucose AUC by dose/BW	-10.4 ± 3.1	3.5 ± 5.2	0.04*	0.90
Glucose AUC by dose/LBM	-10.9 ± 2.8	1.7 ± 5.5	0.06	0.79
Glucose AUC by dose/height	-10.2 ± 3.1	7.9 ± 5.3	0.01*	1.14
Glucose C_{max}	-5.6 ± 4.3	9.0 ± 4.8	0.03*	0.89
Glucose C_{max} by dose/BW	-6.1 ± 3.9	4.7 ± 4.9	0.11	0.67
Glucose C_{max} by dose/LBM	-6.5 ± 3.7	3.0 ± 5.4	0.17	0.57
Glucose C_{max} by dose/height	-10.1 ± 4.5	9.0 ± 4.8	0.001*	1.13
Insulin AUC	-9.0 ± 7.1	5.1 ± 6.5	0.10	0.60
Insulin C_{max}	-7.2 ± 7.2	-0.5 ± 4.1	0.41	0.33

Results are displayed as mean ± SEM, n = 12 males and n = 14 females
* Significance from independent samples t-test, significantly different with p value <0.05.

4.7 Indices of insulin sensitivity/resistance

The results for indices of insulin sensitivity/resistance are reported in Table 4.12. There was no main effect of sex (p=0.43, η_p^2=0.01) or training (p=0.86, $\eta_p^2 \geq 0.00$) and no sex x training interaction (p=0.93, $\eta_p^2 \geq 0.00$) for HOMA-IR. There was no main effect of sex (p=0.86, $\eta_p^2 \geq 0.00$) or training (p=0.65, $\eta_p^2 \geq 0.00$) and no sex x training interaction (p=0.72, $\eta_p^2 \geq 0.00$) for QUICKI. There was no main effect of sex (p=0.88, $\eta_p^2 \geq 0.00$) or training (p=0.53, η_p^2=0.01) and no sex x training interaction (p=0.95, $\eta_p^2 \geq 0.00$) for the Matsuda Index. There was no main effect of sex (p=0.93, $\eta_p^2 \geq 0.00$) or training (p=0.72, $\eta_p^2 \geq 0.00$), and no sex x training interaction (p=0.97, $\eta_p^2 \geq 0.00$) for the Stumvoll index when demographic information was not included in the equation. Similarly, there was no main effect of sex (p=0.56, η_p=0.01) or training (p=0.39, η_p^2=0.02) and no sex x training interaction (p=0.64, η_p^2=0.01) for the Stumvoll index when

demographic information was included in the equation. There was no main effect of sex (p=0.23, η_p=0.03) or training (p=0.46, η_p^2=0.01) and no or sex x training interaction (p=0.72, $\eta_p^2 \geq$0.00) for the 2-h OGIS.

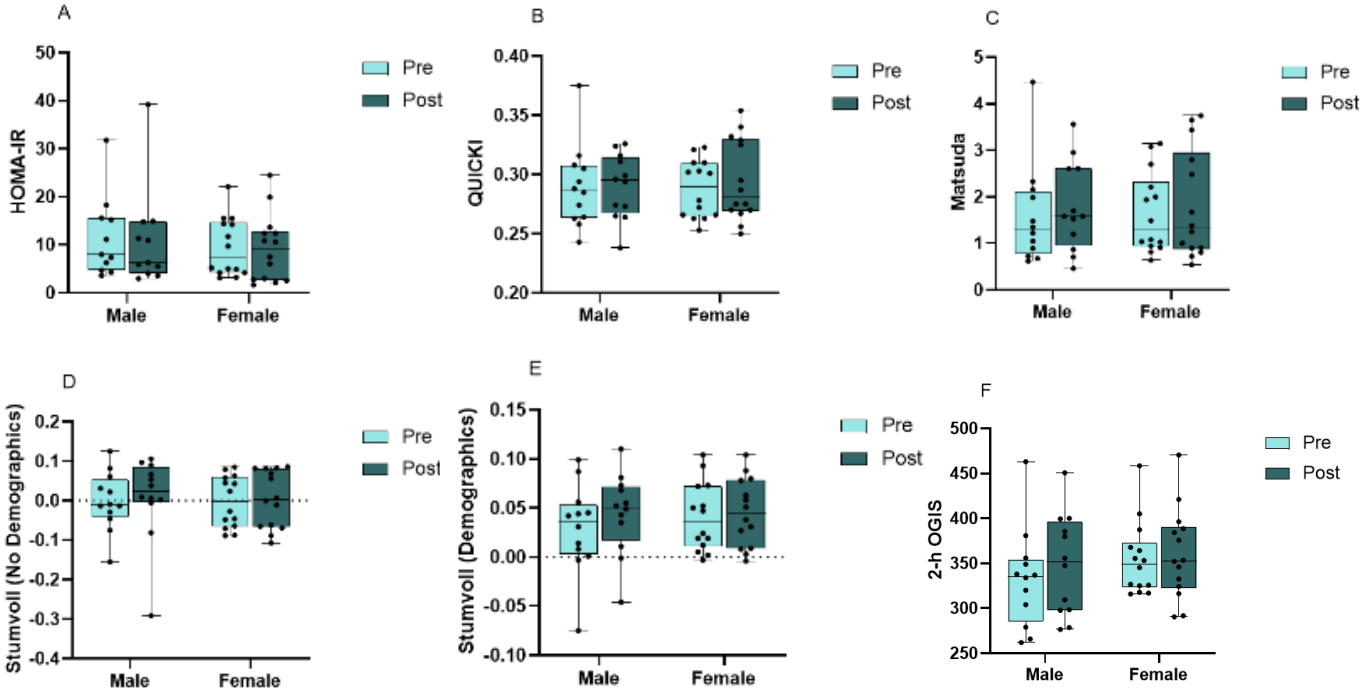

Figure 4.5: Indices of glycemic control before and after the training intervention A) HOMA-IR, B) QUICKI, C) Matsuda, D) Stumvoll equation without demographics, E) Stumvoll equation with demographics, E) 2-h OGIS.

The absolute and percent change for indices of insulin sensitivity/resistance are reported in Tables 4.12 and 4.13 respectively. There were no statistically significant differences in the absolute and percent change in these indices following the training intervention between males and females.

Table 4.12: Absolute change in indices of insulin sensitivity/resistance in response to the mixed-mode training intervention

	Males	Females	*p* value	Cohens *d*
HOMA-IR	-0.6 ± 0.9	-0.2 ± 0.6	0.72	0.14
QUICKI	0.0006 ± 0.01	0.0007 ± 0.01	0.36	0.37
Matsuda	0.2 ± 0.2	0.2 ± 0.12	0.88	0.06
Stumvoll (No demographics)	0.01 ± 0.02	0.01 ± 0.01	0.91	0.04
Stumvoll (Demographics)	0.02 ± 0.01	0.005 ± 0.01	0.37	0.37
2-h OGIS	15.8 ± 14.6	5.6 ± 12.5	0.60	0.21

Results are displayed as mean ± SEM, n = 12 males and n = 14 females
* Significance from independent samples t-test, significantly different with p value <0.05.

Table 4.13: Percent change in indices of insulin sensitivity/resistance in response to the mixed-mode training intervention

	Males	Females	*p* value	Cohens *d*
HOMA-IR	-10.9 ± 5.5	-7.7 ± 8.4	0.76	0.13
QUICKI	0.5 ± 1.4	2.2 ± 1.4	0.43	0.32
Matsuda	18.6 ± 8.7	5.5 ± 7.1	0.25	0.46
Stumvoll (No demographics)	-50.9 ± 50.5	11.2 ± 24.3	0.26	0.45
Stumvoll (Demographics)	432.0 ± 397.1	112.7 ± 82.0	0.40	0.32
2-h OGIS	5.7 ± 12.5	2.0 ± 3.4	0.50	0.27

Results are displayed as mean ± SEM, n = 12 males and n = 14 females
* Significance from independent samples t-test, significantly different with p value <0.05.

4.8 β-cell function

The results for indices of β-cell function are reported in Table 4.14. For glucose sensitivity there was no main effect of sex ($p=0.52$, $\eta_p^2=0.01$) or training ($p=0.54$, $\eta_p^2=0.01$) and no sex x training interaction ($p=0.09$, $\eta_p^2=0.06$); however, there was a medium effect size for the interaction. For rate sensitivity there was no main effect of sex ($p=0.50$, $\eta_p^2=0.02$) or training ($p=0.15$, $\eta_p^2=0.07$) and no sex x training interaction; however, there was a medium effect size for the interaction ($p=0.63$, $\eta_p^2=0.01$). For potentiation factor there was no main effect of sex ($p=0.64$, $\eta_p^2=0.01$) or training ($p=0.12$, $\eta_p^2=0.05$) and no sex x training interaction ($p=0.54$, $\eta_p^2=0.01$). For basal insulin secretion there was no main effect of sex ($p=0.46$, $\eta_p^2=0.01$) or

training ($p=0.79$, $\eta_p^2 \geq 0.00$) and no sex x training interaction ($p=0.64$, $\eta_p^2=0.01$). There was no main effect of sex ($p=0.94$, $\eta_p^2 \geq 0.00$) or training ($p=0.66$, $\eta_p^2 \geq 0.00$) and no sex x training interaction ($p=0.50$, $\eta_p^2=0.01$) for integral of total insulin secretion. There was no main effect of sex ($p=1.00$, $\eta_p^2 \geq 0.00$) or training ($p=0.67$, $\eta_p^2 \geq 0.00$) and no sex x training interaction ($p=0.49$, $\eta_p^2=0.01$) for basal insulin clearance. There was no main effect of sex ($p=0.25$, $\eta_p^2=0.03$) or training ($p=0.73$, $\eta_p^2 \geq 0.00$) and no sex x training interaction ($p=0.54$, $\eta_p^2=0.01$) for mean insulin clearance. For insulin secretion at 5 mmol/L, adjusted for basal potentiation there was no main effect of sex ($p=0.92$, $\eta_p^2 \geq 0.00$) or training ($p=0.68$, $\eta_p^2 \geq 0.00$) and no sex x training interaction ($p=0.44$, $\eta_p^2=0.01$). For insulin secretion at 5.5 mmol/L, adjusted for basal potentiation there was no main effect of sex ($p=0.98$, $\eta_p^2 \geq 0.00$) or training ($p=0.67$, $\eta_p^2 \geq 0.00$) and no sex x training interaction ($p=0.64$, $\eta_p^2=0.01$).

Table 4.14: Measures of B-cell Function

	Male		Female		*p* value		
	Pre	**Post**	**Pre**	**Post**	**S**	**T**	**S*T**
Glucose sensitivity ($pmol \cdot min^{-1} \cdot m^{-2} \cdot mmol^{-1} \cdot L$)	38.3 ± 5.6	58.6 ± 11.8	47.2 ± 8.4	39.1 ± 5.5	0.52	0.54	0.09
Rate sensitivity ($pmol \cdot min^{-2} \cdot mmol^{-1} \cdot L$)	861.2 ± 240.4	495.8 ± 121.4	648.9 ± 186.5	459.8 ± 156.9	0.50	0.15	0.63
Potentiation factor ratio	1.1 ± 0.05	1.3 ± 0.05	1.2 ± 0.07	1.3 ± 0.1	0.64	0.12	0.54
Basal insulin secretion ($pmol \cdot min^{-1} \cdot m^{-2}$)	213.1 ± 13.6	203.5 ± 15.7	198.0 ± 10.1	200.0 ± 10.6	0.46	0.79	0.64
Integral of total insulin secretion ($nmol \cdot m^{-2}$)	41.3 ± 1.3	40.9 ± 1.8	40.3 ± 1.2	41.7 ± 1.2	0.94	0.66	0.50
Basal insulin clearance ($L \cdot min^{-1} \cdot m^{-2}$)	1.5 ± 0.4	1.3 ± 0.3	1.2 ± 0.2	1.6 ± 0.4	1.00	0.67	0.49
Mean insulin clearance ($L \cdot min^{-1} \cdot m^{-2}$)	0.4 ± 0.03	0.5 ± 0.04	0.5 ± 0.07	0.5 ± 0.06	0.25	0.73	0.54
Insulin secretion at 5 mmol/L, adjusted for basal potentiation ($pmol \cdot min^{-1} \cdot m^{-2}$)	205.9 ± 14.1	188.4 ± 18.9	196.4 ± 11.8	200.9 ± 11.0	0.92	0.68	0.44
Insulin secretion at 5.5 mmol/L, adjusted for basal potentiation ($pmol \cdot min^{-1} \cdot m^{-2}$)	223.6 ± 14.5	210.9 ± 16.8	217.6 ± 11.7	217.8 ± 11.7	0.98	0.67	0.64

Results are displayed as mean ± SEM, n = 12 males and n = 14 females
* Significance from a 2-way mixed model ANOVA, significantly different with p value <0.05.

The absolute and percent change for measures of β-cell function are reported in Tables 4.15 and 4.16 respectively. The absolute change in glucose sensitivity (p=0.04, d=0.85) was significantly different between the sexes with a large effect size as it increased in males and decreased in females. The percent change for glucose sensitivity was not statistically significant

but was found to have a medium effect size (p=0.06, d=0.74) with the same trend as the absolute change. For basal insulin secretion, there was a non-significant medium effect size for the absolute (p=0.12, d=0.61) and percent (p=0.14, d=0.64) change indicating that they decreased in males and increased in females. When looking at the integral of total insulin secreted, there was a non-significant medium effect size for the absolute (p=0.17, d=0.54) and percent (p=0.16, d=0.57) change indicating that it decreased in males and increased in females. For basal insulin clearance, there was a non-significant medium effect size for the percent change (p=0.20, d=0.52) indicating that females increased to a greater extent compared to males. For mean insulin clearance, there was a medium effect size for the absolute change (p=0.22, d=0.50) that indicated males increased but females decreased. There was a significant difference in the percent change in the insulin secretion at 5 mmol/L, adjusted for basal potentiation (p=0.04, d=0.87) with a large effect size showing that it decreased in males but increased in females. The absolute change was not statistically different, however, there was a medium effect size (p=0.06, d=0.76) for the same trend.

Table 4.15: Absolute change in indices of β-cell function in response to the mixed-mode training intervention

	Males	Females	*p* value	Cohens *d*
Glucose sensitivity ($pmol \cdot min^{-1} \cdot m^{-2} \cdot mmol^{-1} \cdot L$)	20.3 ± 12.0	-8.1 ± 6.2	0.04*	0.85
Rate sensitivity ($pmol \cdot min^{-2} \cdot mmol^{-1} \cdot L$)	-365.4 ± 269.8	-189.0 ± 96.6	0.51	0.32
Potentiation factor ratio	0.2 ± 0.07	0.07 ± 0.09	0.44	0.31
Basal insulin secretion ($pmol \cdot min^{-1} \cdot m^{-2}$)	-9.6 ± 5.05	2.0 ± 5.5	0.14	0.61
Integral of total insulin secretion ($nmol \cdot m^{-2}$)	-0.4 ± 1.1	1.5 ± 0.8	0.17	0.54
Basal insulin clearance ($L \cdot min^{-1} \cdot m^{-2}$)	-0.1 ± 0.3	0.4 ± 0.2	0.22	0.49
Mean insulin clearance ($L \cdot min^{-1} \cdot m^{-2}$)	0.06 ± 0.03	-0.01 ± 0.04	0.22	0.50
Insulin secretion at 5 mmol/L, adjusted for basal potentiation ($pmol \cdot min^{-1} \cdot m^{-2}$)	-17.5 ± 9.1	4.4 ± 11.0	0.06	0.76
Insulin secretion at 5.5 mmol/L, adjusted for basal potentiation ($pmol \cdot min^{-1} \cdot m^{-2}$)	5.0 ± 8.5	0.2 ± 7.2	0.67	0.17

Results are displayed as mean ± SEM, n = 12 males and n = 14 females
* Significance from independent samples t-test, significantly different with p value <0.05.

Table 4.16: Percent change in indices of β-cell function in response to the mixed-mode training intervention

	Males	Females	*p* value	Cohens *d*
Glucose sensitivity	63.3 ± 36.1	-6.3 ± 11.9	0.06	0.74
Rate sensitivity	-22.0 ± 21.8	-26.3 ± 15.3	0.87	0.08
Potentiation factor ratio	17.1 ± 7.3	7.6 ± 6.9	0.36	0.37
Basal insulin secretion	-4.8 ± 2.5	1.1 ± 2.7	0.12	0.64
Integral of total insulin secretion	-1.0 ± 2.7	3.8 ± 2.0	0.16	0.57
Basal insulin clearance	3.2 ± 9.5	22.7 ± 11.0	0.20	0.52
Mean insulin clearance	14.6 ± 7.3	2.5 ± 7.6	0.27	0.48
Insulin secretion at 5 mmol/L, adjusted for basal potentiation	-9.7 ± 4.5	3.5 ± 4.0	0.04*	0.87
Insulin secretion at 5.5 mmol/L, adjusted for basal potentiation	2.9 ± 4.3	0.7 ± 3.3	0.68	0.16

Results are displayed as mean ± SEM, n = 12 males and n = 14 females
* Significance from independent samples t-test, significantly different with p value <0.05.

4.9 Plasma inflammatory markers

Plasma inflammatory markers prior to and following the training intervention are reported in Table 4.17. IL-1ra, TNF-α and MIP-1β were within range for the analysis but all other analytes were out of range and could not be analyzed in this study. There was no main effect of sex ($p=0.18$, $\eta_p^2=0.05$) or training ($p=0.75$, $\eta_p^2 \geq 0.00$) and no sex x training interaction ($p=0.26$, $\eta_p^2=0.04$) for IL-1ra. As for MIP-1β, there was a large, main effect of sex ($p=0.006$, $\eta_p^2=0.20$) with males having higher concentrations but no main effect of training ($p=0.65$, $\eta_p^2=0.01$) and no sex x training interaction ($p=0.34$, $\eta_p^2=0.03$). Finally for TNF-α, a large, effect of sex ($p=0.04$, $\eta_p^2=0.13$) was found indicating males had higher levels of TNF-α compared to females; however, no main effect of training ($p=0.63$, $\eta_p^2=0.01$) and no sex x training interaction ($p=0.90$, $\eta_p^2 \geq 0.00$) were found.

Table 4.17: Inflammatory markers

	Male		**Female**		***p* value**		
	Pre	**Post**	**Pre**	**Post**	**S**	**T**	**S*T**
IL-1ra (pg/mL)	136.4 ± 29.9	118.2 ± 21.2	84.3 ± 13.4	113.2 ± 15.7	0.18	0.75	0.26
MIP-1β (pg/mL)	21.8 ± 2.8	18.8 ± 1.2	13.8 ± 1.5	14.7 ± 1.8	0.006*	0.65	0.34
TNF-α (pg/mL)	7.9 ± 1.2	8.2 ± 0.9	5.4 ± 1.1	6.1 ± 1.0	0.04*	0.63	0.9

Results are displayed as mean ± SEM, n = 9 males and n = 10 females
* Significance from a 2-way mixed model ANOVA, significantly different with p value <0.05.

The absolute and percent change for inflammatory markers are reported in Tables 4.18 and 4.19 respectively. There was a statistical difference in the absolute change of IL-1ra between the sexes ($p=0.02$, $d=1.20$) with a large effect size indicating that it decreased in males while it increased in females. The percent change was not significantly different but still had a large effect size ($p=0.07$, $d=0.89$) for the same trend. As for MIP-1β, there were no statistical

differences in the absolute and percent change but the absolute change had a large effect size (p=0.10, d=0.81) and the percent change had a medium effect size (p=0.17, d=0.68) showing that it decreased in males while it increased in females. Finally for TNF-α, the percent change was not significantly different but there was a medium effect size (p=0.36, d=0.51) indicating that it increased to a greater extent in females.

Table 4.18: Absolute change in inflammatory markers in response to the mixed-mode training intervention

	Males	Females	*p* value	Cohens *d*
IL-1ra (pg/mL)	-18.2 ± 13.8	28.9 ± 12.3	0.02*	1.20
MIP-1β (pg/mL)	-3.0 ± 1.2	0.9 ± 1.9	0.10	0.81
TNF-α (pg/mL)	0.4 ± 0.4	0.7 ± 1.4	0.86	0.09

Results are displayed as mean ± SEM, n = 9 males and n = 10 females
* Significance from independent samples t-test, significantly different with p value <0.05.

Table 4.19: Percent change in inflammatory markers in response to the mixed-mode training intervention

	Males	Females	*p* value	Cohens *d*
IL-1ra	0.01 ± 11.6	50.0 ± 23.7	0.07	0.89
MIP-1β	-11.8 ± 4.1	18.0 ± 20.2	0.17	0.68
TNF-α	8.8 ± 6.7	157.1 ± 136.1	0.36	0.51

Results are displayed as mean ± SEM, n = 9 males and n = 10 females
* Significance from independent samples t-test, significantly different with p value <0.05.

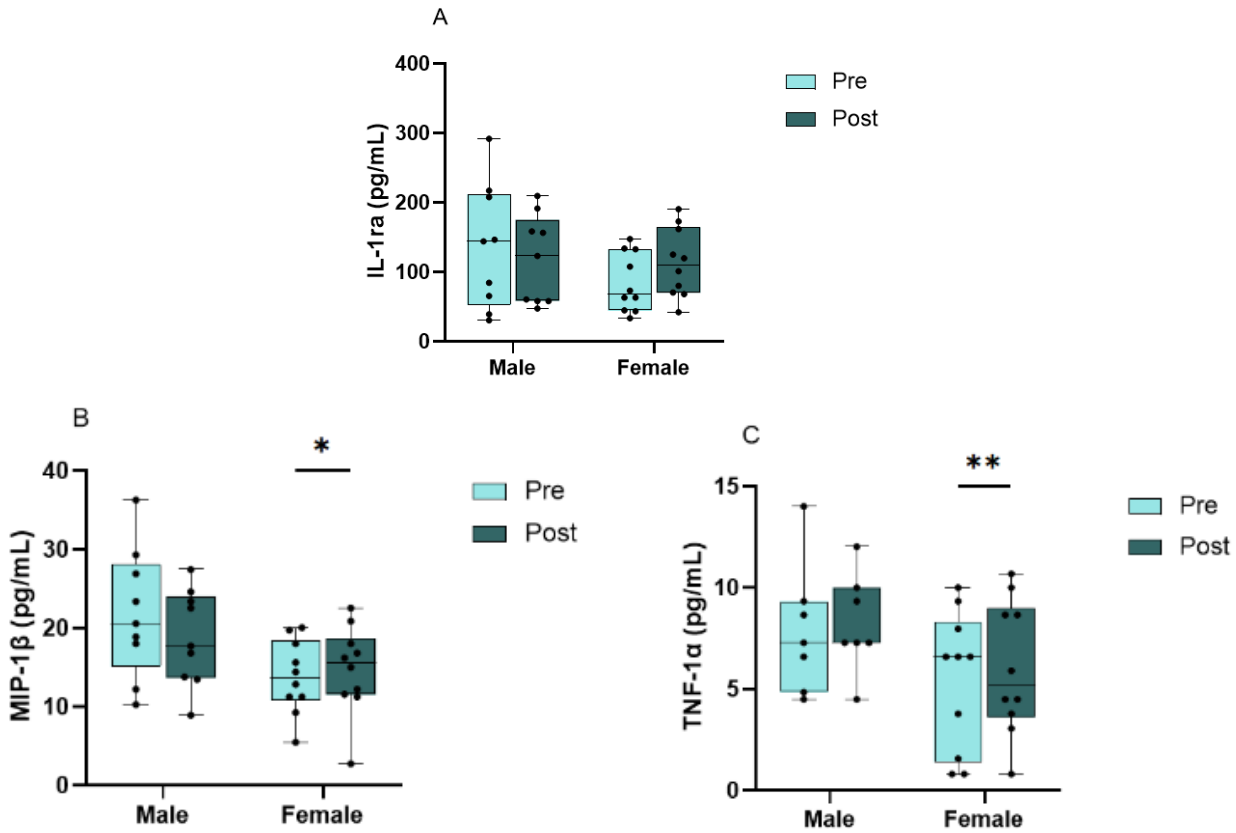

Figure 4.6: Inflammatory markers before and after the training intervention A) IL-1ra B) MIP-1β, * denotes significant main effect of sex (p=0.006, η_p^2=0.20), C) TNF-α, ** denotes significant main effect of sex (p=0.04, η_p^2=0.13).

Chapter 5: Discussion

The overarching goal of this clinical trial was to investigate the influence of biological sex on the effects of a 12-week, mixed mode training intervention on insulin sensitivity and glycemic control in overweight/obese, sedentary individuals. In addition, we looked at changes in β-cell function and inflammatory markers to create a better understanding of how sex may influence the improvement in insulin sensitivity following training. With respect to glycemic control, while we found no difference in glucose AUC and C_{max} between the sexes, sex differences were observed when the data were adjusted for glucose dose relative to LBM with males having higher glucose AUC and C_{max} compared to females. Further, the inflammatory markers TNF-α and MIP-1β were higher in males compared with females. Overall, training increased aerobic fitness and strength in both males and females; however, did not improve glycemic control, insulin sensitivity, pancreatic β-cell function or inflammation. The lack of effect of training on these parameters may be, at least in part, due to a differential effect of training on these outcomes (glycemic control, insulin sensitivity/resistance, beta cell function and inflammation) in males compared with females. In fact, we found that the absolute change in glucose AUC and C_{max} were statistically different between males and females with a large effect size indicating that these measures improved in males and worsened in females. Despite the differences in glycemic control during the OGTT, there were no sex differences or statistical differences in the changes following training for indices of insulin resistance/sensitivity. There was however, a difference in the improvement of glucose sensitivity as the absolute change was seen to increase in males by 20.3 $pmol \cdot min^{-1} \cdot m^{-2} \cdot mmol^{-1} \cdot L$ and decrease in females by 8.1 $pmol \cdot min^{-1} \cdot m^{-2} \cdot mmol^{-1} \cdot L$, which was reflected as a trend ($p=0.09$) for the sex x training interaction. Additionally, we found that the concentration of IL-1ra decreased by 18.2 pg/mL in

the males after training but increased by 28.9 pg/mL in females with a statistically significant difference in the absolute change. Similarly, while not statistically significant, there was a large effect size for there to be a differential response in the absolute change in MIP-1β between males and females (males: -3.0 pg/mL, females: +0.9 pg/mL).

Sex-based differences in glycemic control, insulin sensitivity, pancreatic β-cell function and inflammation

The primary objective of this study was to determine whether sex influenced the effect of mixed mode training on glycemic control and insulin sensitivity/resistance in overweight/obese males and females. While there was no difference in glucose AUC between males and females in response to a 75g dose of glucose, there was a clear sex-based difference in the glucose AUC and the glucose C_{max} values when adjusted for the glucose dose relative to LBM such that males were found to have a higher glucose AUC compared to females. These findings indicate that for a given amount of LBM, females had better glycemic control. These findings contradict a review done by Unwin et al. (2002) that stated that glucose tolerance in worse in females compared to males. However, this review did not consider the impact of anthropometric measures such as BW, LBM and height, which could have altered the conclusions being made. This is crucial as males have been shown to taller in stature and have a higher percentage of LBM compared to females, meaning that for the same weight, males would have a higher amount of metabolically active tissue available for glucose uptake. Using the standard dose of 75 g of glucose without adjusting for anthropometric measures could potentially cause females to be more frequently diagnosed with IFG compared to males. A study by Sicree et al. (2008) found that when height was used to adjust the values of fasting blood glucose and blood glucose during the 2 h OGTT, the fasting blood glucose values were not seen to significantly change however, the blood

glucose values at the 2 h mark were significantly different from the unadjusted values. Similarly, a paper by Palmu et al. (2021) found a negative association between body surface area and 2 h blood glucose concentration during an OGTT. This indicates that individuals who are smaller in stature (typically females) will have higher 2 h blood glucose levels, resulting in a misdiagnosis of a glucose disorder (Palmu et al., 2021). This can also be seen with procedures that use relative doses such as HEC and IVGTT. It was reported for females had better glycemic control during an HEC due to improved insulin-stimulated glucose disposal compared to males (Succurro et al., 2022) in addition to a higher glucose clearance rate in females compared to males during an IVGTT (Clausen et al., 1996). Together our findings and those of these previous trials indicate the need to adjust either the dose of glucose consumed or the measured glucose concentrations for body anthropometrics when comparing between the sexes in order to make accurate conclusions of the influence of sex on glycemic control.

With respect to indices of insulin sensitivity and resistance, there were no significant sex differences between the groups. This differs from the current literature as studies report that pre-menopausal females are more insulin sensitive than age-matched males (Greenhill, 2018; Tramunt et al., 2020; Varlamov et al., 2015). A potential reason for these results conflicting with current literature could be the small sample sized used in the current trial as insulin sensitivity can vary substantially between individuals, specifically with age, and the small sample size could have led to the lack of a statistical significance. A power calculation was done on HOMA-IR and 2-h OGIS values (Appendix 5) and it was concluded that this study was not powered enough to detect differences. Another possible reason could be due to the fitness status of each group when assessing sex differences in insulin sensitivity/resistance. The review by Tramunt et al. (2020) only took into account age when making conclusions about sex differences in insulin resistance.

To recall the trials of Samjoo et al. (2013) and Devries et al. (2008), the male participants in the Samjoo trial were more trained compared to the females in the Devries trial, yet were more insulin resistant at baseline. Therefore, making conclusions regarding sex differences in insulin sensitivity without considering whether the males and females had a similar level of fitness could affect the validity of the results. In a review by Lundsgaard & Kiens (2014) that specifically looked at the sex differences in insulin sensitivity while taking it account matched characteristics, specifically fitness, they reported that when males and females were only matched for BMI and age, a 2:6 ratio of trials concluded females had a greater level of insulin sensitivity compared to males. However, when the matching criteria included aerobic fitness relative to BW/LBM, this ratio changed to 4:3 ratio, favoring the conclusion that females are more insulin sensitive compared to males. These studies show that there is varying research regarding sex differences in insulin sensitivity and we require additional trials that match for baseline characteristics, specifically fitness, in order to make accurate conclusions.

We also did not observe a differences in measures of β-cell function between males and females whereas other trials have reported that females have greater β-cell function than males (Basu et al., 2006; Brownrigg et al., 2022). Specifically, Brownrigg et al. (2022) found that *in vitro* female β-cells had a greater ability to release insulin in a glucose dependent manner under various physiological conditions, including endoplasmic reticulum stress which has been known to be involved in the inflammatory response (Chipurupalli et al., 2021). In addition, it was determined that there are sex differences in the gene expression of β-cells that cause males and females to respond differently with respect to transcriptional processes triggered by the development of T2D (Brownrigg et al., 2022). This coincides with reviews stating that estrogen could be contributing a protective effect on β-cell function in females (Louet et al., 2004),

specifically through the activation of the estrogen receptor which has been found to promote β-cell mass growth and survivability in rodent models (Bernal-Mizrachi et al., 2014). The lack of difference in β-cell function in the current trial could again be due to the relatively small sample size in the current trial or the fact that males and females were matched for fitness as training status is also known to benefit β-cell function (Curran et al., 2020). Our findings are in line with the work of Beaudry et al. (2022) who found no difference in β-cell function between males and females when matched for aerobic fitness. However, in that trial, males and females were young and healthy and thus β-cell function may have been optimal. Further work examining sex-based differences in β-cell function involving larger sample sizes and controlling for fitness status is required to make clear conclusions.

The analysis of inflammatory markers between the sexes is crucial as they have direct impact on glycemic control, insulin sensitivity and β-cell function. TNF-α and MIP-1β were found to be higher in males compared to females. There has been a link determined between estrogen levels and its effects on decreasing transcriptional activity of the TNF-α (An et al., 1999) indicating a possible explanation as to why females have lower levels of this cytokine compared to males. When looking at the influence of TNF-α on glycemic control, studies have shown its influence on glucose uptake through GLUT4 translocation both in cell culture and *in vivo* in human participants (Ciaraldi et al., 1998; Roher et al., 2008). Together, the higher TNF-α in males found in the current trial may provide mechanistic insight into how females, for a given amount of LBM, have better glycemic control. MIP-1β is a pro-inflammatory cytokine and has been shown to be upregulated in patients with IGT and further, elevated with T2D (Chang et al., 2019) indicating its influence on insulin resistance. MIP-1β release from adipocytes is elevated in individuals with obesity and the cytokine is able to trigger elevated levels of TNF-α and IL-6,

further contributing to the development of insulin resistance (Rehman & Akash, 2016). With respect to sex differences, there is little research on the impact of biological sex on MIP-1β and further research is required to further this area. The understanding that males are more likely to develop T2D could assist with the consolidation of this data as males were found to have higher concentrations of MIP-1β compared to females. However, despite males having a higher concentration of both MIP-1β and TNF-α, there were no significant differences in the indices of insulin resistance and sensitivity between the sexes indicating the lack of direct influence of these cytokines on sex differences in insulin resistance.

The influence of sex on the effects of mixed mode training on glycemic control, insulin sensitivity, pancreatic β-cell function and inflammation

The main objective of this trial was to examine the influence of sex on the effects of mixed mode training on glycemic control and insulin resistance. The interaction of sex x training did not reach significance for any measure, however, further analysis of absolute and percent change was done to see if the changes induced by training differed between the sexes. The absolute and percent change for glucose AUC and glucose C_{max} differed between males and females (improving in males and worsening in females). When looking at the insulin data, there was a non-significant difference in the absolute and percent change in insulin AUC and insulin C_{max} (improving in males and worsening in females). Despite these differences, there was no difference in the absolute and percent change of any of the indices of insulin resistance/sensitivity between males and females. It is possible for glucose and/or insulin values to improve in the fasted state and/or during an OGTT and not translate to improvements in indices of insulin resistance/sensitivity as these indices take into account numerous variables (including demographic variables). Our findings are in line with previously published work by

Gillen et al. (2014) in which the 24-hour glucose AUC improved following 6-weeks of SIT in males but did not change in females. However, in the Gillen study, HOMA-IR improved similarly in males and females, whereas our trial did not find an improvement in indices of insulin sensitivity/resistance. With respect to insulin AUC, our results are similar to Potteiger et al. (2003) who found insulin AUC during a 2 h OGTT improved in males, but not females, following 16-months of aerobic training. The difference in insulin AUC was only found at the 16-month mark which makes it difficult to directly compare to this trial as the exercise intervention was only 3 months; however, this suggests that perhaps as training during lengthens, and the difference between the sexes in the effect of training on insulin may be further amplified. Our findings did differ from the findings of other trials (Metcalfe et al., 2012; Søgaard et al., 2018). The Metcalfe et al. (2012) study only found improvements in insulin sensitivity in males but not females, whereas our trial found no improvements in either sex. Furthermore, the Søgaard et al. (2018) trial found improvements in whole body insulin sensitivity in both sexes, but to a greater extent in males, and a sex x training interaction indicating that HbA1C decreased in males while it increased in females. The trials discussed above all had similar, but slightly different findings with respect to insulin sensitivity and glycemic control. A possible reason could have been the mode and duration of exercise as the Gillen, Metcalfe and Søgaard performed high intensity, low volume aerobic exercise under 10 minutes of total physical activity. The decreased duration and high intensity could have contributed to the differences in results. In addition, the Søgaard trial involved older adults as participants, which includes post-menopausal women who would have different sex hormone profiles compared to pre-menopausal women. The findings from this trial further support the hypothesis that exercise training influences glycemic control and insulin sensitivity differently in females compared with

males but a more standardized exercise intervention along with identical populations is required to accurately compare to the current literature.

We also found different effects of mixed mode exercise training on changes in β-cell function between males and females. The absolute change in glucose sensitivity was found to be significantly different between the sexes while the percent change was non-significant but showed a medium effect size. Regardless of the units of change, glucose sensitivity was found to have a differential response in males and females following training.Glucose sensitivity is negatively correlated with insulin resistance, further supporting the idea that exercise training improves glycemic control and insulin sensitivity to a greater extent in males than females. We also found that the percent change in insulin secreted at 5 mmol/L of glucose, adjusted for basal potentiation differed between the sexes, decreasing in males and increasing in females. This finding indicates that for the same glucose concentration, insulin secretion decreased in males and increased in females, indicating the potential for improved insulin sensitivity in males, but not females following training. While training has been found to improve β-cell function, to the best of our knowledge, no previous study has examined whether sex influences this response and further studies are required to confirm the findings of the current trial.

Examining the how sex influences the effects of exercise training on inflammatory markers can offer important mechanistic insight as to why glycemic control and insulin sensitivity have been found to improve to a greater extent in males than females following training. While not significant, there was a large effect size for the change in MIP-1β to be different between the sexes, decreasing in males and increasing in females. The differential effect of exercise training on MIP-1β indicating a decrease in males and an increase in females is in line with the findings of improved glycemic control in males in the current trial. As described

earlier, MIP-1β is a pro-inflammatory cytokine that induces the release of other pro-inflammatory cytokines including TNF-α and IL-6, both of which have been implicated in the pathogenesis of insulin resistance (Rehman & Akash, 2016). Thus, the decline in MIP-1β following training is a potential mechanism by which glycemic control and insulin sensitivity may improve. However, these findings are confounded by the finding that TNF-α did not improve in males following training. However, this may be due to the fact that the change in IL-1ra differed between the sexes, decreasing in males and increasing in females following training. The decrease in IL-1ra in males would remove inhibition on IL-1 signaling, which in turn induce TNF-α release (Pedersen & Febbraio, 2008). Together these findings highlight the importance of measuring multiple markers of inflammation when examining the effects of an intervention on overall inflammatory status. In the current trial, we measured additional cytokines (IL-1β, IL-1α, IL-6, IL-8 IL-10, IL-15); however, upon analysis these analytes were out of the detection range for the kit and could not be analyzed. Overall, there is conflicting information that can be concluded from this trial with regards to cytokines and further research is needed; however, these preliminary findings suggest that differences in the effects of training on inflammatory markers in males and females may be involved in the differential effect of training on glycemic control and insulin sensitivity.

The effects of mixed mode training on glycemic control, insulin sensitivity, pancreatic β-cell function and inflammation.

Following the completion of the 12-week exercise intervention, there were no effects of training on any outcomes relating to glycemic control, insulin sensitivity, pancreatic β-cell function and inflammation. Despite not reaching statistical significance, the rate sensitivity as a measure of β-cell function did have a medium effect size indicative of a decrease following the

training protocol. Rate sensitivity has been found to be inversely proportional to insulin sensitivity and has also been seen to be at lower levels in individuals with T2D (Jorge et al., 2011). Therefore, the decrease in rate sensitivity follow training could be a potential indicator of an improvement in insulin sensitivity and decreased risk of T2D. The lack of a significant effect of training on any of these measures is peculiar as a large majority of randomized controlled trials that include training interventions see changes in at least one of these measures. One of the reasons why the main effect of training was not detected could have been due to the differential response between males and females. Take the glucose AUC data for example, males were seen to decrease following training, but females were seen to increase. The responses in different directions would make it hard for the statistical analysis to detect an overall main effect of training.

In all participants, we found a clear effect of training on improving fitness outcomes, such as $\dot{V}O_{2max}$ relative to BW and LBM in addition to all 6 strength measures, following the 12 weeks of exercise. This indicates that the exercise protocol was followed correctly by participants and shows the direct impact training had on aerobic capacity and measures of strength. When compared to other studies, our trial was able to elicit greater improvements in fitness outcomes. A study by Jorge et al. (2011) only found an increase of 4.4% in $\dot{V}O_{2max}$ relative to BW whereas our trial was effective at improving this measure by 14.9%. The Jorge study was very comparable to our trial (3 x 60 minute sessions a week for 12 weeks, with the aerobic, resistance and mixed modes all performing identical volumes of exercise and included males and females) however they did not find the same level of improvement in fitness measures, which may be because they only included participants with T2D (Jorge et al., 2011). These findings confirm the notion that despite not seeing any main effects of training on

glycemic control, insulin sensitivity/resistance, beta cell function and inflammation, that the training intervention was sufficient to improve fitness. The lack of significant findings in the aforementioned outcomes could be attributed to the differential response induced by training in males and females as our trial was effective at improving fitness measures to greater extent than other trials with similar exercise interventions.

Strengths and Limitations

Trials can be set up with controlling as many variables as possible, however, there are always strengths and limitations to any research design. One strength of the trial was the effectiveness of the training intervention. Despite varying degrees of improvement in other primary outcomes, all fitness measures significantly improved following the 12-week intervention. This ensures that the exercise intervention was effective in improving fitness outcomes and the trial was run effectively. In addition, males and females were properly matched at baseline for BMI, LBM (%), initial aerobic fitness and habitual protein intake. This ensures that differences that were seen throughout the trial were due to the exercise intervention and not due to differences in baseline statistics. As well, all sessions were supervised to ensure participants were adhering to the training protocol and were completing the volume of exercise prescribed. Menstrual cycle was controlled during the trial to permit for sex based differences. Finally, diet was controlled for the OGTT procedure to ensure that diet consumed the day before the procedure did not alter the results of the OGTT. With respect to the limitations, a big limitation was the use of an OGTT instead of an HEC protocol as it is the gold standard for determining insulin sensitivity. Another limitation for this trial was the impact of individual differences in diet between participants as this could impact long term metabolic changes throughout the 3 months. For the OGTT, it could have been more effective to collect 3-5 days'

worth of diet prior to the procedure to account for variability. In addition, participants were instructed to keep their diet the same during the 3 months of exercise but research has shown that there is an increase in calories consumed with individuals who begin to exercise (Melzer et al., 2005; Snyder et al., 1997). A future modification could be the incorporation of a target calorie intake for participants to achieve during the trial to help mitigate any influences diet may have on the outcomes of this research. This trial solely looked at analytes within blood to make conclusions about insulin sensitivity however, it would have been more effective to examine the molecular effects of training on skeletal muscle through a muscle biopsy. Another limitation to this research could have been the timing of the cohorts. Due to lack of interest with recruitment, we were required to conduct 3 cohorts at different times. Ideally, all participants should have completed the 12 weeks of training at the same time to avoid any variations in times of the year that could impact the outcomes such as times of high stress from work, vacations over the weekends or holidays that could have altered diet. Finally, controlling for menstrual cycle during the mid to late follicular phase is effective however, it would be prudent to include comparisons during the luteal phase as both are included within a normal menstrual cycle and must be investigated to have a full understanding of the sex based differences.

Future Directions

A future direction could include a larger scale, sex difference based trial that separates experimental groups into a control, aerobic only, resistance only and mixed mode training. The volume of exercise should be comparable between the arms of the trial to ensure any changes seen are due to the modality and not due to variances in the volume of exercise. This would permit further comprehension of how each type of exercise affects metabolic measures compared to each other and the mixed mode. This type of research is lacking as most trials collapse sexes

in their comparisons which impede the ability to detect sex differences between modalities. In addition, having a standardized way of expressing exercise volume would be crucial for an accurate comparison of results concluded between the results. This area of exercise physiology has the potential to further tailor exercise prescription programs for individuals who are interested in improving specific health measures.

An additional area to investigate with this type of research would be the mechanistic impacts that sex has on the insulin signaling pathway following a training intervention. The use of muscle biopsies would be beneficial in analyzing changes in overall protein content of insulin signaling molecules in addition to activity of these molecules through the ratio of phosphorylated:unphosphorylated molecules. This could provide insight on the specific area on the pathway that is impacted by exercise and the extent of this change between sexes in order to assess the potential causes of this change (inflammation, oxidative stress etc.).

Another future direction for this area of research could be the investigation of administering oral glucose doses relative to specific body composition measures, specifically looking at the grams of glucose relative to absolute LBM of the individuals. As females have been found to have higher glucose clearance for relative doses, they are more likely to be falsely diagnosed with impaired glucose tolerance comparted to their male counterparts. Furthermore, this could create a discussion regarding the adjustment of cut off criteria for conclusions made using OGTT tests for clinical practice to improve the accuracy of care given to patients.

The use of biological males and females in this trial was done to investigate the presence of any type of sex differences in the general population, however, there are numerous individuals who have different sex hormonal profiles including females in various stage of menstrual cycle, individuals with sex chromosome abnormalities and trans individuals taking hormone

replacement therapies. The area of exercise physiology with respect to individuals that have different sex hormone profiles has not be well researched and would be interesting to see the changes in insulin sensitivity based on graded levels of sex hormones. This could provide information about minimum levels of a specific sex hormone or combination of sex hormones required to elicit a particular response not only with respect to preventing T2D but with other metabolic outcomes as well.

Conclusion

In conclusion, the data from the current study provides further evidence that the effects of exercise training on glycemic control are blunted in females compared with males, with novel data suggesting that the effect of training on pancreatic β-cell function is also blunted in females. Furthermore, our data suggests that the differences in the responses between males and females may be mediated by differential effects of training on inflammatory markers; however, further examination of additional cytokines is required before conclusions can be made. These differential responses after the training intervention with males improving and females worsening, further supports the need for research in females specifically and careful examinations of sex-based differences in exercise physiology, muscle metabolism and glycemic control in order to optimize the prevention and management of T2D in females. Furthermore, our data showing that glucose AUC and C_{max} are lower in females for a given amount of LBM highlights an important question related to the appropriateness of using a standard 75g glucose dose OGTT in for the diagnosis of IGT and T2D.

References

Abdul-Ghani, M. A., & DeFronzo, R. A. (2010). Pathogenesis of insulin resistance in skeletal muscle. *Journal of Biomedicine & Biotechnology, 2010*, 476279. https://doi.org/10.1155/2010/476279 [doi]

Adeva-Andany, M., Pérez-Felpete, N., Fernández-Fernández, C., Donapetry-García, C., & Pazos-García, C. (2016). Liver glucose metabolism in humans. *Bioscience Reports, 36*(6), e00416. https://doi.org/10.1042/BSR20160385

Adkins, A., Basu, R., Persson, M., Dicke, B., Shah, P., Vella, A., Schwenk, W. F., & Rizza, R. (2003). Higher insulin concentrations are required to suppress gluconeogenesis than glycogenolysis in nondiabetic humans. *Diabetes, 52*(9), 2213–2220. https://doi.org/10.2337/diabetes.52.9.2213 [doi]

Akash, M. S. H., Rehman, K., & Liaqat, A. (2018). Tumor Necrosis Factor-Alpha: Role in Development of Insulin Resistance and Pathogenesis of Type 2 Diabetes Mellitus. *Journal of Cellular Biochemistry*, *119*(1), 105–110. https://doi.org/https://doi.org/10.1002/jcb.26174

Al-Goblan, A., Al-Alfi, M., & Khan, M. Z. (2014). Mechanism linking diabetes mellitus and obesity. *Diabetes, Metabolic Syndrome and Obesity : Targets and Therapy*, *7*, 587–591. https://doi.org/10.2147/DMSO.S67400

Amador, M., Meza, C. A., McAinch, A. J., King, G. A., Covington, J. D., & Bajpeyi, S. (2020). Exercise-Induced Improvements in Insulin Sensitivity Are Not Attenuated by a Family History of Type 2 Diabetes. *Frontiers in Endocrinology*, *11*. https://www.frontiersin.org/articles/10.3389/fendo.2020.00120

Amin, M. N., El-Mowafy, M., Mobark, A., Abass, N., & Elgaml, A. (2021). Exercise-induced downregulation of serum interleukin-6 and tumor necrosis factor-alpha in Egyptian handball players. *Saudi Journal of Biological Sciences*, *28*(1), 724–730. https://doi.org/https://doi.org/10.1016/j.sjbs.2020.10.065

An, J., Ribeiro, R. C. J., Webb, P., Gustafsson, J.-Å., Kushner, P. J., Baxter, J. D., & Leitman, D. C. (1999). Estradiol repression of tumor necrosis factor-α transcription requires estrogen receptor activation function-2 and is enhanced by coactivators. *Proceedings of the National Academy of Sciences*, *96*(26), 15161–15166.

Arad, A. D., DiMenna, F. J., Thomas, N., Tamis-Holland, J., Weil, R., Geliebter, A., & Albu, J. B. (2015). High-intensity interval training without weight loss improves exercise but not basal or insulin-induced metabolism in overweight/obese African American women. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *119*(4), 352–362. https://doi.org/10.1152/japplphysiol.00306.2015 [doi]

Baum, K., Votteler, T., & Schiab, J. (2007). Efficiency of vibration exercise for glycemic control in type 2 diabetes patients. *International Journal of Medical Sciences*, *4*(3), 159–163. https://doi.org/jmsv04p0159 [pii]

Beaudry, K. M., & Devries, M. C. (2019). Sex-based differences in hepatic and skeletal muscle triglyceride storage and metabolism. *Applied Physiology, Nutrition, and Metabolism*, *44*(8), 805–813. https://doi.org/10.1139/apnm-2018-0635

Beaudry, K. M., Surdi, J. C., Mari, A., & Devries, M. C. (2022). Exercise mode influences post-exercise glucose sensitivity and insulin clearance in young, healthy males and females in a sex-dependent manner: A randomized control trial. *Physiological Reports*, *10*(13), e15354. https://doi.org/https://doi.org/10.14814/phy2.15354

Beaudry, K. M., Surdi, J. C., Wilkinson, J. A., & Devries, M. C. (2023). TBC1D1 Ser237 phosphorylation, but not insulin sensitivity, is higher following a bout of high-intensity interval exercise in healthy males as compared with females. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *324*(6), R720–R734. https://doi.org/10.1152/ajpregu.00281.2021

Bernardi, S., Toffoli, B., Tonon, F., Francica, M., Campagnolo, E., Ferretti, T., Comar, S., Giudici, F., Stenner, E., & Fabris, B. (2020). Sex Differences in Proatherogenic Cytokine Levels. *International Journal of Molecular Sciences*, *21*(11). https://doi.org/10.3390/ijms21113861

Bhasin, S., Pencina, M., Jasuja, G. K., Travison, T. G., Coviello, A., Orwoll, E., Wang, P. Y., Nielson, C., Wu, F., Tajar, A., Labrie, F., Vesper, H., Zhang, A., Ulloor, J., Singh, R., D'Agostino, R., & Vasan, R. S. (2011). Reference Ranges for Testosterone in Men Generated Using Liquid Chromatography Tandem Mass Spectrometry in a Community-Based Sample of Healthy Nonobese Young Men in the Framingham Heart Study and Applied to Three Geographically Distinct Cohorts. *The Journal of Clinical Endocrinology & Metabolism*, *96*(8), 2430–2439. https://doi.org/10.1210/jc.2010-3012

Bloor, I. D., & Symonds, M. E. (2014). Sexual dimorphism in white and brown adipose tissue with obesity and inflammation. *Hormones and Behavior*, *66*(1), 95–103. https://doi.org/https://doi.org/10.1016/j.yhbeh.2014.02.007

Bogdan, C., Paik, J., Vodovotz, Y., & Nathan, C. (1992). Contrasting mechanisms for suppression of macrophage cytokine release by transforming growth factor-beta and interleukin-10. *Journal of Biological Chemistry*, *267*(32), 23301–23308. https://doi.org/https://doi.org/10.1016/S0021-9258(18)50091-0

Braunstein, G. D., Reitz, R. E., Buch, A., Schnell, D., & Caulfield, M. P. (2011). Testosterone Reference Ranges in Normally Cycling Healthy Premenopausal Women. *The Journal of Sexual Medicine*, *8*(10), 2924–2934. https://doi.org/https://doi.org/10.1111/j.1743-6109.2011.02380.x

Brownrigg, G. P., Xia, Y. H., Chu, C. M. J., Wang, S., Chao, C., Zhang, J. A., Skovsø, S., Panzhinskiy, E., Hu, X., Johnson, J. D., & Rideout, E. J. (2022). Sex differences in islet stress responses support female beta cell resilience. *BioRxiv*, 2022.05.10.491428. https://doi.org/10.1101/2022.05.10.491428

Burhans, M. S., Hagman, D. K., Kuzma, J. N., Schmidt, K. A., & Kratz, M. (2018). Contribution of Adipose Tissue Inflammation to the Development of Type 2 Diabetes Mellitus. In *Comprehensive Physiology* (pp. 1–58). https://doi.org/https://doi.org/10.1002/cphy.c170040

Bweir, S., Al-Jarrah, M., Almalty, A. M., Maayah, M., Smirnova, I. V, Novikova, L., & Stehno-Bittel, L. (2009). Resistance exercise training lowers HbA1c more than aerobic training in adults with type 2 diabetes. *Diabetology & Metabolic Syndrome*, *1*, 27. https://doi.org/10.1186/1758-5996-1-27 [doi]

Cartier, A., Côté, M., Lemieux, I., Pérusse, L., Tremblay, A., Bouchard, C., & Després, J.-P. (2009). Sex differences in inflammatory markers: what is the contribution of visceral adiposity? *The American Journal of Clinical Nutrition*, *89*(5), 1307–1314. https://doi.org/10.3945/ajcn.2008.27030

Castaneda, C., Layne, J. E., Munoz-Orians, L., Gordon, P. L., Walsmith, J., Foldvari, M., Roubenoff, R., Tucker, K. L., & Nelson, M. E. (2002). A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. *Diabetes Care*, *25*(12), 2335–2341. https://doi.org/10.2337/diacare.25.12.2335 [doi]

Cederholm, J., & Wibell, L. (1990). Insulin release and peripheral sensitivity at the oral glucose tolerance test. *Diabetes Research and Clinical Practice*, *10*(2), 167–175. https://doi.org/10.1016/0168-8227(90)90040-Z

Centers for Disease Control and Prevention, (CDC). (2004). Prevalence of overweight and obesity among adults with diagnosed diabetes--United States, 1988-1994 and 1999-2002. *MMWR.Morbidity and Mortality Weekly Report*, *53*(45), 1066–1068. https://doi.org/mm5345a2 [pii]

Cerf, M. E. (2013). Beta cell dysfunction and insulin resistance. *Frontiers in Endocrinology*, *4*, 37. https://doi.org/10.3389/fendo.2013.00037

Chadt, A., & Al-Hasani, H. (2020). Glucose transporters in adipose tissue, liver, and skeletal muscle in metabolic health and disease. *Pflügers Archiv - European Journal of Physiology*, *472*(9), 1273–1298. https://doi.org/10.1007/s00424-020-02417-x

Chang, T.-T., Lin, L.-Y., & Chen, J.-W. (2019). Inhibition of macrophage inflammatory protein-1β improves endothelial progenitor cell function and ischemia-induced angiogenesis in diabetes. *Angiogenesis*, *22*(1), 53–65. https://doi.org/10.1007/s10456-018-9636-3

Chen, H., Sullivan, G., Yue, L. Q., Katz, A., & Quon, M. J. (2003). QUICKI is a useful index of insulin sensitivity in subjects with hypertension. *American Journal of Physiology.Endocrinology and Metabolism*, *284*(4), 804. https://doi.org/10.1152/ajpendo.00330.2002 [doi]

Chen, X., Li, X., Huang, H., Li, X., & Lin, J. (2006). [Effects of testosterone on insulin receptor substrate-1 and glucose transporter 4 expression in cells sensitive to insulin]. *Zhonghua yi xue za zhi*, *86*(21), 1474–1477. http://europepmc.org/abstract/MED/16842700

Cho, N. H., Shaw, J. E., Karuranga, S., Huang, Y., da Rocha Fernandes, J. D., Ohlrogge, A. W., & Malanda, B. (2018). IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Research and Clinical Practice*, *138*, 271–281. https://doi.org/https://doi.org/10.1016/j.diabres.2018.02.023

Church, T. S., Blair, S. N., Cocreham, S., Johannsen, N., Johnson, W., Kramer, K., Mikus, C. R., Myers, V., Nauta, M., Rodarte, R. Q., Sparks, L., Thompson, A., & Earnest, C. P. (2010). Effects of Aerobic and Resistance Training on Hemoglobin A1c Levels in Patients With Type 2 Diabetes : A Randomized Controlled Trial. *JAMA*, *304*(20), 2253–2262. https://doi.org/10.1001/jama.2010.1710

Ciaraldi, T. P., Carter, L., Mudaliar, S., Kern, P. A., & Henry, R. R. (1998). Effects of tumor necrosis factor-α on glucose metabolism in cultured human muscle cells from nondiabetic and type 2 diabetic subjects. *Endocrinology*, *139*(12), 4793–4800.

Clausen, J. O., Borch-Johnsen, K., Ibsen, H., Bergman, R. N., Hougaard, P., Winther, K., & Pedersen, O. (1996). Insulin sensitivity index, acute insulin response, and glucose effectiveness in a population-based sample of 380 young healthy Caucasians. Analysis of the impact of gender, body fat, physical fitness, and life-style factors. *The Journal of Clinical Investigation*, *98*(5), 1195–1209. https://doi.org/10.1172/JCI118903 [doi]

Colberg, S. R., Sigal, R. J., Fernhall, B., Regensteiner, J. G., Blissmer, B. J., Rubin, R. R., Chasan-Taber, L., Albright, A. L., Braun, B., American College of, S. M., & American, D. A. (2010). Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care*, *33*(12), e147–e167. https://doi.org/10.2337/dc10-9990

Colberg, S. R., Sigal, R. J., Fernhall, B., Regensteiner, J. G., Blissmer, B. J., Rubin, R. R., Chasan-Taber, L., Albright, A. L., Braun, B., Medicine, A. C. of S., & Association, A. D. (2010). Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care*, *33*(12), e147–e167. https://doi.org/10.2337/dc10-9990

Cusi, K., Maezono, K., Osman, A., Pendergrass, M., Patti, M. E., Pratipanawatr, T., DeFronzo, R. A., Kahn, C. R., & Mandarino, L. J. (2000). Insulin resistance differentially affects the PI 3-kinase- and MAP kinase-mediated signaling in human muscle. *The Journal of Clinical Investigation*, *105*(3), 311–320. https://doi.org/07535 [pii]

da Cruz Rodrigues, K. C., Martins Pereira, R., Peruca, G. F., Torres Barbosa, L. W., Ramos Sant'Ana, M., Rosetto Muñoz, V., Morelli, A. P., Moreira Simabuco, F., Sanchez Ramos da Silva, A., Esper Cintra, D., Rochete Ropelle, E., Pauli, J. R., & de Moura, L. P. (2021). Short-Term Strength Exercise Reduces Hepatic Insulin Resistance in Obese Mice by Reducing PTP1B Content, Regardless of Changes in Body Weight. *International Journal of Molecular Sciences*, *22*(12), 6402. doi: 10.3390/ijms22126402. https://doi.org/10.3390/ijms22126402 [doi]

Damirchi, A., Tehrani, B. S., Alamdari, K. A., & Babaei, P. (2014). Influence of aerobic training and detraining on serum BDNF, insulin resistance, and metabolic risk factors in middle-

aged men diagnosed with metabolic syndrome. *Clinical Journal of Sport Medicine : Official Journal of the Canadian Academy of Sport Medicine*, *24*(6), 513–518. https://doi.org/10.1097/JSM.0000000000000082 [doi]

de Alvaro, C., Teruel, T., Hernandez, R., & Lorenzo, M. (2004). Tumor Necrosis Factor α Produces Insulin Resistance in Skeletal Muscle by Activation of Inhibitor κB Kinase in a p38 MAPK-dependent Manner*. *Journal of Biological Chemistry*, *279*(17), 17070–17078. https://doi.org/https://doi.org/10.1074/jbc.M312021200

DeFronzo, R. A., Ferrannini, E., Groop, L., Henry, R. R., Herman, W. H., Holst, J. J., Hu, F. B., Kahn, C. R., Raz, I., Shulman, G. I., Simonson, D. C., Testa, M. A., & Weiss, R. (2015). Type 2 diabetes mellitus. *Nature Reviews Disease Primers*, *1*(1), 15019. https://doi.org/10.1038/nrdp.2015.19

De Paoli, M., Zakharia, A., & Werstuck, G. (2021). *The Role of Estrogen in Insulin Resistance*. *191*(9), 1490–1498. https://doi.org/10.1016/j.ajpath.2021.05.011

de Rooij, S. R., Nijpels, G., Nilsson, P. M., Nolan, J. J., Gabriel, R., Bobbioni-Harsch, E., Mingrone, G., Dekker, J. M., & Investigators, R. B. I. S. and C. D. (RISC). (2009). Low-grade chronic inflammation in the relationship between insulin sensitivity and cardiovascular disease (RISC) population: associations with insulin resistance and cardiometabolic risk profile. *Diabetes Care*, *32*(7), 1295–1301. https://doi.org/10.2337/dc08-1795 [doi]

de Salles, B., Simão, R., Fleck, S., Dias, I., Kraemer-Aguiar, L., & Bouskela, E. (2010). Effects of Resistance Training on Cytokines. *International Journal of Sports Medicine*, *31*, 441–450. https://doi.org/10.1055/s-0030-1251994

Devries, M. C., Hamadeh, M. J., Glover, A. W., Raha, S., Samjoo, I. A., & Tarnopolsky, M. A. (2008). Endurance training without weight loss lowers systemic, but not muscle, oxidative stress with no effect on inflammation in lean and obese women. *Free Radical Biology and Medicine*, *45*(4), 503–511. https://doi.org/https://doi.org/10.1016/j.freeradbiomed.2008.04.039

Devries, M. C., Hamadeh, M. J., Graham, T. E., & Tarnopolsky, M. A. (2005). 17β-Estradiol Supplementation Decreases Glucose Rate of Appearance and Disappearance with No Effect on Glycogen Utilization during Moderate Intensity Exercise in Men. *The Journal of Clinical Endocrinology & Metabolism*, *90*(11), 6218–6225. https://doi.org/10.1210/jc.2005-0926

Devries, M. C., Samjoo, I. A., Hamadeh, M. J., McCready, C., Raha, S., Watt, M. J., Steinberg, G. R., & Tarnopolsky, M. A. (2013). Endurance Training Modulates Intramyocellular Lipid Compartmentalization and Morphology in Skeletal Muscle of Lean and Obese Women. *The Journal of Clinical Endocrinology & Metabolism*, *98*(12), 4852–4862. https://doi.org/10.1210/jc.2013-2044

Donges, C. E., Duffield, R., & Drinkwater, E. J. (2010). Effects of Resistance or Aerobic Exercise Training on Interleukin-6, C-Reactive Protein, and Body Composition. *Medicine & Science in*

Sports & Exercise, *42*(2). https://journals.lww.com/acsm-msse/Fulltext/2010/02000/Effects_of_Resistance_or_Aerobic_Exercise_Training.12.aspx

Dorneles, G. P., Haddad, D. O., Fagundes, V. O., Vargas, B. K., Kloecker, A., Romão, P. R. T., & Peres, A. (2016). High intensity interval exercise decreases IL-8 and enhances the immunomodulatory cytokine interleukin-10 in lean and overweight–obese individuals. *Cytokine*, *77*, 1–9. https://doi.org/https://doi.org/10.1016/j.cyto.2015.10.003

El-Kader, S. M. A., & Al-Shreef, F. M. (2018). Inflammatory cytokines and immune system modulation by aerobic versus resisted exercise training for elderly. *Afr Helath Sci*, *18*(1).

Ellulu, M. S., Patimah, I., Khaza'ai, H., Rahmat, A., & Abed, Y. (2017). Obesity and inflammation: the linking mechanism and the complications. *Archives of Medical Science : AMS*, *13*(4), 851–863. https://doi.org/10.5114/aoms.2016.58928

Erdmann, J., Kallabis, B., Oppel, U., Sypchenko, O., Wagenpfeil, S., & Schusdziarra, V. (2008). Development of hyperinsulinemia and insulin resistance during the early stage of weight gain. *American Journal of Physiology-Endocrinology and Metabolism*, *294*(3), E568–E575. https://doi.org/10.1152/ajpendo.00560.2007

Ershler, W. B., & Keller, E. T. (2000). Age-Associated Increased Interleukin-6 Gene Expression, Late-Life Diseases, and Frailty. *Annual Review of Medicine*, *51*(1), 245–270. https://doi.org/10.1146/annurev.med.51.1.245

Esser, N., Legrand-Poels, S., Piette, J., Scheen, A. J., & Paquot, N. (2014). Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Research and Clinical Practice*, *105*(2), 141–150. https://doi.org/https://doi.org/10.1016/j.diabres.2014.04.006

Eves, N. D., & Plotnikoff, R. C. (2006). Resistance training and type 2 diabetes: Considerations for implementation at the population level. *Diabetes Care*, *29*(8), 1933–1941. https://doi.org/29/8/1933 [pii]

Fasshauer, M., & Paschke, R. (2003). Regulation of adipocytokines and insulin resistance. *Diabetologia*, *46*(12), 1594–1603. https://doi.org/10.1007/s00125-003-1228-z [doi]

Ferrannini, E., Gastaldelli, A., Miyazaki, Y., Matsuda, M., Mari, A., & DeFronzo, R. A. (2005). β-Cell Function in Subjects Spanning the Range from Normal Glucose Tolerance to Overt Diabetes: A New Analysis. *The Journal of Clinical Endocrinology & Metabolism*, *90*(1), 493–500. https://doi.org/10.1210/jc.2004-1133

Ferrari, F., Bock, P. M., Motta, M. T., & Helal, L. (2019). Biochemical and Molecular Mechanisms of Glucose Uptake Stimulated by Physical Exercise in Insulin Resistance State: Role of Inflammation. *Arquivos Brasileiros de Cardiologia*, *113*(6), 1139–1148. https://doi.org/10.5935/abc.20190224

Forti, L. N., Van Roie, E., Njemini, R., Coudyzer, W., Beyer, I., Delecluse, C., & Bautmans, I. (2017). Effects of resistance training at different loads on inflammatory markers in young adults.

European Journal of Applied Physiology, *117*(3), 511–519. https://doi.org/10.1007/s00421-017-3548-6

Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. (2020). Pathophysiology of Type 2 Diabetes Mellitus. *International Journal of Molecular Sciences*, *21*(17). https://doi.org/10.3390/ijms21176275

Geer, E. B., & Shen, W. (2009). Gender differences in insulin resistance, body composition, and energy balance. *Gender Medicine*, *6*, 60–75. https://doi.org/https://doi.org/10.1016/j.genm.2009.02.002

Gelaye, B., Revilla, L., Lopez, T., Suarez, L., Sanchez, S. E., Hevner, K., Fitzpatrick, A. L., & Williams, M. A. (2010). Association between insulin resistance and c-reactive protein among Peruvian adults. *Diabetology & Metabolic Syndrome*, *2*(1), 30. https://doi.org/10.1186/1758-5996-2-30

Gillen, J. B., Martin, B. J., MacInnis, M. J., Skelly, L. E., Tarnopolsky, M. A., & Gibala, M. J. (2016). Twelve Weeks of Sprint Interval Training Improves Indices of Cardiometabolic Health Similar to Traditional Endurance Training despite a Five-Fold Lower Exercise Volume and Time Commitment. *PloS One*, *11*(4), e0154075. https://doi.org/10.1371/journal.pone.0154075 [doi]

Gillen, J. B., Percival, M. E., Skelly, L. E., Martin, B. J., Tan, R. B., Tarnopolsky, M. A., & Gibala, M. J. (2014). Three Minutes of All-Out Intermittent Exercise per Week Increases Skeletal Muscle Oxidative Capacity and Improves Cardiometabolic Health. *PLOS ONE*, *9*(11), e111489. https://doi.org/10.1371/journal.pone.0111489

Gilliver, S. C. (2010). Sex steroids as inflammatory regulators. *The Journal of Steroid Biochemistry and Molecular Biology; Steroids: Modulators of Inflammation and Immunity*, *120*(2), 105–115. https://doi.org/https://doi.org/10.1016/j.jsbmb.2009.12.015

Giri, B., Dey, S., Das, T., Sarkar, M., Banerjee, J., & Dash, S. K. (2018). Chronic hyperglycemia mediated physiological alteration and metabolic distortion leads to organ dysfunction, infection, cancer progression and other pathophysiological consequences: An update on glucose toxicity. *Biomedicine & Pharmacotherapy*, *107*, 306–328. https://doi.org/https://doi.org/10.1016/j.biopha.2018.07.157

Gordon, B. A., Benson, A. C., Bird, S. R., & Fraser, S. F. (2009). Resistance training improves metabolic health in type 2 diabetes: A systematic review. *Diabetes Research and Clinical Practice*, *83*(2), 157–175. https://doi.org/https://doi.org/10.1016/j.diabres.2008.11.024

Grace, A., Chan, E., Giallauria, F., Graham, P. L., & Smart, N. A. (2017). Clinical outcomes and glycaemic responses to different aerobic exercise training intensities in type II diabetes: a systematic review and meta-analysis. *Cardiovascular Diabetology*, *16*(1), 37. https://doi.org/10.1186/s12933-017-0518-6

Greenhill, C. (2018). Sex differences in insulin resistance. *Nature Reviews Endocrinology*, *14*(2), 65. https://doi.org/10.1038/nrendo.2017.168

Gregory, J. M., Muldowney, J. A., Engelhardt, B. G., Tyree, R., Marks-Shulman, P., Silver, H. J., Donahue, E. P., Edgerton, D. S., & Winnick, J. J. (2019). Aerobic exercise training improves hepatic and muscle insulin sensitivity, but reduces splanchnic glucose uptake in obese humans with type 2 diabetes. *Nutrition & Diabetes*, *9*(1), 25.

Greising, S. M., Baltgalvis, K. A., Lowe, D. A., & Warren, G. L. (2009). Hormone therapy and skeletal muscle strength: a meta-analysis. *The Journals of Gerontology.Series A, Biological Sciences and Medical Sciences*, *64*(10), 1071–1081. https://doi.org/10.1093/gerona/glp082 [doi]

Gutch, M., Kumar, S., Razi, S. M., Gupta, K. K., & Gupta, A. (2015). Assessment of insulin sensitivity/resistance. *Indian Journal of Endocrinology and Metabolism*, *19*(1), 160–164. https://doi.org/10.4103/2230-8210.146874

Hatting, M., Tavares, C. D. J., Sharabi, K., Rines, A. K., & Puigserver, P. (2018). Insulin regulation of gluconeogenesis. *Annals of the New York Academy of Sciences*, *1411*(1), 21–35. https://doi.org/10.1111/nyas.13435

Hayashino, Y., Jackson, J. L., Hirata, T., Fukumori, N., Nakamura, F., Fukuhara, S., Tsujii, S., & Ishii, H. (2014). Effects of exercise on C-reactive protein, inflammatory cytokine and adipokine in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. *Metabolism: Clinical and Experimental*, *63*(3), 431–440. https://doi.org/S0026-0495(13)00397-1 [pii]

Henderson, V. W. (2018). Progesterone and human cognition. *Climacteric : The Journal of the International Menopause Society*, *21*(4), 333–340. https://doi.org/10.1080/13697137.2018.1476484 [doi]

Henquin, J.-C., Ishiyama, N., Nenquin, M., Ravier, M. A., & Jonas, J.-C. (2002). Signals and Pools Underlying Biphasic Insulin Secretion. *Diabetes*, *51*(suppl_1), S60–S67. https://doi.org/10.2337/diabetes.51.2007.S60

Holst, J. J., Gasbjerg, L. S., & Rosenkilde, M. M. (2021). The Role of Incretins on Insulin Function and Glucose Homeostasis. *Endocrinology*, *162*(7), bqab065. https://doi.org/10.1210/endocr/bqab065

Hong, A. R., & Kim, S. W. (2018). Effects of Resistance Exercise on Bone Health. *Endocrinology and Metabolism*, *33*(4).

Horstman, A. M., Dillon, E. L., Urban, R. J., & Sheffield-Moore, M. (2012). The role of androgens and estrogens on healthy aging and longevity. *The Journals of Gerontology.Series A, Biological Sciences and Medical Sciences*, *67*(11), 1140–1152. https://doi.org/10.1093/gerona/gls068

Houlden, R. L. (2022). *Introduction*. https://www.diabetes.ca/health-care-providers/clinical-practice-guidelines/chapter-1#panel-tab_FullText

Huang, M., & Joseph, J. W. (2014). Assessment of the Metabolic Pathways Associated With Glucose-Stimulated Biphasic Insulin Secretion. *Endocrinology*, *155*(5), 1653–1666. https://doi.org/10.1210/en.2013-1805

Hu, F. B., Manson, J. E., Stampfer, M. J., Colditz, G., Liu, S., Solomon, C. G., & Willett, W. C. (2001). Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *The New England Journal of Medicine*, *345*(11), 790–797. https://doi.org/10.1056/NEJMoa010492 [doi]

Jagannathan, R., Neves, J. S., Dorcely, B., Chung, S. T., Tamura, K., Rhee, M., & Bergman, M. (2020). The Oral Glucose Tolerance Test: 100 Years Later. *Diabetes, Metabolic Syndrome and Obesity : Targets and Therapy*, *13*, 3787–3805. https://doi.org/10.2147/DMSO.S246062 [doi]

Jensen, J., Rustad, P. I., Kolnes, A. J., & Lai, Y.-C. (2011). The role of skeletal muscle glycogen breakdown for regulation of insulin sensitivity by exercise. *Frontiers in Physiology*, *2*, 112. https://doi.org/10.3389/fphys.2011.00112

Jia, W. P., Pang, C., Chen, L., Bao, Y. Q., Lu, J. X., Lu, H. J., Tang, J. L., Wu, Y. M., Zuo, Y. H., Jiang, S. Y., & Xiang, K. S. (2007). Epidemiological characteristics of diabetes mellitus and impaired glucose regulation in a Chinese adult population: the Shanghai Diabetes Studies, a cross-sectional 3-year follow-up study in Shanghai urban communities. *Diabetologia*, *50*(2), 286–292. https://doi.org/10.1007/s00125-006-0503-1

Jiménez-Maldonado, A., Montero, S., Lemus, M., Cerna-Cortés, J., Rodríguez-Hernández, A., Mendoza, M. A., Melnikov, V., Gamboa-Domínguez, A., Muñiz, J., & Virgen-Ortiz, A. (2019). Moderate and high intensity chronic exercise reduces plasma tumor necrosis factor alpha and increases the Langerhans islet area in healthy rats. *Journal of Musculoskeletal & Neuronal Interactions*, *19*(3), 354.

Jornayvaz, F. R., & Shulman, G. I. (2012). Diacylglycerol activation of protein kinase Cε and hepatic insulin resistance. *Cell Metabolism*, *15*(5), 574–584. https://doi.org/10.1016/j.cmet.2012.03.005 [doi]

Kahn, S. E., Hull, R. L., & Utzschneider, K. M. (2006). Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*, *444*(7121), 840–846. https://doi.org/nature05482 [pii]

Kemnitz, J. W., Gibber, J. R., Lindsay, K. A., & Eisele, S. G. (1989). Effects of ovarian hormones on eating behaviors, body weight, and glucoregulation in rhesus monkeys. *Hormones and Behavior*, *23*(2), 235–250. https://doi.org/https://doi.org/10.1016/0018-506X(89)90064-0

Khalili, S., & Nouri, R. (2013). The Effect of Eight Weeks Resistance Training on Leptin and Insulin Resistance in Obese Female. *Avicenna J Clin Med*, *20*(1), 59–65. http://sjh.umsha.ac.ir/article-1-153-en.html

Khera, A., McGuire, D. K., Murphy, S. A., Stanek, H. G., Das, S. R., Vongpatanasin, W., Wians, F. H., Grundy, S. M., & de Lemos, J. A. (2005). Race and Gender Differences in C-Reactive Protein Levels. *Journal of the American College of Cardiology*, *46*(3), 464–469. https://doi.org/https://doi.org/10.1016/j.jacc.2005.04.051

Kim, J. J., & Sears, D. D. (2010). TLR4 and Insulin Resistance. *Gastroenterology Research and Practice, 2010*, 10.1155/2010/212563. Epub 2010 Aug 10. https://doi.org/212563 [pii]

Kim, J. K. (2009). Hyperinsulinemic-euglycemic clamp to assess insulin sensitivity in vivo. *Methods in Molecular Biology (Clifton, N.J.)*, *560*, 221–238. https://doi.org/10.1007/978-1-59745-448-3_15 [doi]

Kim, T. H., Choi, S. E., Ha, E. S., Jung, J. G., Han, S. J., Kim, H. J., Kim, D. J., Kang, Y., & Lee, K. W. (2013). IL-6 induction of TLR-4 gene expression via STAT3 has an effect on insulin resistance in human skeletal muscle. *Acta Diabetologica*, *50*(2), 189–200. https://doi.org/10.1007/s00592-011-0259-z

Kim, Y. J., Tamadon, A., Park, H. T., Kim, H., & Ku, S.-Y. (2016). The role of sex steroid hormones in the pathophysiology and treatment of sarcopenia. *Osteoporosis and Sarcopenia*, *2*(3), 140–155. https://doi.org/https://doi.org/10.1016/j.afos.2016.06.002

Klein, S. L., & Flanagan, K. L. (2016). Sex differences in immune responses. *Nature Reviews Immunology*, *16*(10), 626–638. https://doi.org/10.1038/nri.2016.90

Koh, H.-C. E., Cao, C., & Mittendorfer, B. (2022). Insulin Clearance in Obesity and Type 2 Diabetes. *International Journal of Molecular Sciences*, *23*(2), 596. https://doi.org/10.3390/ijms23020596

Krentz, A. J., Heinemann, L., & Hompesch, M. (2015). Methods for Quantifying Insulin Sensitivity and Determining Insulin Time-Action Profiles. In A. J. Krentz, L. Heinemann, & M. Hompesch (Eds.), *Translational Research Methods for Diabetes, Obesity and Cardiometabolic Drug Development: A Focus on Early Phase Clinical Studies* (pp. 3–43). Springer London. https://doi.org/10.1007/978-1-4471-4920-0_1

Kuhl, J., Hilding, A., Ostenson, C. G., Grill, V., Efendic, S., & Båvenholm, P. (2005). Characterisation of subjects with early abnormalities of glucose tolerance in the Stockholm Diabetes Prevention Programme: the impact of sex and type 2 diabetes heredity. *Diabetologia*, *48*(1), 35–40. https://doi.org/10.1007/s00125-004-1614-1 [doi]

Lakoski, S. G., Cushman, M., Criqui, M., Rundek, T., Blumenthal, R. S., D'Agostino, R. B., & Herrington, D. M. (2006). Gender and C-reactive protein: Data from the Multiethnic Study of Atherosclerosis (MESA) cohort. *American Heart Journal*, *152*(3), 593–598. https://doi.org/https://doi.org/10.1016/j.ahj.2006.02.015

Lauritzen, H. P. M. M. (2013). Insulin- and Contraction-Induced Glucose Transporter 4 Traffic in Muscle: Insights From a Novel Imaging Approach. *Exercise and Sport Sciences Reviews*, *41*(2). https://journals.lww.com/acsm-essr/Fulltext/2013/04000/Insulin__and_Contraction_Induced_Glucose.3.aspx

LeBlanc, A. G., Jun Gao, Y., McRae, L., & Pelletier, C. (2019). At-a-glance - Twenty years of diabetes surveillance using the Canadian Chronic Disease Surveillance System. *Health Promotion and Chronic Disease Prevention in Canada : Research, Policy and Practice*, *39*(11), 306–309. https://doi.org/10.24095/hpcdp.39.11.03

Lee, S., Deldin, A. R., White, D., Kim, Y., Libman, I., Rivera-Vega, M., Kuk, J. L., Sandoval, S., Boesch, C., & Arslanian, S. (2013). Aerobic exercise but not resistance exercise reduces

intrahepatic lipid content and visceral fat and improves insulin sensitivity in obese adolescent girls: a randomized controlled trial. *American Journal of Physiology-Endocrinology and Metabolism*, *305*(10), E1222–E1229. https://doi.org/10.1152/ajpendo.00285.2013

Lenters-Westra, E., Schindhelm, R. K., Bilo, H. J., Groenier, K. H., & Slingerland, R. J. (2014). Differences in interpretation of haemoglobin A1c values among diabetes care professionals. *Neth J Med*, *72*(9), 462–466.

Ley, S. H., Ardisson Korat, A. V, Sun, Q., Tobias, D. K., Zhang, C., Qi, L., Willett, W. C., Manson, J. E., & Hu, F. B. (2016). Contribution of the Nurses' Health Studies to Uncovering Risk Factors for Type 2 Diabetes: Diet, Lifestyle, Biomarkers, and Genetics. *American Journal of Public Health*, *106*(9), 1624–1630. https://doi.org/10.2105/AJPH.2016.303314

Lindheim, S. R., Buchanan, T. A., Duffy, D. M., Vijod, M. A., Kojima, T., Stanczyk, F. Z., & Lobo, R. A. (1994). Original ArticlesComparison of Estimates of Insulin Sensitivity in Pre- and Postmenopausal Women Using the Insulin Tolerance Test and the Frequently Sampled Intravenous Glucose Tolerance Test. *Journal of the Society for Gynecologic Investigation*, *1*(2), 150–154. https://doi.org/10.1177/107155769400100210

Lipscombe, L. L., & Hux, J. E. (2007). Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995–2005: a population-based study. *The Lancet*, *369*(9563), 750–756. https://doi.org/https://doi.org/10.1016/S0140-6736(07)60361-4

Li, Q., Wang, X., Ni, Y., Hao, H., Liu, Z., Wen, S., Shao, X., Wu, X., Yu, W., & Hu, W. (2019). Epidemiological characteristics and risk factors of T2DM in Chinese premenopausal and postmenopausal women. *Lipids in Health and Disease*, *18*(1), 155. https://doi.org/10.1186/s12944-019-1091-7

Liva, S. M., & Voskuhl, R. R. (2001). Testosterone acts directly on CD4± T lymphocytes to increase IL-10 production. *Journal of Immunology (Baltimore, Md.: 1950)*, *167*(4), 2060–2067. https://doi.org/10.4049/jimmunol.167.4.2060 [doi]

Lundsgaard, A.-M., & Kiens, B. (2014). Gender Differences in Skeletal Muscle Substrate Metabolism – Molecular Mechanisms and Insulin Sensitivity. *Frontiers in Endocrinology*, *5*, 195. https://www.frontiersin.org/article/10.3389/fendo.2014.00195

Macêdo Santiago, L. Â., Neto, L. G. L., Borges Pereira, G., Leite, R. D., Mostarda, C. T., de Oliveira Brito Monzani, J., Sousa, W. R., Rodrigues Pinheiro, A. J. M., & Navarro, F. (2018). Effects of Resistance Training on Immunoinflammatory Response, TNF-Alpha Gene Expression, and Body Composition in Elderly Women. *Journal of Aging Research*, *2018*, 1467025. https://doi.org/10.1155/2018/1467025

Marchetti, P., Bugliani, M., Lupi, R., Marselli, L., Masini, M., Boggi, U., Filipponi, F., Weir, G. C., Eizirik, D. L., & Cnop, M. (2007). The endoplasmic reticulum in pancreatic beta cells of type 2 diabetes patients. *Diabetologia*, *50*(12), 2486–2494. https://doi.org/10.1007/s00125-007-0816-8

Mari, A., Pacini, G., Murphy, E., Ludvik, B., & Nolan, J. J. (2001). A Model-Based Method for Assessing Insulin Sensitivity From the Oral Glucose Tolerance Test. *Diabetes Care*, *24*(3), 539–548. https://doi.org/10.2337/diacare.24.3.539

Marini, M. A., Frontoni, S., Succurro, E., Arturi, F., Sciacqua, A., Hribal, M. L., Perticone, F., & Sesti, G. (2014). Insulin sensitivity, and β-cell function in relation to hemoglobin A1C. *Nutrition, Metabolism, and Cardiovascular Diseases : NMCD*, *24*(1), 27–33. https://doi.org/S0939-4753(13)00031-8 [pii]

Martins, A. R., Nachbar, R. T., Gorjao, R., Vinolo, M. A., Festuccia, W. T., Lambertucci, R. H., Cury-Boaventura, M. F., Silveira, L. R., Curi, R., & Hirabara, S. M. (2012). Mechanisms underlying skeletal muscle insulin resistance induced by fatty acids: importance of the mitochondrial function. *Lipids in Health and Disease*, *11*(1), 30. https://doi.org/10.1186/1476-511X-11-30

Matsuda, M., & DeFronzo, R. A. (1999). Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care*, *22*(9), 1462–1470. https://doi.org/10.2337/diacare.22.9.1462 [doi]

Matthews, D. R., Hosker, J. P., Rudenski, A. S., Naylor, B. A., Treacher, D. F., & Turner, R. C. (1985). Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, *28*(7), 412–419. https://doi.org/10.1007/BF00280883 [doi]

Matute, M. L., & Kalkhoff, R. K. (1973). Sex Steroid Influence on Hepatic Gluconeogenesis and Glycogen Formation1. *Endocrinology*, *92*(3), 762–768. https://doi.org/10.1210/endo-92-3-762

McAuley, K. A., Williams, S. M., Mann, J. I., Walker, R. J., Lewis-Barned, N. J., Temple, L. A., & Duncan, A. W. (2001). Diagnosing Insulin Resistance in the General Population. *Diabetes Care*, *24*(3), 460–464. https://doi.org/10.2337/diacare.24.3.460

Medzhitov, R. (2010). Inflammation 2010: new adventures of an old flame. *Cell*, *140*(6), 771–776. https://doi.org/10.1016/j.cell.2010.03.006 [doi]

Melzer, K., Kayser, B., Saris, W. H. M., & Pichard, C. (2005). Effects of physical activity on food intake. *Clinical Nutrition*, *24*(6), 885–895. https://doi.org/https://doi.org/10.1016/j.clnu.2005.06.003

Meshkani, R., & Adeli, K. (2009). Hepatic insulin resistance, metabolic syndrome and cardiovascular disease. *Clinical Biochemistry*, *42*(13), 1331–1346. https://doi.org/https://doi.org/10.1016/j.clinbiochem.2009.05.018

Metcalfe, R. S., Babraj, J. A., Fawkner, S. G., & Vollaard, N. B. (2012). Towards the minimal amount of exercise for improving metabolic health: beneficial effects of reduced-exertion high-intensity interval training. *European Journal of Applied Physiology*, *112*(7), 2767–2775. https://doi.org/10.1007/s00421-011-2254-z [doi]

Metcalfe, R. S., Tardif, N., Thompson, D., & Vollaard, N. B. J. (2016). Changes in aerobic capacity and glycaemic control in response to reduced-exertion high-intensity interval training (REHIT) are not different between sedentary men and women. *Applied Physiology, Nutrition, and Metabolism*, *41*(11), 1117–1123. https://doi.org/10.1139/apnm-2016-0253

Moreno, M., Ordoñez, P., Alonso, A., Díaz, F., Tolivia, J., & González, C. (2010). Chronic 17β-estradiol treatment improves skeletal muscle insulin signaling pathway components in insulin resistance associated with aging. *AGE*, *32*(1), 1–13. https://doi.org/10.1007/s11357-009-9095-2

Motahari-Tabari, N., Ahmad Shirvani, M., Shirzad-E-Ahoodashty, M., Yousefi-Abdolmaleki, E., & Teimourzadeh, M. (2014). The effect of 8 weeks aerobic exercise on insulin resistance in type 2 diabetes: a randomized clinical trial. *Global Journal of Health Science*, *7*(1), 115–121. https://doi.org/10.5539/gjhs.v7n1p115 [doi]

Motahari-Tabari, N., Shirvani, M. A., Shirzad-e-Ahoodashty, M., Yousefi-Abdolmaleki, E., & Teimourzadeh, M. (2015). The effect of 8 weeks aerobic exercise on insulin resistance in type 2 diabetes: a randomized clinical trial. *Global Journal of Health Science*, *7*(1), 115.

Muniyappa, R., Lee, S., Chen, H., & Quon, M. J. (2008). Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. *American Journal of Physiology-Endocrinology and Metabolism*, *294*(1), E15–E26. https://doi.org/10.1152/ajpendo.00645.2007

Muniyappa, R., Madan, R., & Varghese, R. (2021). Assessing Insulin Sensitivity and Resistance in Humans. In *Endotext [Internet]*.

Najjar, S. M., & Perdomo, G. (2019). Hepatic Insulin Clearance: Mechanism and Physiology. *Physiology (Bethesda, Md.)*, *34*(3), 198–215. https://doi.org/10.1152/physiol.00048.2018

Niemelä, M., Kangastupa, P., Niemelä, O., Bloigu, R., & Juvonen, T. (2016). Acute Changes in Inflammatory Biomarker Levels in Recreational Runners Participating in a Marathon or Half-Marathon. *Sports Medicine - Open*, *2*(1), 21. https://doi.org/10.1186/s40798-016-0045-0

Nunes, V. A., Portioli-Sanches, E. P., Rosim, M. P., Araujo, M. S., Praxedes-Garcia, P., Valle, M. M., Roma, L. P., Hahn, C., Gurgul-Convey, E., Lenzen, S., & Azevedo-Martins, A. K. (2014). Progesterone induces apoptosis of insulin-secreting cells: insights into the molecular mechanism. *The Journal of Endocrinology*, *221*(2), 273–284. https://doi.org/10.1530/JOE-13-0202 [doi]

Nystoriak, M. A., & Bhatnagar, A. (2018). Cardiovascular Effects and Benefits of Exercise. *Frontiers in Cardiovascular Medicine*, *5*. https://www.frontiersin.org/articles/10.3389/fcvm.2018.00135

Olokoba, A. B., Obateru, O. A., & Olokoba, L. B. (2012). Type 2 diabetes mellitus: a review of current trends. *Oman Medical Journal*, *27*(4), 269–273. https://doi.org/10.5001/omj.2012.68 [doi]

Ottarsdottir, K., Nilsson, A. G., Hellgren, M., Lindblad, U., & Daka, B. (2018). The association between serum testosterone and insulin resistance: a longitudinal study. *Endocrine Connections*, *7*(12), 1491–1500. https://doi.org/10.1530/EC-18-0480

Otten, J., Ahrén, B., & Olsson, T. (2014). Surrogate measures of insulin sensitivity vs the hyperinsulinaemic–euglycaemic clamp: a meta-analysis. *Diabetologia*, *57*(9), 1781–1788. https://doi.org/10.1007/s00125-014-3285-x

Palmu, S., Kuneinen, S., Kautiainen, H., Eriksson, J. G., & Korhonen, P. E. (2021). Body surface area may explain sex differences in findings from the oral glucose tolerance test among subjects with normal glucose tolerance. *Nutrition, Metabolism and Cardiovascular Diseases*, *31*(9), 2678–2684. https://doi.org/10.1016/j.numecd.2021.05.018

Patarrão, R. S., Wayne Lautt, W., & Paula Macedo, M. (2014). Assessment of methods and indexes of insulin sensitivity. *Revista Portuguesa de Endocrinologia, Diabetes e Metabolismo*, *9*(1), 65–73. https://doi.org/10.1016/j.rpedm.2013.10.004

Patel, Y. R., Gadiraju, T. V, Gaziano, J. M., & Djoussé, L. (2018). Adherence to healthy lifestyle factors and risk of death in men with diabetes mellitus: The Physicians' Health Study. *Clinical Nutrition*, *37*(1), 139–143. https://doi.org/https://doi.org/10.1016/j.clnu.2016.11.003

Pedersen, B. K. (2000). Exercise and cytokines. *Immunology & Cell Biology*, *78*(5), 532–535. https://doi.org/https://doi.org/10.1111/j.1440-1711.2000.t01-11-.x

Pedersen, B. K. (2017). Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. *European Journal of Clinical Investigation*, *47*(8), 600–611. https://doi.org/10.1111/eci.12781 [doi]

Pedersen, B. K., & Febbraio, M. A. (2008). Muscle as an Endocrine Organ: Focus on Muscle-Derived Interleukin-6. *Physiological Reviews*, *88*(4), 1379–1406. https://doi.org/10.1152/physrev.90100.2007

Pedersen, B. K., Steensberg, A., & Schjerling, P. (2001). Muscle-derived interleukin-6: possible biological effects. *The Journal of Physiology*, *536*(2), 329–337. https://doi.org/https://doi.org/10.1111/j.1469-7793.2001.0329c.xd

Pereira, R. M., Rodrigues, K. C. da C., Anaruma, C. P., Sant'Ana, M. R., de Campos Dantis Pereira, T., Gaspar, R. S., Canciglieri, R. dos S., de Melo, D. G., Mekary, R. A., da Silva Sanchez Ramos, A., Cintra, D. E., Ropelle, E. R., Pauli, J. R., & de Moura, L. P. (2019). Short-term strength training reduces gluconeogenesis and NAFLD in obese mice. *Journal of Endocrinology*, *241*(1), 59–70. https://doi.org/10.1530/JOE-18-0567

Petersen, A. M. W., & Pedersen, B. K. (2005). The anti-inflammatory effect of exercise. *Journal of Applied Physiology*, *98*(4), 1154–1162. https://doi.org/10.1152/japplphysiol.00164.2004

Petersen, K. F., Laurent, D., Rothman, D. L., Cline, G. W., & Shulman, G. I. (1998). Mechanism by which glucose and insulin inhibit net hepatic glycogenolysis in humans. *The Journal of Clinical Investigation*, *101*(6), 1203–1209. https://doi.org/10.1172/JCI579

Petersen, M. C., & Shulman, G. I. (2018). Mechanisms of Insulin Action and Insulin Resistance. *Physiological Reviews*, *98*(4), 2133–2223. https://doi.org/10.1152/physrev.00063.2017

Petersen, M. C., Vatner, D. F., & Shulman, G. I. (2017). Regulation of hepatic glucose metabolism in health and disease. *Nature Reviews.Endocrinology*, *13*(10), 572–587. https://doi.org/10.1038/nrendo.2017.80

Picard, F., Wanatabe, M., Schoonjans, K., Lydon, J., O'Malley, B. W., & Auwerx, J. (2002). Progesterone receptor knockout mice have an improved glucose homeostasis secondary to beta - cell proliferation. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(24), 15644–15648. https://doi.org/202612199 [pii]

Pitteloud, N., Mootha, V. K., Dwyer, A. A., Hardin, M., Lee, H., Eriksson, K.-F., Tripathy, D., Yialamas, M., Groop, L., Elahi, D., & Hayes, F. J. (2005). Relationship Between Testosterone Levels, Insulin Sensitivity, and Mitochondrial Function in Men. *Diabetes Care*, *28*(7), 1636–1642. https://doi.org/10.2337/diacare.28.7.1636

Ploeger, H., Takken, T., de Greef, M., & Timmons, B. (2009). The effects of acute and chronic exercise on inflammatory markers in children and adults with a chronic inflammatory disease: A systematic review. *Exercise Immunology Review*, *15*, 6–41.

Potteiger, J. A., Jacobsen, D. J., Donnelly, J. E., Hill, J. O., & Trial, M. E. (2003). Glucose and insulin responses following 16 months of exercise training in overweight adults: the Midwest Exercise Trial. *Metabolism: Clinical and Experimental*, *52*(9), 1175–1181. https://doi.org/S002604950300146X [pii]

Pratap, U. P., Sharma, H. R., Mohanty, A., Kale, P., Gopinath, S., Hima, L., Priyanka, H. P., & ThyagaRajan, S. (2015). Estrogen upregulates inflammatory signals through NF-κB, IFN-γ, and nitric oxide via Akt/mTOR pathway in the lymph node lymphocytes of middle-aged female rats. *International Immunopharmacology*, *29*(2), 591–598. https://doi.org/https://doi.org/10.1016/j.intimp.2015.09.024

Prior, S. J., Blumenthal, J. B., Katzel, L. I., Goldberg, A. P., & Ryan, A. S. (2014). Increased skeletal muscle capillarization after aerobic exercise training and weight loss improves insulin sensitivity in adults with IGT. *Diabetes Care*, *37*(5), 1469–1475. https://doi.org/10.2337/dc13-2358 [doi]

Pulido, J. M. E., & Salazar, M. A. (1999). Changes in Insulin Sensitivity, Secretion and Glucose Effectiveness During Menstrual Cycle. *Archives of Medical Research*, *30*(1), 19–22. https://doi.org/https://doi.org/10.1016/S0188-0128(98)00008-6

Punthakee, Z., Goldenberg, R., & Katz, P. (2020). *Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome*. https://www.diabetes.ca/health-care-providers/clinical-practice-guidelines/chapter-3#panel-tab_FullText

Rahman, Z. A., Abdullah, N., Singh, R., & Sosroseno, W. (2010). Effect of acute exercise on the levels of salivary cortisol, tumor necrosis factor-α and nitric oxide. *Journal of Oral Science*, *52*(1), 133–136. https://doi.org/10.2334/josnusd.52.133

Rao, P. M., Kelly, D. M., & Jones, T. H. (2013). Testosterone and insulin resistance in the metabolic syndrome and T2DM in men. *Nature Reviews Endocrinology*, *9*(8), 479–493. https://doi.org/10.1038/nrendo.2013.122

Reed, B., & Carr, B. (2021). The Normal Menstrual Cycle and the Control of Ovulation. In *Endotext [Internet]*.

Rehman, K., & Akash, M. S. H. (2016). Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? *Journal of Biomedical Science*, *23*(1), 87. https://doi.org/10.1186/s12929-016-0303-y

Reichkendler, M. H., Auerbach, P., Rosenkilde, M., Christensen, A. N., Holm, S., Petersen, M. B., Lagerberg, A., Larsson, H. B., Rostrup, E., Mosbech, T. H., Sjödin, A., Kjaer, A., Ploug, T., Hoejgaard, L., & Stallknecht, B. (2013). Exercise training favors increased insulin-stimulated glucose uptake in skeletal muscle in contrast to adipose tissue: a randomized study using FDG PET imaging. *American Journal of Physiology.Endocrinology and Metabolism*, *305*(4), 496. https://doi.org/10.1152/ajpendo.00128.2013 [doi]

Richter, E. A. (2020). Is GLUT4 translocation the answer to exercise-stimulated muscle glucose uptake? *American Journal of Physiology-Endocrinology and Metabolism*, *320*(2), E240–E243. https://doi.org/10.1152/ajpendo.00503.2020

Richter, E. A., & Hargreaves, M. (2013). Exercise, GLUT4, and Skeletal Muscle Glucose Uptake. *Physiological Reviews*, *93*(3), 993–1017. https://doi.org/10.1152/physrev.00038.2012

Roher, N., Samokhvalov, V., Díaz, M., MacKenzie, S., Klip, A., & Planas, J. V. (2008). The Proinflammatory Cytokine Tumor Necrosis Factor-α Increases the Amount of Glucose Transporter-4 at the Surface of Muscle Cells Independently of Changes in Interleukin-6. *Endocrinology*, *149*(4), 1880–1889. https://doi.org/10.1210/en.2007-1045

Ryan, A. S., Nicklas, B. J., & Berman, D. M. (2002). Hormone Replacement Therapy, Insulin Sensitivity, and Abdominal Obesity in Postmenopausal Women. *Diabetes Care*, *25*(1), 127–133. https://doi.org/10.2337/diacare.25.1.127

Saini, V. (2010). Molecular mechanisms of insulin resistance in type 2 diabetes mellitus. *World Journal of Diabetes*, *1*(3), 68–75. https://doi.org/10.4239/wjd.v1.i3.68 [doi]

Saisho, Y. (2015). β-cell dysfunction: Its critical role in prevention and management of type 2 diabetes. *World Journal of Diabetes*, *6*(1), 109–124. https://doi.org/10.4239/wjd.v6.i1.109

Sakaguchi, K., Takeda, K., Maeda, M., Ogawa, W., Sato, T., Okada, S., Ohnishi, Y., Nakajima, H., & Kashiwagi, A. (2015). Glucose area under the curve during oral glucose tolerance test as an index of glucose intolerance. *Diabetology International*, *7*(1), 53–58. https://doi.org/10.1007/s13340-015-0212-4 [doi]

Samjoo, I. A., Safdar, A., Hamadeh, M. J., Glover, A. W., Mocellin, N. J., Santana, J., Little, J. P., Steinberg, G. R., Raha, S., & Tarnopolsky, M. A. (2013). Markers of Skeletal Muscle Mitochondrial Function and Lipid Accumulation Are Moderately Associated with the

Homeostasis Model Assessment Index of Insulin Resistance in Obese Men. *PLOS ONE*, *8*(6), e66322-. https://doi.org/10.1371/journal.pone.0066322

Samjoo, I. A., Safdar, A., Hamadeh, M. J., Raha, S., & Tarnopolsky, M. A. (2013). The effect of endurance exercise on both skeletal muscle and systemic oxidative stress in previously sedentary obese men. *Nutrition & Diabetes*, *3*(9), e88–e88. https://doi.org/10.1038/nutd.2013.30

Sarafidis, P. A., Lasaridis, A. N., Nilsson, P. M., Pikilidou, M. I., Stafilas, P. C., Kanaki, A., Kazakos, K., Yovos, J., & Bakris, G. L. (2007). Validity and reproducibility of HOMA-IR, 1/HOMA-IR, QUICKI and McAuley's indices in patients with hypertension and type II diabetes. *Journal of Human Hypertension*, *21*(9), 709–716. https://doi.org/10.1038/sj.jhh.1002201

Sardeli, A. V., Tomeleri, C. M., Cyrino, E. S., Fernhall, B., Cavaglieri, C. R., & Chacon-Mikahil, M. P. T. (2018). Effect of resistance training on inflammatory markers of older adults: A meta-analysis. *Experimental Gerontology*, *111*, 188–196. https://doi.org/https://doi.org/10.1016/j.exger.2018.07.021

Schmidt, F. M., Weschenfelder, J., Sander, C., Minkwitz, J., Thormann, J., Chittka, T., Mergl, R., Kirkby, K. C., Faßhauer, M., Stumvoll, M., Holdt, L. M., Teupser, D., Hegerl, U., & Himmerich, H. (2015). Inflammatory Cytokines in General and Central Obesity and Modulating Effects of Physical Activity. *PLOS ONE*, *10*(3), e0121971-. https://doi.org/10.1371/journal.pone.0121971

Schober, E., Holl, R. W., Grabert, M., Thon, A., Rami, B., Kapellen, T., Seewi, O., & Reinehr, T. (2005). Diabetes mellitus type 2 in childhood and adolescence in Germany and parts of Austria. *European Journal of Pediatrics*, *164*(11), 705–707. https://doi.org/10.1007/s00431-005-1709-9

Senn, J. J., Klover, P. J., Nowak, I. A., & Mooney, R. A. (2002). Interleukin-6 Induces Cellular Insulin Resistance in Hepatocytes. *Diabetes*, *51*(12), 3391–3399. https://doi.org/10.2337/diabetes.51.12.3391

SHAIBI, G. Q., CRUZ, M. L., BALL, G. D. C., WEIGENSBERG, M. J., SALEM, G. J., CRESPO, N. O. E. C., & GORAN, M. I. (2006). Effects of Resistance Training on Insulin Sensitivity in Overweight Latino Adolescent Males. *Medicine & Science in Sports & Exercise*, *38*(7). https://journals.lww.com/acsm-msse/Fulltext/2006/07000/Effects_of_Resistance_Training_on_Insulin.3.aspx

Sherwani, S. I., Khan, H. A., Ekhzaimy, A., Masood, A., & Sakharkar, M. K. (2016). Significance of HbA1c Test in Diagnosis and Prognosis of Diabetic Patients. *Biomarker Insights*, *11*, 95–104. https://doi.org/10.4137/BMI.S38440

Shojaee-Moradie, F., Baynes, K. C., Pentecost, C., Bell, J. D., Thomas, E. L., Jackson, N. C., Stolinski, M., Whyte, M., Lovell, D., Bowes, S. B., Gibney, J., Jones, R. H., & Umpleby, A. M. (2007). Exercise training reduces fatty acid availability and improves the insulin sensitivity of glucose metabolism. *Diabetologia*, *50*(2), 404–413. https://doi.org/10.1007/s00125-006-0498-7 [doi]

Shulman, G. I. (1999). Cellular mechanisms of insulin resistance in humans. *The American Journal of Cardiology*, *84*(1, Supplement 1), 3–10. https://doi.org/https://doi.org/10.1016/S0002-9149(99)00350-1

Sicree, R. A., Zimmet, P. Z., Dunstan, D. W., Cameron, A. J., Welborn, T. A., & Shaw, J. E. (2008a). Differences in height explain gender differences in the response to the oral glucose tolerance test— the AusDiab study. *Diabetic Medicine*, *25*(3), 296–302. https://doi.org/https://doi.org/10.1111/j.1464-5491.2007.02362.x

Sicree, R. A., Zimmet, P. Z., Dunstan, D. W., Cameron, A. J., Welborn, T. A., & Shaw, J. E. (2008b). Differences in height explain gender differences in the response to the oral glucose tolerance test— the AusDiab study. *Diabetic Medicine*, *25*(3), 296–302. https://doi.org/https://doi.org/10.1111/j.1464-5491.2007.02362.x

Sigal, R. J., Kenny, G. P., Boulé, N. G., Wells, G. A., Prud'homme, D., Fortier, M., Reid, R. D., Tulloch, H., Coyle, D., Phillips, P., Jennings, A., & Jaffey, J. (2007). Effects of Aerobic Training, Resistance Training, or Both on Glycemic Control in Type 2 Diabetes. *Ann Intern Med*, *147*(6), 357–369. https://doi.org/10.7326/0003-4819-147-6-200709180-00005

Singal, P., Muniyappa, R., Chisholm, R., Hall, G., Chen, H., Quon, M. J., & Mather, K. J. (2010). Simple modeling allows prediction of steady-state glucose disposal rate from early data in hyperinsulinemic glucose clamps. *American Journal of Physiology.Endocrinology and Metabolism*, *298*(2), E229–E236. https://doi.org/10.1152/ajpendo.00603.2009

Siu, A. L. (2015). Screening for Abnormal Blood Glucose and Type 2 Diabetes Mellitus: U.S. Preventive Services Task Force Recommendation Statement. *Annals of Internal Medicine*, *163*(11), 861–868. https://doi.org/10.7326/M15-2345

Sjøberg, K. A., Frøsig, C., Kjøbsted, R., Sylow, L., Kleinert, M., Betik, A. C., Shaw, C. S., Kiens, B., Wojtaszewski, J. F. P., Rattigan, S., Richter, E. A., & McConell, G. K. (2017). Exercise Increases Human Skeletal Muscle Insulin Sensitivity via Coordinated Increases in Microvascular Perfusion and Molecular Signaling. *Diabetes*, *66*(6), 1501–1510. https://doi.org/10.2337/db16-1327

Snyder, K. A., Donnelly, J. E., Jabobsen, D. J., Hertner, G., & Jakicic, J. M. (1997). The effects of long-term, moderate intensity, intermittent exercise on aerobic capacity, body composition, blood lipids, insulin and glucose in overweight females. *International Journal of Obesity*, *21*(12), 1180–1189. https://doi.org/10.1038/sj.ijo.0800533

Soonthornpun, S., Setasuban, W., Thamprasit, A., Chayanunnukul, W., Rattarasarn, C., & Geater, A. (2003). Novel Insulin Sensitivity Index Derived from Oral Glucose Tolerance Test. *The Journal of Clinical Endocrinology & Metabolism*, *88*(3), 1019–1023. https://doi.org/10.1210/jc.2002-021127

Statistics Canada. (2019, June 25). *Overweight and obese adults, 2018*.

Stern, S. E., Williams, K., Ferrannini, E., DeFronzo, R. A., Bogardus, C., & Stern, M. P. (2005). Identification of Individuals With Insulin Resistance Using Routine Clinical Measurements. *Diabetes*, *54*(2), 333–339. https://doi.org/10.2337/diabetes.54.2.333

Straub, R. H. (2007). The Complex Role of Estrogens in Inflammation. *Endocrine Reviews*, *28*(5), 521–574. https://doi.org/10.1210/er.2007-0001

Stumvoll, M., Van Haeften, T., Fritsche, A., & Gerich, J. (2001). Oral Glucose Tolerance Test Indexes for Insulin Sensitivity and Secretion Based on Various Availabilities of Sampling Times. *Diabetes Care*, *24*(4), 796–797. https://doi.org/10.2337/diacare.24.4.796

Tabák, A. G., Kivimäki, M., Brunner, E. J., Lowe, G. D., Jokela, M., Akbaraly, T. N., Singh-Manoux, A., Ferrie, J. E., & Witte, D. R. (2010). Changes in C-reactive protein levels before type 2 diabetes and cardiovascular death: the Whitehall II study. *European Journal of Endocrinology*, *163*(1), 89–95. https://doi.org/10.1530/EJE-10-0277

ter Horst, R., van den Munckhof, I. C. L., Schraa, K., Aguirre-Gamboa, R., Jaeger, M., Smeekens, S. P., Brand, T., Lemmers, H., Dijkstra, H., Galesloot, T. E., de Graaf, J., Xavier, R. J., Li, Y., Joosten, L. A. B., Rutten, J. H. W., Netea, M. G., & Riksen, N. P. (2020). Sex-Specific Regulation of Inflammation and Metabolic Syndrome in Obesity. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *40*(7), 1787–1800. https://doi.org/10.1161/ATVBAHA.120.314508

Thomas, D. D., Corkey, B. E., Istfan, N. W., & Apovian, C. M. (2019). Hyperinsulinemia: An Early Indicator of Metabolic Dysfunction. *Journal of the Endocrine Society*, *3*(9), 1727–1747. https://doi.org/10.1210/js.2019-00065

Titchenell, P. M., Chu, Q., Monks, B. R., & Birnbaum, M. J. (2015). Hepatic insulin signalling is dispensable for suppression of glucose output by insulin in vivo. *Nature Communications*, *6*, 7078. https://doi.org/10.1038/ncomms8078

Tracey, M. L., McHugh, S. M., Buckley, C. M., Canavan, R. J., Fitzgerald, A. P., & Kearney, P. M. (2016). The prevalence of Type 2 diabetes and related complications in a nationally representative sample of adults aged 50 and over in the Republic of Ireland. *Diabetic Medicine*, *33*(4), 441–445. https://doi.org/https://doi.org/10.1111/dme.12845

Trachta, P., Drápalová, J., Kaválková, P., Toušková, V., Cinkajzlová, A., Lacinová, Z., Matoulek, M., Zelinka, T., Widimský Jr, J., Mráz, M., & Haluzík, M. (2014). Three months of regular aerobic exercise in patients with obesity improve systemic subclinical inflammation without major influence on blood pressure and endocrine production of subcutaneous fat. *Physiological Research*, *63*(Suppl 2), 299. https://doi.org/932792 [pii]

Tramunt, B., Smati, S., Grandgeorge, N., Lenfant, F., Arnal, J.-F., Montagner, A., & Gourdy, P. (2020a). Sex differences in metabolic regulation and diabetes susceptibility. *Diabetologia*, *63*(3), 453–461. https://doi.org/10.1007/s00125-019-05040-3

Unwin, N., Shaw, J., Zimmet, P., & Alberti, K. G. (2002). Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabetic*

Medicine : A Journal of the British Diabetic Association, *19*(9), 708–723. https://doi.org/835 [pii]

Utzschneider, K. M., Prigeon, R. L., Tong, J., Gerchman, F., Carr, D. B., Zraika, S., Udayasankar, J., Montgomery, B., Mari, A., & Kahn, S. E. (2007). Within-subject variability of measures of beta cell function derived from a 2 h OGTT: implications for research studies. *Diabetologia*, *50*(12), 2516–2525. https://doi.org/10.1007/s00125-007-0819-5

van der Heijden, G.-J., Toffolo, G., Manesso, E., Sauer, P. J. J., & Sunehag, A. L. (2009). Aerobic Exercise Increases Peripheral and Hepatic Insulin Sensitivity in Sedentary Adolescents. *The Journal of Clinical Endocrinology & Metabolism*, *94*(11), 4292–4299. https://doi.org/10.1210/jc.2009-1379

van Hall, G., Steensberg, A., Sacchetti, M., Fischer, C., Keller, C., Schjerling, P., Hiscock, N., Møller, K., Saltin, B., Febbraio, M. A., & Pedersen, B. K. (2003). Interleukin-6 stimulates lipolysis and fat oxidation in humans. *The Journal of Clinical Endocrinology and Metabolism*, *88*(7), 3005–3010. https://doi.org/10.1210/jc.2002-021687 [doi]

Varlamov, O., Bethea, C. L., & Roberts Jr, C. T. (2015). Sex-specific differences in lipid and glucose metabolism. *Frontiers in Endocrinology*, *5*, 241.

Wada, T., Hori, S., Sugiyama, M., Fujisawa, E., Nakano, T., Tsuneki, H., Nagira, K., Saito, S., & Sasaoka, T. (2010). Progesterone inhibits glucose uptake by affecting diverse steps of insulin signaling in 3T3-L1 adipocytes. *American Journal of Physiology.Endocrinology and Metabolism*, *298*(4), 881. https://doi.org/10.1152/ajpendo.00649.2009 [doi]

Wang, M., Li, S., Wang, F., Zou, J., & Zhang, Y. (2018). Aerobic exercise regulates blood lipid and insulin resistance via the toll-like receptor 4-mediated extracellular signal-regulated kinases/AMP-activated protein kinases signaling pathway. *Molecular Medicine Reports*, *17*(6), 8339–8348. https://doi.org/10.3892/mmr.2018.8863 [doi]

Wang, P., Wu, P., Anthes, J. C., Siegel, M. I., Egan, R. W., & Billah, M. M. (1994). Interleukin-10 Inhibits Interleukin-8 Production in Human Neutrophils. *Blood*, *83*(9), 2678–2683. https://doi.org/https://doi.org/10.1182/blood.V83.9.2678.2678

Way, K. L., Hackett, D. A., Baker, M. K., & Johnson, N. A. (2016). The Effect of Regular Exercise on Insulin Sensitivity in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Diabetes & Metabolism Journal*, *40*(4), 253–271. https://doi.org/10.4093/dmj.2016.40.4.253

Wener, M. H., Daum, P. R., & McQuillan, G. M. (2000). The influence of age, sex, and race on the upper reference limit of serum C-reactive protein concentration. *The Journal of Rheumatology*, *27*(10), 2351–2359. http://europepmc.org/abstract/MED/11036829

Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care*, *27*(5), 1047–1053. https://doi.org/10.2337/diacare.27.5.1047

Winnick, J. J., Gaillard, T., & Schuster, D. P. (2008). Resistance training differentially affects weight loss and glucose metabolism of White and African American patients with type 2 diabetes mellitus. *Ethnicity & Disease*, *18*(2), 152–156.

Winnick, J. J., Sherman, W. M., Habash, D. L., Stout, M. B., Failla, M. L., Belury, M. A., & Schuster, D. P. (2008). Short-Term Aerobic Exercise Training in Obese Humans with Type 2 Diabetes Mellitus Improves Whole-Body Insulin Sensitivity through Gains in Peripheral, not Hepatic Insulin Sensitivity. *The Journal of Clinical Endocrinology & Metabolism*, *93*(3), 771–778. https://doi.org/10.1210/jc.2007-1524

Wise, P. M., Suzuki, S., & Brown, C. M. (2009). Estradiol: a hormone with diverse and contradictory neuroprotective actions. *Dialogues in Clinical Neuroscience*, *11*(3), 297–303. https://doi.org/10.31887/DCNS.2009.11.3/pmwise [doi]

Wolsk, E., Mygind, H., Grøndahl, T. S., Pedersen, B. K., & van Hall, G. (2010). IL-6 selectively stimulates fat metabolism in human skeletal muscle. *American Journal of Physiology.Endocrinology and Metabolism*, *299*(5), 832. https://doi.org/10.1152/ajpendo.00328.2010 [doi]

Wueest, S., & Konrad, D. (2018). The role of adipocyte-specific IL-6-type cytokine signaling in FFA and leptin release. *Adipocyte*, *7*(3), 226–228. https://doi.org/10.1080/21623945.2018.1493901

Yaribeygi, H., Atkin, S. L., Simental-Mendía, L. E., & Sahebkar, A. (2019). Molecular mechanisms by which aerobic exercise induces insulin sensitivity. *Journal of Cellular Physiology*, *234*(8), 12385–12392. https://doi.org/10.1002/jcp.28066 [doi]

Yuan, J., Wang, L., Lin, Y., Chen, J., & Hu, J. (2015). *Differences of plasma IL-1 and TNF-α in healthy Chinese Population*. *10*(1). https://doi.org/doi:10.1515/med-2015-0044

Yue, Y., Zhang, C., Zhao, X., Liu, S., Lv, X., Zhang, S., Yang, J., Chen, L., Duan, H., Zhang, Y., Yao, Z., & Niu, W. (2021). Tiam1 mediates Rac1 activation and contraction-induced glucose uptake in skeletal muscle cells. *The FASEB Journal*, *35*(2), e21210. https://doi.org/https://doi.org/10.1096/fj.202001312R

Zatterale, F., Longo, M., Naderi, J., Raciti, G. A., Desiderio, A., Miele, C., & Beguinot, F. (2020). Chronic Adipose Tissue Inflammation Linking Obesity to Insulin Resistance and Type 2 Diabetes. In *Frontiers in Physiology* (Vol. 10). Frontiers Media S.A. https://doi.org/10.3389/fphys.2019.01607

Zhang, H., Ni, J., Yu, C., Wu, Y., Li, J., Liu, J., Tu, J., Ning, X., He, Q., & Wang, J. (2019). Sex-Based Differences in Diabetes Prevalence and Risk Factors: A Population-Based Cross-Sectional Study Among Low-Income Adults in China. *Frontiers in Endocrinology*, *10*. https://www.frontiersin.org/article/10.3389/fendo.2019.00658

Zhang, J. M., & An, J. (2007). Cytokines, inflammation, and pain. *International Anesthesiology Clinics*, *45*(2), 27–37. https://doi.org/00004311-200704520-00004 [pii]

Zheng, G., Qiu, P., Xia, R., Lin, H., Ye, B., Tao, J., & Chen, L. (2019). Effect of Aerobic Exercise on Inflammatory Markers in Healthy Middle-Aged and Older Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Frontiers in Aging Neuroscience, 11*, 98. https://doi.org/10.3389/fnagi.2019.00098

Appendices

Appendix 1: Power Calculation from Previous Data

Data from Metcalfe et al. (2012) was used for values in the simulation. This study used reduced exertion high intensity interval training (REHIT) 3 sessions a week for 6 weeks, 10 minutes each sessions. Protocol: low intensity cycling (60 W) with two all-out cycling sprints (except for the 1st session that had one sprint).

Table 6.1: Data used for power calculation from Metcalfe et al. 2012

	Male		Female		Common Standard Deviation	Common correlation factor
	Pre	Post	Pre	Post		
Glucose AUC (mmol min l^{-1})	789 ± 172.0	695 ± 140.2	671 ± 189.5	712 ± 215.0	182.4	0.8
Cederholm Index (mg l^2 $mmol^{-1}$ mU^{-1} min^{-1})	55 ± 13.2	69 ± 7.9	68 ± 8.5	62 ± 11.3	10.2	0.8

Effects of REHIT protocol on glucose AUC and Cederholm Index. Data shown is mean ± standard deviation.

Power Analysis Output

Power for ANOVA Effects

	power	effect_size
anova_SEX	12.35	0.05
anova_TRAINING	23.10	0.08
anova_SEX:TRAINING	86.60	0.28

Power for Pairwise Comparisons with t-tests

	power	effect_size
p_SEX_male_TRAINING_pre_SEX_male_TRAINING_post	84.15	-0.87
p_SEX_male_TRAINING_pre_SEX_femake_TRAINING_pre	40.30	-0.66
p_SEX_male_TRAINING_pre_SEX_femake_TRAINING_post	19.50	-0.42
p_SEX_male_TRAINING_post_SEX_femake_TRAINING_pre	6.70	-0.12
p_SEX_male_TRAINING_post_SEX_femake_TRAINING_post	6.70	0.11
p_SEX_femake_TRAINING_pre_SEX_femake_TRAINING_post	25.10	0.38

Figure 6.1: ANOVA Power and Estimated Marginal Means table from ANOVA power report for glucose AUC. This simulation assumed an alpha of 0.05, a sphericity correction of GG and no adjustments for multiple comparisons. A total of 2000 iterations were included in this simulation.

Power Analysis Output

Power for ANOVA Effects

	power	effect_size
anova_SEX	13.85	0.06
anova_TRAINING	90.65	0.29
anova_SEX:TRAINING	100.00	0.72

Power for Pairwise Comparisons with t-tests

	power	effect_size
p_SEX_male_TRAINING_pre_SEX_male_TRAINING_post	100.00	2.27
p_SEX_male_TRAINING_pre_SEX_female_TRAINING_pre	92.00	1.31
p_SEX_male_TRAINING_pre_SEX_female_TRAINING_post	45.05	0.71
p_SEX_male_TRAINING_post_SEX_female_TRAINING_pre	5.70	-0.09
p_SEX_male_TRAINING_post_SEX_female_TRAINING_post	42.60	-0.70
p_SEX_female_TRAINING_pre_SEX_female_TRAINING_post	92.35	-0.98

Figure 6.2: ANOVA Power and Estimated Marginal Means table from ANOVA power report for Cederholm Index. This simulation assumed an alpha of 0.05, a sphericity correction of GG and no adjustments for multiple comparisons. A total of 2000 iterations were included in this simulation.

Appendix 2: Training Program

DAY 1 (Monday):

1. **Alternate MICT aerobic exercise with Fartlek Exercise**

   MICT: 30 min at 55% $\dot{V}O_{2max}$, progressing to 65% $\dot{V}O_{2max}$ (increase to 60% $\dot{V}O_{2max}$ at week 5 and 65% $\dot{V}O_{2max}$ at week 9).

   Fartlek:

   Table 6.2: 30 min Fartlek protocol

Intensity	Time
50% $\dot{V}O_{2max}$	5
60% $\dot{V}O_{2max}$	1
50% $\dot{V}O_{2max}$	1
70% $\dot{V}O_{2max}$	1
50% $\dot{V}O_{2max}$	1
80% $\dot{V}O_{2max}$	1
50% $\dot{V}O_{2max}$	10
60% $\dot{V}O_{2max}$	1
50% $\dot{V}O_{2max}$	1
70% $\dot{V}O_{2max}$	1
50% $\dot{V}O_{2max}$	1
80% $\dot{V}O_{2max}$	1
50% $\dot{V}O_{2max}$	5

This table shows the time and intensity for each stage of the Fartlek protocol.

2. **Circuit training** – 3 circuits, 35% 1RM, 45 seconds for each exercise with 25 seconds of rest, aiming for 20-25 reps for circuits 1 and 2, last set of each exercise to failure, 1 minutes rest between circuits

   Machines
   1. Leg press
   2. Knee extension
   3. Hamstring curls

4. Lat pulldown

Dumbbells

5. Biceps curls
6. Triceps extension
7. Dumbbell chest press
8. Lateral to front shoulder raises

Medicine balls

9. Medicine ball squat to calf raise
10. Seated Russian twist with medicine ball

DAY 2 (Wednesday):

1. **HIIT:** 10 x 1-minute (HIIT) at 90% $\dot{V}O_{2max}$ interspersed with 1 minute low intervals at 50W for male and 30W for female
2. **Circuit training**: Same as Day 1

Day 3: (Friday):

1. **30-minute aerobic class (lead virtually by one of the study investigators):** Moderate intensity (RPE 12-15) continuous aerobic exercise. Varying formats including boxing, calisthenics (jumping jacks, running on the spot). Starts with a 5-minute warm up and ends with a 5 min cool down.

2. **Resistance exercise**: Theraband circuit – 3 circuits, 20-25 reps/exercise (~30 sec/set), last circuit to failure
    1. Chair Squat
    2. Chest press
    3. Seated knee extension
    4. Seated row
    5. Knee flexion
    6. Seated lateral raise
    7. Seated hip flexion
    8. Seated biceps curl
    9. Seated dorsi flexion
    10. Seated triceps extension
    11. Calf raise
    12. Seated abdominal crunch

Appendix 3: Virtual Cardio Videos

Aerobic Routine #2 – Gabriela Ocampo

30 MIN ALL STANDING Cardio HIIT Workout – No Equipment, No Repeat, Home Workout to make you sweat - growingannanas

30 MIN HIIT CARDIO Workout – ALL STANDING – Full Body, No Equipment, No Repeats – growingannanas

30 MIN WALKING CARDIO WORKOUT | Intense Full Body Fat Burn at Home ~ Emi – emi wong

5000 STEPS IN 30 MIN AT HOME | Do it twice to get 10000 STEPS | Weight Loss Workout | NO JUMPING – Eleni Fit

5000 STEPS IN 30 MIN – Walking Cardio Dance Workout to Burn Fat, Mood Booster, No Repeat, No Jumping – Eleni Fit

30-Minute At-Home Cardio Boxing and Kickboxing Workout – POPSUGAR Fitness

30 Min Walking Cardio Workout | Intense Full Body Fat Burn | All Standing, No Jumping | No Repeat – Eleni Fit

Appendix 4: Participant diet information

Table 6.3: Participant diet before and after training

	Male		Female		*p* value		
	Pre	**Post**	**Pre**	**Post**	**S**	**T**	**S*T**
Total energy intake (kcal)	2,238.7 ± 269.8	1,830.7 ± 141.0	1,843.5 ± 172.2	1474.8 ± 107.7	0.04*	0.03*	0.91
Carbohydrates (g)	271.2 ± 29.6	200.0 ± 16.8	193.9 ± 20.2	153.5 ± 11.4	0.003*	0.009*	0.44
Carbohydrates (% of total kcal)	49.4 ± 1.9	43.6 ± 1.5	41.6 ± 2.4	42.2 ± 1.6	0.02*	0.24	0.11
Fats (g)	90.6 ± 14.4	75.0 ± 7.0	74.7 ± 6.3	64.6 ± 7.0	0.14	0.16	0.76
Fats (% of total kcal)	35.2 ± 1.6	36.5 ± 1.13	38.2 ± 2.3	38.5 ± 2.1	0.96	0.94	0.91
Protein (g)	90.0 ± 10.5	92.7 ± 6.1	81.0 ± 11.1	64.3 ± 3.9	0.03*	0.35	0.26
Protein (% of total kcal)	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.2	0.8 ± 0.1	0.70	0.13	0.11
Protein ($g/kg_{BW/d}$)	16.4 ± 1.5	20.6 ± 0.8	18.0 ± 1.5	18.1 ± 1.0	0.90	0.38	0.31

Results are displayed as mean ± SEM, n = 12 males and n = 15 females

* Significance from a 2-way mixed model ANOVA, significantly different with p value <0.05.

Table 6.4: Absolute change in participant diet following training

	Males	Females	*p* value	Cohens *d*
Total energy intake (kcal)	-408.0 ± 325.3	-368.7 ± 189.0	0.91	0.04
Carbohydrates (g)	-71.6 ± 34.4	-40.4 ± 19.8	0.42	0.31
Carbohydrates (% of total kcal)	-5.8 ± 1.6	0.5 ± 2.4	0.05	0.81
Fats (g)	-15.7 ± 16.5	-10.2 ± 8.1	0.75	0.12
Fats (% of total kcal)	1.4 ± 1.8	0.3 ± 1.5	0.65	0.18
Protein (g)	2.7 ± 14.3	-16.7 ± 12.3	0.31	0.40
Protein (% of total kcal)	0.03 ± 0.2	-0.2 ± 0.2	0.31	0.40
Protein ($g/kg_{BW/d}$)	4.2 ± 1.3	0.1 ± 1.5	0.05	0.12

Results are displayed as mean ± SEM, n = 12 males and n = 15 females
* Significance from independent samples t-test, significantly different with p value <0.05.

Table 6.5: Percent change in participant diet following training

	Males	Females	*p* value	Cohens *d*
Total energy intake (kcal)	-7.1 ± 12.4	-10.5 ± 10.3	0.83	0.08
Carbohydrates (g)	-19.9 ± 8.7	2.7 ± 24.4	0.43	0.32
Carbohydrates (% of total kcal)	-11.1 ± 2.7	7.9 ± 9.6	0.10	0.70
Fats (g)	1.52 ± 16.5	-8.3 ± 10.0	0.60	0.20
Fats (% of total kcal)	6.0 ± 5.5	2.9 ± 4.3	0.65	0.18
Protein (g)	33.24 ± 29.9	-5.7 ± 10.3	0.19	0.50
Protein (% of total kcal)	34.2 ± 30.5	-0.8 ± 11.6	0.26	0.43
Protein ($g/kg_{BW/d}$)	34.8 ± 11.4	10.1 ± 10.2	0.12	0.63

Results are displayed as mean ± SEM, n = 12 males and n = 15 females
* Significance from independent samples t-test, significantly different with p value <0.05.

Appendix 5: Power Calculation of Insulin Resistance

Data from Metcalfe et al. (2012) was used for values in the simulation. This study used reduced exertion high intensity interval training (REHIT) 3 sessions a week for 6 weeks, 10 minutes each sessions. Protocol: low intensity cycling (60 W) with two all-out cycling sprints (except for the 1st session that had one sprint).

Table 6.6: Data used for power calculation from our trial

	Male		Female		Common Standard Deviation	Common correlation factor
	Pre	Post	Pre	Post		
HOMA-IR	11.5 ± 8.4	10.9 ± 10.3	9.3 ± 6.3	9.0 ± 7.2	8.1	0.8
2-h OGIS	332.5 ± 55.1	348.3 ± 56.2	354.7 ± 40.7	360.3 ± 50.1	50.4	0.8

Results of insulin resistance and sensitivity before and after training intervention. Data shown is mean ± standard deviation.

Power Analysis Output

Power for ANOVA Effects

	power	effect_size
anova_SEX	9.60	0.06
anova_TRAINING	7.10	0.05
anova_SEX:TRAINING	5.50	0.04

Power for Pairwise Comparisons with t-tests

	power	effect_size
p_SEX_male_TRAINING_pre_SEX_male_TRAINING_post	2.35	-0.07
p_SEX_male_TRAINING_pre_SEX_female_TRAINING_pre	9.40	-0.28
p_SEX_male_TRAINING_pre_SEX_female_TRAINING_post	11.60	-0.32
p_SEX_male_TRAINING_post_SEX_female_TRAINING_pre	7.65	-0.21
p_SEX_male_TRAINING_post_SEX_female_TRAINING_post	9.20	-0.24
p_SEX_female_TRAINING_pre_SEX_female_TRAINING_post	6.15	-0.06

Figure 6.3: ANOVA Power and Estimated Marginal Means table from ANOVA power report for HOMA-IR. This simulation assumed an alpha of 0.05, a sphericity correction of GG and no adjustments for multiple comparisons. A total of 2000 iterations were included in this simulation.

Power Analysis Output

Power for ANOVA Effects

	power	effect_size
anova_SEX	13.05	0.07
anova_TRAINING	33.60	0.13
anova_SEX:TRAINING	11.25	0.07

Power for Pairwise Comparisons with t-tests

	power	effect_size
p_SEX_male_TRAINING_pre_SEX_male_TRAINING_post	12.05	0.33
p_SEX_male_TRAINING_pre_SEX_female_TRAINING_pre	18.65	0.44
p_SEX_male_TRAINING_pre_SEX_female_TRAINING_post	27.05	0.56
p_SEX_male_TRAINING_post_SEX_female_TRAINING_pre	5.70	0.12
p_SEX_male_TRAINING_post_SEX_female_TRAINING_post	8.70	0.24
p_SEX_female_TRAINING_pre_SEX_female_TRAINING_post	9.05	0.19

Figure 6.4: ANOVA Power and Estimated Marginal Means table from ANOVA power report for 2-h OGIS. This simulation assumed an alpha of 0.05, a sphericity correction of GG and no adjustments for multiple comparisons. A total of 2000 iterations were included in this simulation.