UNDERSTANDING AND IMPROVING INDIVIDUAL RESPONSES TO EXERCISE TRAINING FOR THOSE AT RISK FOR, OR LIVING WITH, TYPE 2 DIABETES MELLITUS

by

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Abstract

Background: Prediabetes and type 2 diabetes mellitus (T2DM) are highly prevalent chronic diseases. Exercise is recommended to improve glycemic control and prevent progression from prediabetes to T2DM. However, a significant proportion of individuals do not experience the desired benefits (referred to as non-responders). Currently, there are a number of recommended methods, conflicting theories, and many unanswered questions associated with individual exercise response research. Two of the most pertinent questions are how to best implement these methods and interpret the results in a clinical setting, and what to do once an individual is determined to be a non-responder.

Aims: 1) Use currently recommended methods to identify if prescribing high intensity exercise to youth at risk of T2DM increases the likelihood of experiencing the targeted benefits (responding) to exercise, and; 2) Investigate if increasing exercise intensity can be used as a method to adapt an exercise prescription to improve the response categorization for individuals living with prediabetes or T2DM who were previously identified as non-responders.

Methods: The dissertation is broken into two studies: (1) An analysis calculating the influence of exercise on response heterogeneity for cardiometabolic risk factors in youth at risk of T2DM. Subsequently, the proportion of responders for each risk factor was estimated; and (2) A randomized trial identifying non-responders among individuals living with prediabetes or T2DM, prior to exploring if increasing exercise intensity would improve the response categorization for non-responders.

Results: We found the proportion of youth estimated to respond spanned from 36% to 69%, depending on the intensity of exercise and the outcome of interest. Moreover, it was found that maintaining and increasing the intensity of exercise is capable of improving the

response categorization of a small number of participants, although the likelihood of success is small.

Conclusion: This dissertation outlined the influence of exercise on response heterogeneity. The inconsistent response to exercise training was brought to light and for the first time discussed in the context of T2DM. Moreover, a unique attempt to improve the response categorization of individuals categorized as non-responders provided an outline for how to transition these methods to a clinical setting.

Dedication

This dissertation is dedicated to the Toronto Maple Leafs for being a constant source of comedic relief, a reminder to focus on the things I can control, and a lifelong reason to stay humble.

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List of Abbreviations

AMP: Adenosine monophosphate

AMPK: AMP-activated protein kinase

ATP: Adenosine triphosphate

BMI: Body mass index

Ca^{2+}: Calcium

CRF: Cardiorespiratory fitness

CI: Confidence interval

DPP-4: Dipeptidyl peptidase 4

ET: Exercise training

GLP-1: Glucagon-like peptide-1

GLUT4: Glucose transporter type 4

GIP: Glucose-dependent insuliotropic polypeptide

HbA1c: glycated hemoglobin

HIIT: High-intensity interval training

IFG: Impaired fasting glucose

IGT: Impaired glucose tolerance

MCID: Minimal clinically important difference

MCIC: Minimal clinically important change

METs: Metabolic equivalent tasks

OGTT: Oral glucose tolerance test

SD_{IR}: Standard deviation of individual responses

SD_{CON}: Standard deviation of the observed change scores in the control group

SD_{INT}: Standard deviation of the observed change scores in intervention group

SWD: Smallest worthwhile difference

T2DM: Type 2 Diabetes Mellitus

TE_M: Typical error of the measurement

TE_Δ: Typical error of the change score

TZD: Thiazolidinedione

VO_2R: VO_2 reserve

VO_{2peak}: VO_2 peak

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Chapter 1.0 Introduction

1.1 Background

Type 2 diabetes mellitus (T2DM) is one of the most prevalent health issues facing Canadians. The World Health Organization estimates high blood glucose is the third highest risk factor for premature mortality, and rates of T2DM in Canada are on the rise (Geneva, Switzerland: World Health Organization, 2009). Diabetes Canada estimates the prevalence of T2DM was 3.4 million, or 9.3% of the population in 2015, and has predicted a rise to 5 million (12.1% of the population) by 2025, representing a 44% increase (Diabetes Canada, 2017). In New Brunswick it is estimated the prevalence of T2DM may have been as high as 14.9% of the population in 2014, with the potential to reach up to 29.1% by 2038 (Gupta, 2017). The costs associated with T2DM treatment and care are substantial, with an estimated national 10-year health care cost of approximately $15 billion, with out-of-pocket costs of approximately $1,200 - $1,900 per year (Anja & Laura, 2017; Diabetes Canada, 2017).

Of additional concern is the 22.1% of the population estimated to have prediabetes (Diabetes Canada, 2017). Prediabetes is characterized by a chronic state of hyperglycemia, representing a transition from normoglycemia to impaired glucose tolerance (DeFronzo, 2004). Approximately 25-50% of individuals diagnosed with prediabetes will develop T2DM within five years of the diagnosis, a rate 20 times higher than those with normoglycemia (DiMenna & Arad, 2018; Zhang et al., 2010), with 70% of those diagnosed likely to reach T2DM within 10 years (Tabák et al., 2012). Identifying methods to slow the progression from prediabetes to T2DM are of key interest to health care providers. Moreover, the direct and indirect costs associated with treating an individual

with prediabetes are approximately $7,000 per year less than treating T2DM (American Diabetes Association, 2013; Vojta, et al., 2012), underscoring the financial benefits of slowing or preventing such a progression.

1.2 Pathophysiology and Progression from Prediabetes to Type 2 Diabetes Mellitus

To properly understand the pathophysiology associated with the progression towards prediabetes and T2DM, it is beneficial to review the components of healthy glucose homeostasis.

Healthy glucose homeostasis

In a post-absorptive (fasted) state the body is reliant on the liver to produce glucose endogenously and provide fuel for insulin-independent tissue (e.g., neural tissue); however a small portion is also metabolized by insulin-dependent tissue (Abdul-Ghani & DeFronzo, 2010; DeFronzo, 2004). Hepatic glucose production occurs via two primary mechanisms, known as glycogenolysis and gluconeogenesis (Cherrington, 1999). Glycogenolysis is the process of breaking down stored glycogen into glucose for release into the bloodstream. Conversely, gluconeogenesis generates glucose from non-carbohydrate substrates such as lactate, glycerol, and amino acids (Pelley, 2012).

Without the influence of exogenous glucose, homeostasis is largely dependent on the continuous feedback loop between hepatic glucose and pancreatic insulin production. Low glucose concentrations signal the release of glucagon from the α-cells of the pancreas, which in turn activate hepatic glucose production. The subsequent rise in plasma glucose concentrations signal insulin secretion from the pancreatic ß-cells, increasing insulin concentrations which exert an inhibitory effect on glucagon production, thereby slowing hepatic glucose production. In a healthy state, the relationship between hepatic glucose production and insulin is very tightly controlled (DeFronzo, 2004). Should the

feedback loop be interrupted, or hepatic glucose production go unopposed by a subsequent increase in insulin secretion, the homeostatic state of glucose control is disturbed.

Healthy glucose homeostasis following a meal

Ingestion of a carbohydrate-containing meal introduces exogenous glucose to the blood stream, raising plasma glucose concentrations. The resultant hyperglycemia stimulates insulin release from the ß-cells of the pancreas. The consequential onset of hyperinsulinemia contributes to a variety of physiological adaptations, working in unison to clear glucose from the bloodstream and restore homeostasis. First, similar to what is observed in the fasted state, hepatic glucose production will be suppressed (Basu et al., 2013). Additionally, the gastrointestinal method of glucose entry will result in enhanced splanchnic (primarily hepatic) glucose uptake and disposal during the hyperglycemic state (DeFronzo, Ferrannini et al., 1983; Ferrannini et al., 1985). Finally, and most notably, peripheral insulin-dependent tissues – primarily skeletal muscle tissue – will significantly increase their glucose uptake when in the presence of insulin (Basu et al., 2000; DeFronzo, 2004; DeFronzo et al., 1983; Rizza, 2010). Peripheral glucose uptake represents the most significant contributing factor associated with blood glucose clearance and the re-establishment of homeostasis following the ingestion of carbohydrates.

Additional sources of influence on glucose homeostasis

Adipose tissue and the release of free fatty acids also influence glucose homeostasis. In a pre-prandial state, free fatty acids inhibit insulin secretion, stimulate fatty acid oxidation in the muscle, and stimulate hepatic glucose production (DeFronzo & Tripathy, 2009; Groop et al., 1989; Prato, 2009; Röder et al., 2016). When insulin (a potent antilipolytic hormone) concentrations increase in response to hyperglycemia, free fatty acid concentrations are reduced (Boden, 1997). The reduction of free fatty acids in the

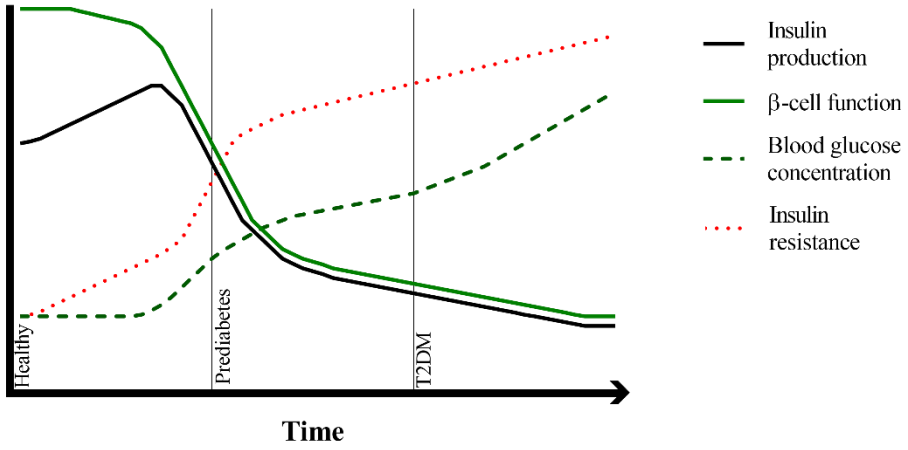
bloodstream reduces the availability a potential fuel source, thus promoting glucose uptake by the periphery, while also contributing to the inhibition of hepatic glucose production (Groop et al., 1989).

Post-prandial glucose clearance is largely aided through the incretin response (Holst et al., 2011; Seino, 2011). Following consumption of glucose, amino acids, and/or free fatty acids, the hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insuliotropic polypeptide (GIP) are released from the intestine. These 'incretin' hormones bind to ß-cell receptors in the pancreas and promote additional insulin secretion. The incretin response is estimated to aid in upwards of 50-70% of total insulin secretion following oral glucose consumption (Chaudhury et al., 2017; Röder et al., 2016). Moreover, GLP-1 supresses hepatic glucose production, pancreatic glucagon secretion, and increases ß-cell insulin sensitivity.

Progression from normoglycemia to Type 2 Diabetes Mellitus

The progression from normoglycemia to T2DM is best described as a continuous degradation in the ability to adequately compensate for a progressive resistance to insulin. Weir and Bonner-Weir (2004) suggest the progression is composed of five clear stages, with insulin resistance starting a pathophysiological degradation taking place across a number of years (Figure 1).

Figure 1. Progression from normoglycemia to T2DM



Early in the progression towards T2DM insulin resistance is established in otherwise insulin-sensitive tissues, resulting in a decreased response to the hormone. Although the exact cause of the initial insulin resistance is yet to be fully delineated, lipotoxicity (the negative effects of chronically elevated of free fatty acid concentrations) has been connected to increased gluconeogenesis in the liver and impaired insulin signal transduction in skeletal muscle; thus suggesting a potential connection to its development (Boden, 1997; DeFronzo & Tripathy, 2009; DiMenna & Arad, 2018; Prato, 2009). Resistance to insulin impairs glucose transport into insulin-dependent tissues, resulting in increased circulating glucose concentrations. However, in the early stages of the disease pathology, pancreatic ß-cells successfully compensate for the dysfunction by increasing insulin production (Gastaldelli, et al., 2004). More specifically, the pancreatic ß-cell mass increases in response to the demand for higher insulin concentrations, allowing glucose stimulated insulin secretion to remain intact (Weir & Bonner-Weir, 2004). As a result, despite the establishment of insulin resistance, glucose concentrations remain relatively

stable. This state of compensation represents the first stage of the progression towards T2DM.

Stage two begins if the state of insulin resistance persists or worsens, as the ß-cell's ability to produce compensatory levels of insulin will degrade, eventually becoming unable to produce enough insulin to maintain a healthy concentration of glucose. Accordingly, a persistent rise in glucose is associated with drastic reductions in ß-cell function (by approximately 40-60%), resulting in the diagnosis of prediabetes (Butler et al., 2003; Ferrannini et al., 2005; Gastaldelli et al., 2004; Weyer et al., 1999).

The underlying pathology producing prediabetes, be it impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both, depends on the tissue(s) that become insulin resistant. If the primary site of insulin resistance is the liver, hepatic glucose production will be inadequately suppressed despite pre-prandial homeostasis. As a result, gluconeogenesis will unnecessarily continue, and elevated concentrations of glucose will be detected in the blood. The resultant diagnosis of prediabetes is then made as a result of IFG. (Abdul-Ghani & DeFronzo, 2010; Basu et al., 2013; Basu et al., 2004; Bock et al., 2006; Petersen, Vatner, & Shulman, 2017). If peripheral muscle tissue is the primary site of insulin resistance, glucose clearance following the consumption of a glucose-containing meal is reduced and/or delayed. Postprandial blood glucose concentrations therefore remain elevated for a longer period of time than what would be considered 'normal', and prediabetes is diagnosed by way of IGT (Abdul-Ghani & DeFronzo, 2010; DeFronzo et al., 1985; DeFronzo, 2009; Meyer et al., 2006).

A key consequence associated with the degradation ß-cell function is the impairment of acute glucose stimulated insulin release, also referred to as the first phase insulin response (DeFronzo, 2004; Weir & Bonner-Weir, 2004). Typically, the initial ß-

cell response to an influx of glucose is a rapid release of insulin, meant to prepare insulin sensitive-tissues and signal the liver to stop hepatic glucose production (Curry et al., 1968). However, loss of the first phase insulin response leads to higher levels of endogenous glucose, and delayed clearance of exogenous glucose following a meal (Bock et al., 2006; Gastaldelli et al., 2004; Meyer et al., 2006). Together, the effects associated with losing the first phase insulin response prolong the time spent with elevated glucose concentrations, further degrading ß-cell function.

Prediabetes can be maintained for a number of years (Weir & Bonner-Weir, 2004). However, without intensive lifestyle modification and/or pharmaceutical assistance, ß-cell function will continue to degrade, the condition will worsen and blood glucose concentrations will continue to rise, described as stage three of the model outlined by Weir and Bonner-Weir (2004). The sustained hyperglycemia experienced with improper management will have a negative effect on the remaining functional ß-cells, as reactive oxygen species limit the ability to produce insulin and in some cases induce apoptosis (Robertson, et al., 2003). Such a cascade leads to severe impairment in ß-cell function and mass, subsequent increases in blood glucose concentrations, and the eventual diagnosis of T2DM. Typically, by the time a diagnosis of T2DM can be made, ß-cell mass is reduced by 40-50% (DeFronzo, 2004; Weir & Bonner-Weir, 2004). Stage four and five of the progression to T2DM consist of the eventual diagnosis of T2DM, and the eventual state of ketosis that may be achieved if the condition remains untreated.

Interestingly, Basu et al., (2004) used a euglycemic-hyperinsulinemic clamp to show that despite the onset of T2DM, increasing plasma insulin concentrations to a state of hyperinsulinemia can still suppress hepatic glucose production to a level similar to normoglycemic participants. Therefore, the eventual progression from living with

prediabetes to living with T2DM is characterized by the failure of the pancreatic ß-cells to produce insulin at the rate necessary to overcome insulin resistance. It is theorized the pace of the ß-cell failure and the resultant reduction in insulin secretion will ultimately determine the rate at which an individual progresses from normal glucose tolerance, to prediabetes, to living with T2DM (DeFronzo, 2009).

Lipotoxicity and glucotoxicity as causes of ß-cell failure

A number of determinants have been associated with the progressive degradation of ß-cell function. While evidence exists for the contribution of genetics, advancing age and amyloid deposits within the pancreas, chronic increases in plasma free fatty acids (lipotoxicity), and chronic increases in the plasma glucose concentrations (glucotoxicity), have been targeted as the primary causes (DeFronzo, 2009; Donath & Shoelson, 2011; Halban et al., 2014; Kashyap et al., 2003; Prato, 2009).

Free fatty acids aid in both the stimulation and inhibition of insulin secretion (DeFronzo, 2004; McGarry, 2002; Röder et al., 2016). However, when free fatty acid concentrations are chronically elevated, the typical regulatory actions produce adverse affects on the ß-cell's ability to secret insulin (Kruit et al., 2011; McGarry, 2002; Prato, 2009). Numerous mechanisms proliferate the toxic effects, including the introduction of reactive oxygen species, the accumulation of fatty acids within the cell, and fatty-acid induced apoptosis (Halban et al., 2014; Lupi & Del Prato, 2008). The accumulation of fatty acids within the ß-cells leads to depressed biosynthesis of insulin, thereby reducing total insulin content and inhibiting the magnitude of response when glucose is introduced to the bloodstream (Bollheimer et al., 1998; Lupi et al., 2002; Zhou & Grill, 1995). The negative effect of elevated free fatty acid concentrations on insulin secretory patterns was displayed by Kashyap et al. (2003), who successfully reduced first and second-phase

insulin response by 25 and 42%, respectively, using a 4-day lipid infusion. The importance of the first-phase insulin response to maintaining an appropriate response to elevated glucose concentrations, and the subsequent insulin release termed 'second-phase insulin response' to restoring homeostatic glucose concentrations cannot be understated. Therefore, the loss of these processes as a result of elevated free fatty acid concentrations indicates the potential role of lipotoxicity in the deterioration of glycemic control, likely occurring before glucotoxicity in the natural course of the disease (Prato, 2009).

The chronic elevation of glucose (glucotoxicity) also exerts a negative effect on ß-cell function. Leahy et al. (1986) were among the first to show this, using a hyperglycemic rat model to produce to a 50% reduction in pancreatic insulin stores. Numerous studies have replicated these results leading to the belief that maintained over-stimulation of glucose leads to a reduction in the ß-cell response, in part due to the necessity for prolonged insulin secretion and the gradual depletion of insulin stores (Björklund & Grill, 1993; Bolaffi et al., 1986; Kaiser, Leibowitz, & Nesher, 2003). The negative effects of glucotoxicity are believed to largely be a result of reactive oxygen species and the oxidative stress they impose (Guerra et al., 2005; Kaiser et al., 2003; Lupi et al., 2007; Newsholme et al., 2007; Prato, 2009). Specifically, reactive oxygen species have been linked to ß-cell apoptosis and to reducing the activity of signal transducing enzymes (Guerra et al., 2005; Kaiser et al., 2003; Newsholme et al., 2007). The concomitant effect of glucotoxicity following the loss of first-phase insulin response (as a result of initial lipotoxicity) exacerbates the detrimental effects of each condition, thus producing and maintaining a vicious cycle (Prato, 2009; Weir & Bonner-Weir, 2004). Interrupting this cycle, be it with lifestyle change or pharmaceutical intervention, is vital to preventing the progression from prediabetes to T2DM.

1.3 The Diagnosis of Prediabetes and Type 2 Diabetes Mellitus

Three tests are currently recognized as valid for the diagnosis of prediabetes and T2DM: fasting blood glucose concentrations, the oral glucose tolerance test (OGTT), and the percent of HbA1c While the end point of T2DM may be similar for each of these tests, the pathological mechanisms behind each abnormality differs. Fasting blood glucose and the OGTT in particular represent two distinct pathophysiological disturbances that contribute to the progression towards T2DM.

Fasting Blood Glucose

An individual with a fasting blood glucose concentration of 5.6 to 6.9 mmol/L (100 to 125 mg/dL) would be classified as living with prediabetes, based on having IFG. The progression to a fasting blood glucose of 7.0 mmol/L (126 mg/dL) or above, as verified by duplicate testing, would indicate the individual is living with T2DM (American Diabetes Association, 2010).

Testing the fasting blood glucose concentration provides a reflection of pre-prandial glucose homeostasis, when glucose homeostasis is primarily controlled by the feedback loop between the production of endogenous glucose from the liver, and pancreatic ß-cell insulin secretion. The majority of glucose uptake and disposal occurs through insulin-independent tissue, meaning the primary role of insulin is to aid in glucose homeostasis by limiting hepatic glucose production. Hepatic insulin resistance disrupts the feedback loop between the liver the pancreas, disrupting insulin's ability to stop hepatic glucose production and ultimately resulting in increased fasting blood glucose concentrations. Accordingly, a rise in the fasting plasma glucose concentration is associated with maintained hepatic glucose production despite the presence of glucose, leading to chronically elevated glucose concentrations. Individuals who present solely

with IFG typically display relatively healthy glucose clearance following an OGTT (Abdul-Ghani et al., 2006; Bock et al., 2006; Gastaldelli et al., 2004). This is due to peripheral tissue (e.g. muscle tissue) remaining sensitive to the actions of insulin despite the progressive worsening of hepatic insulin resistance. (Basu et al., 2000).

Testing for IFG (determining the fasting blood glucose concentration) is relatively inexpensive and requires patients to complete an 8-hour fast prior to testing (American Diabetes Association, 2003). A major limitation associated with IFG testing is the unavoidable variation associated with the measurement, with testing often displaying a 12.5% coefficient of variation (Lacher et al., 2005; Sacks, 2011; Selvin et al., 2007). Moreover, numerous extraneous factors can acutely impact fasting glucose concentrations, including current medications, body posture, recent exercise, illness, diurnal variation, and acute stress (Asano et al., 2014; Sacks, 2011; Selvin et al., 2007; Troisi et al., 2000). As such, duplicate testing is required to ensure accuracy in the diagnosis of prediabetes or T2DM, leading to practical limitations in its utility. Testing of the sample must also completed within a strict timeline, as glucose concentrations may decrease by 5-7% per hour as blood remains in a test tube (Sacks et al., 2011).

Oral Glucose Tolerance Test

An individual with a blood glucose concentration of 7.8 to 11.0 mmol/L (140 to 199 mg/dL) following the completion of the two-hour OGTT would be classified as living with prediabetes, based on having IGT. The progression to a blood glucose concentration of 11.1 mmol/L (200 mg/dL) or above after the OGTT, as verified by duplicate testing, would indicate the individual is living with T2DM (American Diabetes Association, 2010).

The OGTT provides a reflection of glucose homeostasis in a postprandial state, reflecting glucose tolerance and encapsulating the sensitivity of the ß-cells to hyperglycemia, the suppression of hepatic glucose production, and peripheral insulin sensitivity (Bock et al., 2006; Gastaldelli et al., 2004; Meyer et al., 2006). If ß-cell glucose sensitivity is impaired, a reduction in first phase insulin response will be observed within the first 30-minutes of the OGTT. A reduction in insulin secretion from the ß-cells, typically observed alongside peripheral insulin resistance, will result in elevated glucose concentrations from the 60-minute timepoint of the OGTT onwards. If concentrations remain elevated at the 120-minute post-ingestion timepoint, impaired second phase insulin secretion alongside IGT is confirmed.

The ability of the OGTT to provide a two-hour time course of glucose control in 30 minute intervals is a key benefit in its utility, in that it provides information pertaining to both IGT and IFG statuses. If the test indicates elevated blood glucose concentrations at baseline and 30-miuntes, but not throughout the remainder of the test, elevated hepatic glucose production, hepatic insulin resistance, and IFG can be inferred (Abdul-Ghani et al., 2006). Likewise, if glucose is within a healthy range at baseline, but becomes and remains abnormally high throughout the test, peripheral insulin resistance and IGT can be inferred (Abdul-Ghani et al., 2006).

It is possible to simultaneously present with both IFG and IGT. The defects associated with each of these unique metabolic abnormalities have an additive effect when both are present (Meyer et al., 2006). In such a case, hepatic insulin resistance, peripheral insulin resistance, and reduced ß-cell function would all contribute to the observed OGTT outcome. Increased gluconeogenesis would lead to an elevated fasting plasma glucose concentration before the start of the OGTT, reduced ß-cell sensitivity would then delay

the first phase insulin response, and reduced ß-cell function would diminish the second phase insulin response. The additive effects lead to higher peak plasma glucose concentrations than what are typically observed as a result of IGT or IFG alone, prolonged hyperglycemia, and elevated glucose concentrations following the OGTT (Abdul-Ghani et al., 2006; Bock et al., 2006; Meyer et al., 2006).

To conduct an OGTT, patients consume a beverage containing 75 grams of glucose within one minute and remain seated for two hours. Blood draws are taken before the start of the test, and every 30 minutes thereafter for two hours. Prior to the test, patients fast for a minimum of 10 hours and ingest at least 150 grams of carbohydrate during each of the prior three days (Sacks, 2011; Selvin et al., 2007). Similar to fasting blood glucose measurements, a major limitation for the OGTT is the variability associated with its measurement, with a coefficient of variation of approximately 16.6% (Selvin et al., 2007). Likewise, many of the factors potentially influencing fasting blood glucose measurements also influence the OGTT, including recent exercise, stress, sample handling, and illness (Asano et al., 2014; Sacks, 2011; Selvin et al., 2007). As a result, duplicate testing is also a requirement for the diagnosis of IGT via an OGTT, and steps should be taken to limit the influence of extraneous factors.

Glycated Hemoglobin

An individual with an HbA1c of 5.7 to 6.4% would be classified as living with prediabetes. Progression to an HbA1c of 6.5% or above would indicate that the individual is living with T2DM (American Diabetes Association, 2010).

The glycation of hemoglobin proteins occurs in the blood via the non-enzymatic, irreversible attachment of glucose to the ß-chain of hemoglobin (Sherwani et al., 2016). As the attachment is irreversible in nature, it will persist for the entirety of the approximate

120 day lifespan of the hemoglobin. The formation of HbA1c occurs naturally, making up approximately 5% of HbA proteins in healthy individuals (Florkowski, 2013; Koenig et al., 1976; Sherwani et al., 2016). However, as red blood cells are freely permeable to glucose, the rate at which HbA1c is formed will be proportional to the concentration of glucose within the blood throughout the red blood cell's lifespan. (Makris & Spanou, 2011; Shapiro et al., 1980). This was confirmed by Nathan et al., (2008) who found the percentage of HbA1c in the blood reflected the average blood glucose concentration across the preceding three month period. Therefore, HbA1c evaluations provide a representation of chronic blood glucose concentrations (Florkowski, 2013; Koenig et al., 1976; Sherwani et al., 2016).

When using HbA1c to track the progression from normoglycemia to living with T2DM, a clinician is tracking the rise in average blood glucose concentration, which may be caused by IFG, IGT, or a combination of the two. As the nature of an HbA1c measurement represents the chronic status of the glycemic state it provides a substantially more convenient diagnostic method, due to the minimal impact of acute fluctuations in glycemia. Short-term lifestyle alterations including recent exercise, stress, acute illness, diurnal rhythm, or the consumption of food will not perturb the results of an HbA1c measurement, meaning usable blood samples can be taken without substantial preparation (e.g. being fasted) (Bruns & Knowler, 2009; Florkowski, 2013; Sacks, 2011; Ziemer et al., 2010). Additionally, the HbA1c assay only requires a single blood draw and is subject to relatively small variance, with a coefficient of variation of approximately 3.6% (Sacks et al., 2011; Selvin et al., 2007). Due to these factors, the HbA1c measurement is currently the recommended standard of care for testing and monitoring T2DM (American Diabetes Association, 2003).

While the benefits of using HbA1c to diagnose prediabetes or T2DM are clear, there are some definite considerations to be made. HbA1c measurements can vary based on race, with Caucasian patients displaying lower values when compared to Mexican or Black patients (Davidson & Schriger, 2010; Florkowski, 2013; Herman & Cohen, 2012; Wisdom et al., 1997; Ziemer et al., 2010). Therefore, relying on the standardized diagnostic cut-offs alone may inaccurately categorize patients of different races as living with prediabetes. Additionally, as the interpretation of HbA1c is highly dependent on the function and lifespan of red blood cells, hemolytic diseases, conditions with shortened red blood cell survival, iron deficiency, or recent bouts of acute blood loss (and thus a recent influx of young blood cells), may influence the HbA1c outcome (Kilpatrick, 2008; Makris & Spanou, 2011). A key limitation when utilizing HbA1c as a diagnostic tool in individuals living with prediabetes is the inability to distinguish between IFG and IGT. Using HbA1c does not provide additional information pertaining to the mechanism associated with the increase in the plasma glucose concentration. Whereas a fasting blood glucose measurement can indicate IFG, and the OGTT can provide information on either IFG or IGT, HbA1c can only provide a universal indication of an abnormality. In other words, while it is clear that the average blood glucose concentration is increasing, the clinician remains uncertain as to exactly why. This limits the ability to target the root cause of the dysfunction, thus restricting the individualization of pharmaceutical treatment.

1.4 Medications to Treat Prediabetes and Type 2 Diabetes Mellitus

Once the underlying mechanism leading to prediabetes or T2DM has been identified, pharmaceutical intervention is often used in an attempt to re-establish a degree of glycemic control. The chosen medication is typically individualized to the patient based on a variety of factors, including current risk, the degree of the dysfunction, medication

efficacy, ease of use, cost, and the associated side effects. A number of medication options exist, including agents used to enhance insulin secretion, to improve insulin sensitivity at the target organ(s), or to reduce glucose absorption from the gastrointestinal tract. Lastly, some patients will directly medicate through the utility of insulin therapy.

Medications to enhance insulin secretion

Sulfonylureas. Sulfonylureas are insulin secretagogues which bind to receptors in the pancreas and directly influence endogenous insulin release. Sulfonylureas also decrease lipolysis and reduce hepatic insulin clearance (Proks et al., 2002). As a result, they have been shown to improve glucose uptake by insulin-dependent tissues, and reduce hepatic glycogenolysis and gluconeogenesis (Kolterman et al., 1984; Overkamp et al., 2002).

The mechanisms by which sulfonylureas act do not provide any direct protective effects for the ß-cells. Therefore, while an initial drop in HbA1c is typically observed a progressive deterioration in ß-cell function may still occur. This has led to patients experiencing rises in HbA1c that are similar to those who receive ‘standard care’ (UK Prospectice Diabetes Study (UKPDS) Group, 1998). One key potential side effect associated with sulfonylurea use is hypoglycemia, brought on as a result of the sudden increase in insulin availability (Chaudhury et al., 2017).

Incretin Mimetics. Drugs designed to mimic the effect of the incretin hormones are used to enhance insulin secretion from the pancreas. The incretin effect is typically reduced or non-existent in T2DM, and GLP-1 receptor agonists or dipeptidyl peptidase 4 (DPP-4; the hormone responsible for hydrolyzing incretins) inhibitors can be used to maintain, or potentially re-establish, the effect. GLP-1 receptor agonists are designed to increase insulin release through due to an increased resistance to degradation by DPP-4.

Conversely, DPP-4 inhibitors prolong incretin action by inhibiting the DPP-4's hydrolyzing effects. These drugs have a potent ability to augment ß-cell function, resulting in reductions in hepatic glucose production and glucagon secretion, and improving overall glycemic control (Bunck et al., 2009; DeFronzo, 2009; DeFronzo et al., 2005). As an added benefit incretin mimetics slow gastric emptying, limiting the feeling of hunger and thus promoting weight loss (Buse et al., 2010; DeFronzo, 2009; Harris & McCarty, 2015).

An important characteristic of GLP-1 analogues are the drug's glucose-dependent mechanism of action, in that its stimulatory effect will dissipate as normoglycemia is achieved. Therefore, unlike sulfonylureas, GLP-1 analogue action will recede in accordance with glucose concentrations, preventing the onset of hypoglycemia (Chaudhury et al., 2017; DeFronzo, 2009; Elahi et al., 1994; Elliott et al., 1993; Holz, Leech, & Habener, 1995; Nathan et al., 1992). Incretin mimetics exert a beneficial influence on HbA1c concentrations that is believed to persist for years, while also helping maintain ß-cells (Farilla et al., 2003; Klonoff et al., 2008). Potential side effects are relatively minimal, including nausea, gastrointestinal irritation, and vomiting (Buse et al., 2010; Moretto et al., 2008; Ratner et al., 2006, 2010; Zinman et al., 2009).

Medications to improve insulin sensitivity

Metformin. Metformin is the most widely used, first line drug of choice in the management of T2DM, enhancing both hepatic and peripheral glucose uptake by inhibiting gluconeogenesis, increasing insulin gene expression within the ß-cells, and reducing lipotoxicity-induced defects (Hundal et al., 2000; Jiang et al., 2014; Lupi et al., 2002; Musi et al., 2002; Viollet et al., 2012). The side effects associated with Metformin use are relatively mild (Chaudhury et al., 2017; Seifarth et al., 2013). In the initial stages of T2DM metformin can be highly efficient, producing a reduction in HbA1c (Chaudhury

et al., 2017; Kahn et al., 2006; Lupi et al., 2002; UK Prospectice DIabetes Study (UKPDS) Group, 1998). However, its utility is highly dependent on the ability of ß-cells to produce sufficient levels of insulin. Therefore, as T2DM progresses and ß-cell function declines, Metformin will eventually diminish in its effectiveness. As early as three years into Metformin use, approximately 50% of T2DM patients have been shown to require additional medication to re-establish glycemic control (Group, 1998; Turner et al., 1999). Moreover, the ADOPTrial (A Diabetes Outcome Progression Trial) outlined the association of Metformin with a decline in ß-cell function – and the subsequent increase in HbA1c – following a year of utility, indicating the potential for a truly short term benefit associated with its use (S. E. Kahn et al., 2006).

Thiazolidinedione. Similar to Metformin, thiazolidinedione (TZD) improves insulin action by improving insulin sensitivity in adipose, muscle and liver tissue (Chaudhury et al., 2017). TZDs promote lipogenesis and develop new fat cells, augmenting free fatty acid removal from the blood and increasing the preference for peripheral tissue to utilize glucose (Röder et al., 2016). The increased rate of lipogenesis projects additional benefit to the ß-cells, reducing the inflammatory effects of free fatty acids and preserving ß-cell integrity and function, preventing apoptosis and potentially increasing overall ß-cell mass (Diani et al., 2004; Ishida et al., 2004). The actions of TZDs lead to initial reductions in HbA1c of approximately 1 – 2%, which can be maintained for well over a year (S. E. Kahn et al., 2006; Rosenstock et al., 2006; Tan et al., 2005). Moreover, when provided to patients living with prediabetes, the risk of progressing to T2DM has been shown to be reduced by 62% (The DREAM Trial Investigators, 2006).

However, while the impact of TZDs are certainly encouraging, the potential risks associated with their utility need to be considered. The increase in lipogenesis often leads

to weight gain, and earlier versions of the drug have been connected to liver toxicity and increased risk of cardiovascular events (Murphy et al., 2000; Nissen & Wolski, 2007; Smith et al., 2005).

Medications to reduce glucose absorption

Alpha-glucosidase inhibitors reduce the level of glucose entering the blood stream and thus lower blood glucose fluctuations following a meal (Hillebrand et al., 1979). They promote an improvement in overall insulin sensitivity and triglyceride levels, and aid in preventing further reductions in ß-cell mass (Hillebrand et al., 1979; Röder et al., 2016; Wolever et al., 1998). However, the effect on HbA1c is somewhat limited, as they are typically associated with a 0.5% – 1.0% reduction (Hanefeld & Schaper, 2008).

Insulin as a medication

Insulin is typically recommended for patients who have recently been diagnosed as living with T2DM, those who are clearly symptomatic, or those who have severely elevated blood glucose levels (an HbA1c concentration of 10% or above) (American Diabetes Association, 2019). Many individuals diagnosed as living with T2DM will require insulin at some point during the course of the disease, with an ideal regimen mimicking healthy physiological insulin release to provide optimal glycemic control (Chaudhury et al., 2017). Basal insulin is the initial method of insulin treatment, with the severity of hyperglycemia determining the required dose, and if an additional medicinal agent is necessary. If HbA1c concentrations remain above the targeted level, mealtime insulin doses may be added to the treatment plan (Chaudhury et al., 2017).

Insulin therapy should effectively reduce hyperglycemia and minimize the glucotoxic effects on the ß-cells. At the point of improved glycemic control oral medications can be successfully implemented into the routine, and in some cases, insulin

treatment can be reduced (Chaudhury et al., 2017). However, when taking insulin, patients need to closely monitor their glycemic state due to a high risk for hypoglycemia (UK Prospectice DIabetes Study (UKPDS) Group, 1998).

1.5 Exercise as a Treatment for Prediabetes and Type 2 Diabetes Mellitus

While pharmaceutical intervention is undeniably an important consideration for the clinical management of T2DM, lifestyle intervention – including participation in regular exercise – is considered an integral piece to prediabetes and T2DM management. Current treatment recommendations from the United States, Canada, and the World Health Organization recommend exercise as part of an overall management plan for those living with either condition, often alongside changes in diet, alcohol consumption and tobacco use (Colberg et al., 2016; Diabetes Canada Clinical Practice Guidelines Expert Committee, 2018; World Health Organization, 2010).

Physiological adaptations

From a physiological perspective, the benefits associated with exercise are logical. Skeletal muscle plays a significant role in glycemic control, and is the primary site for insulin-induced glucose uptake (DeFronzo et al., 1983; Egan, Hawley, & Zierath, 2016). In individuals who are apparently healthy, as well as those living with prediabetes or T2DM, acute bouts of exercise are capable of increasing skeletal muscle glucose uptake, primarily attributed to the enhanced and prolonged activation of the glucose transporter system – particularly glucose transporter type 4 (GLUT4) – and via the depletion of liver and skeletal muscle glycogen stores (Frøsig & Richter, 2009; Garcia-Roves et al., 2003; Kang et al., 1999; Mann et al., 2014; Pencek et al., 2005; Roberts, Little, & Thyfault, 2013; Röhling et al., 2016; Sriwijitkamol et al., 2007; Watt et al., 2002).

GLUT4 is the primary protein responsible for transporting glucose from the circulation to muscle or adipose tissue (Huang & Czech, 2007). It is acutely stimulated in skeletal muscle tissue by direct recruitment via insulin signaling, or independent of insulin by way muscular contraction. When stimulated by muscular contraction, a number of metabolic pathways act to enhance the translocation of GLUT4 vesicles to the cell membrane, however the two key activators for the exercise mediated uptake of glucose (by way of GLUT4 translocation) are AMP-activated protein kinase (AMPK) and the calcium (Ca^{2+})/calmodulin signaling pathways (Egan & Zierath, 2013; Huang & Czech, 2007; Röhling et al., 2016).

The AMPK enzyme plays an extensive role in cellular metabolism. It is regulated by the energy demands placed on a cell, acting to conserve and replenish cellular adenosine triphosphate (ATP) as needed. Depletion of ATP and the coincident rise in adenosine monophosphate (AMP) within a metabolically active cell will produce a change in the AMP/ATP ratio, thus providing a key signal of change in cellular energy status and stimulating AMPK (Egan & Zierath, 2013; Kahn, Alquier, Carling, & Hardie, 2005; Röhling et al., 2016). During acute exercise cellular ATP is used to produce muscular contractions; altering the energy status of the cell and activating AMPK. Higher intensities of exercise induce a higher ATP turnover rate, and AMPK action will increase proportionally (Green et al., 1992; Howlett et al., 1998; Kahn et al., 2005; Wojtaszewski et al., 2000). Activation of AMPK will supress glycogen and protein synthesis, activate lipid metabolism and signal for GLUT4 translocation to the cell membrane, thus facilitating the transport of glucose into the cell (Bolster et al., 2002; Carling & Hardie, 1989; Merrill et al., 1997). Increased AMPK action by way of acute participation in exercise is associated with increased uptake of glucose by skeletal muscle in people who

are otherwise healthy, as well as those living with T2DM, in an intensity-dependent manner (Kemp et al., 1999; Röhling et al., 2016; Sriwijitkamol et al., 2007).

The Ca^{2+}/calmodulin signaling pathway is also directly related to skeletal muscle contractions during exercise. Muscle contraction increases cytosolic Ca^{2+} concentrations, leading to a proliferation of Ca^{2+}/calmodulin complexes (Egan et al., 2016; Röhling et al., 2016). The overall concentration of Ca^{2+} is positively associated with the intensity and the duration of muscle contraction, meaning more intense and/or longer contractions generate high quantities of Ca^{2+}, and therefore more Ca^{2+}/calmodulin complexes (Egan et al., 2010; Rose et al., 2006). In the context of glucose transport, an important downstream effect of Ca^{2+}/calmodulin is the enhanced expression of GLUT4, thus enhancing the ability of skeletal muscle to uptake glucose in an intensity-dependent manner (Park et al., 2015).

The acute translocation of GLUT4 to the skeletal muscle cell membrane through the downstream influence of AMPK or Ca^{2+}/calmodulin signalling will improve glucose transport into the skeletal muscle cells (Röhling et al., 2016). These processes will have a beneficial effect throughout the participation in, and immediately following, a bout of aerobic or resistance training exercise, regardless of the current diabetic state (Christ-Roberts et al., 2004; Cuff et al., 2003; O'Gorman et al., 2006). Moreover, the beneficial effects of exercise can persist, influencing glucose uptake following the cessation of exercise for 24 – 72 hours (Boulé et al., 2005; Cartee et al., 1989; Garcia-Roves et al., 2003; King et al., 1995).

The depletion of inter-cellular glycogen will provide an additional influence for improved glucose transport. Cellular glycogen stores provide the primary source of carbohydrate for working skeletal muscle (particularly during moderate to vigorous exercise), with the rate of glycogen utility proportionally linked to exercise intensity

(Bergman et al., 1999; Egan & Zierath, 2013; Kang et al., 1999). As glycogen stores are depleted, be it due to prolonged engagement in moderate intensity exercise or repeated bouts of high-intensity exercise, muscle tissue will increase its uptake and usage of circulating glucose and free fatty acids from adipose tissue. Glucose uptake will also persist following the cessation of exercise to support the resynthesizing of glycogen stores (Bergman et al., 1999; Kang et al., 1999; Malin et al., 2016; Watt et al., 2002). For individuals living with T2DM, this process occurs through the aforementioned exercise-induced translocation of GLUT4, and may continue for 42 – 66 hours following the cessation of the exercise bout (Garcia-Roves et al., 2003).

Ongoing participation in exercise training is associated with structural, adaptive, tissue specific physiological responses beneficial for individuals with prediabetes or T2DM. More specifically, aerobic and resistance training will lead to increased skeletal muscle capillarization, with programs designed to improve endurance resulting in mitochondrial upregulation (Henriksson, 1992; Maiorana et al., 2003; Malin et al., 2013; Mandroukas et al., 1986; Prior et al., 2014; Prior et al., 2015). Together, alongside improved aerobic capacity, these adaptations enhance lipid metabolism, thereby reducing lipotoxicity and the associated degradation of pancreatic ß-cells (DiMenna & Arad, 2018; Duncan et al., 2003; Goodpaster et al., 2003; Henriksson, 1992; Kelley & Kelley, 2007; Segal et al., 1991). Chronic AMPK activation brought on by regular exercise aids in mitochondrial biogenesis, alters gene expression to favour additional GLUT4 translocation, and also improves glucose uptake (Bergeron et al., 2001; Egan & Zierath, 2013; Röhling et al., 2016). Resistance training exercise programs may increase skeletal muscle area, enhancing GLUT4 concentrations and producing a 30-70% increase in

GLUT4 translocation (Christ-Roberts et al., 2004; Cuff et al., 2003; S. Mann et al., 2014; O'Gorman et al., 2006; C. K. Roberts et al., 2013).

Practical application of exercise as treatment

In practice, exercise has been investigated (mostly in conjunction with dietary and/or medication changes) as a method for preventing the progression from prediabetes to T2DM, and in attempts to improve glycemic control in individuals with these conditions.

Exercise to Prevent the Progression to T2DM.

Three major trials have used exercise as part of an overall lifestyle intervention to prevent the progression from prediabetes to T2DM; the Finnish Diabetes Prevention Study, the Diabetes Prevention Program, and the Da Qing Prevention Trial.

The Finnish Diabetes Prevention study was a longitudinal trial developed to track 522 middle age, overweight subjects between 40 – 65 years old living with prediabetes. Participants were randomized to either a control group (provided written and oral diet and exercise advice at baseline and annual visits), or an intervention group. The intervention group received detailed, personally tailored dietary advice four times per year, seven sessions with a nutritionist during the first year of the study (one session every three months thereafter), and individual guidance on increasing physical activity (Tuomilehto et al., 2001). At the three year follow-up, 23% of the control group and 11% of the intervention group progressed to T2DM, representing a 58% risk reduction by participating in the intervention (Tuomilehto et al., 2001). The intervention persisted for four years, with additional follow-ups at seven and 13 years (Lindström et al., 2013; Lindström et al., 2006). Seven years following the initiation of the program, T2DM incidence was 4.3 per 100 person-years in the intervention group and 7.4 per 100 person-

years in the controls, a 43% reduction in relative risk (Lindström et al., 2006). At the most recent 13-year follow-up the incidence rate of T2DM was 4.5 per 100 person-years in the intervention group and 7.2 amongst the controls, representing an absolute risk reduction of 19.4% (Lindström et al., 2013). These outcomes outline the ability of intensive lifestyle intervention to reduce the incidence of T2DM and provide long-term protection against T2DM amongst middle age adults with prediabetes.

Similarly, the Diabetes Prevention Program was a longitudinal, 27 center randomized control trial designed to observe the effects of lifestyle intervention compared to medication among 3,234 overweight individuals over the age of 25, living with prediabetes (Knowler et al., 2002). Participants were randomized to one of a control, Metformin treatment, or intensive lifestyle intervention group. Controls were provided standard lifestyle advice during annual 20-30 minute meetings, where they were encouraged to follow the current food guide, reduce their weight, increase overall physical activity, and were prescribed twice daily placebo medication. The Metformin group received the same lifestyle advice as the control group, alongside a twice daily prescription of 850mg Metformin. The goals for the lifestyle intervention group were to achieve and maintain a 7% body weight reduction through a low-calorie, low-fat diet, and to engage in moderate intensity physical activity for at least 150 minutes per week. To achieve these goals participants partook in a 16-lesson, personally individualized curriculum, spanning a 24-week period and delivered in a one-on-one setting. Subsequently, monthly sessions were delivered over a three-year period to support and reinforce all behavioural changes. Following the program the crude incidence of T2DM amongst participants was 11.0 cases per 100 person years for the control group, 7.8 cases per 100 years for the metformin group, and 4.8 cases per 100 years for the lifestyle group; representing a 58% reduction

in T2DM incidence amongst the lifestyle group when compared to controls, and a 39% reduction compared to Metformin treatment (Knowler et al., 2002). Similar results were observed across sexes, racial groups and ethnic groups. Participants were then informed of the results and unmasked of their treatment, and those participants in the control and metformin groups were offered a group-administrated version of the 16-session lifestyle curriculum. All participants were then offered the chance to attend lifestyle counselling sessions every three months. Participants randomized to the lifestyle group were offered the additional opportunity to attend four group sessions a year to reinvigorate their self-management behaviours for weight loss. Outcome assessments were continued on a 6-month schedule until a 10-year follow-up was available, at which point T2DM incidence was reduced by 34% amongst the lifestyle group and 18% amongst the placebo group (Diabetes Prevention Program Research Group, 2009). The findings from the Diabetes Prevention Program further support the ability of intensive lifestyle intervention to prevent or delay progression from prediabetes to T2DM, and suggest lifestyle intervention as a superior method when compared to Metformin medication.

Lastly, the Da Qing IGT and Diabetes Study randomized 530 men and women with prediabetes across 33 health care clinics in China to one of a diet, exercise, diet and exercise, or control group (Xiao-Ren et al., 1997). The diet group was prescribed a diet composed of specific quantities of macro-nutrients and received individual counseling concerning daily food intake each week for one month, monthly for three months, then once every three months for the remainder of the six-year intervention. The exercise group was taught and encouraged to partake in 65 minutes (if above 50 years of age) or 130 minutes (if younger than 50) of exercise per day, composed of a variety of mild, moderate, strenuous, and very strenuous activity. The exercise group also received individual

counseling to achieve these exercise goals once a week for one month, monthly for three months, then once every three months for the remainder of the study. The diet and exercise group received the instructions and counselling that both the diet and the exercise groups received. The control group was exposed to general information about T2DM and prediabetes, and provided general instructions for diet and exercise. Incidence of T2DM six years following the implementation of the study were 15.7 cases per 100 person years for the control group, 10.0 cases for the diet group, 8.3 cases for exercise, and 9.6 cases for the diet and exercise group, representing a significant reduction from the controls, but with no significant differences existing between the various interventions (Xiao-Ren et al., 1997). A twenty-year follow-up was conducted in 2006, and those participants originally randomized to one of the three intervention groups were found to have a 43% lower incidence of T2DM than those from the control group. Moreover, participants in the intervention groups who were ultimately diagnosed with T2DM averaged 3.6 fewer years with T2DM than the controls (Li et al., 2008).

Together, these three seminal studies provide a strong foundation of evidence for the effectiveness of exercise as part of a lifestyle intervention strategy to prevent, or at least slow, the progression of prediabetes to T2DM. Recently, a meta-analysis conducted by Glechner et al., (2018) aggregated and summarized much of the remaining literature outlining the beneficial effects of lifestyle intervention for individuals with prediabetes. Interventions implementing exercise as part of a treatment plan led to a 36-54% lower risk of progressing to T2DM from one to three years when compared to ‘standard care’, further highlighting the importance of exercise as a component of a T2DM prevention plan.

However, the number of trials attempting to investigate the independent effects of exercise are limited. The results from the exercise branch of the Da Qing IGT and Diabetes

Study are seemingly the lone longitudinal intervention arm designed to determine the independent influence of exercise on T2DM prevention (Xiao-Ren et al., 1997). Cross-sectionally, the Studies of Targeted Risk Reduction Interventions through Defined Exercise [in individuals with Prediabetes] (STRRIDE-PD) was undertaken to determine the independent influence of six months of exercise on glucose homeostasis, outline the potential influence of exercise intensity, and understand the extent to which overall exercise volume contributes to these changes (Slentz et al., 2016). Men and women between the ages of 45 and 75 years who were living with prediabetes were randomized to partake in one of four intervention arms for six months: (1) low-amount moderate-intensity (LAMI: energy expenditure of 42 kJ/ kg of body weight per week [KKW] at 50% of VO_2 reserve), (2) high-amount moderate-intensity (HAMI: 67 KKW at 50% of VO_2 reserve), (3) high-amount vigorous-intensity (HAVI: 67 KKW at 75% of VO_2 reserve), or (4) a clinical lifestyle intervention (a dietary intervention modelled to replicate that of the Diabetes Prevention Program, alongside 42 KKW of exercise at 50% of VO_2 reserve). The authors found a significant improvement in fasting glucose (the primary outcome) solely as a result of the diet and exercise lifestyle intervention (Group 4). However, the HAMI group experienced improvements in glucose tolerance that were similar to that of the diet and exercise group, with results superior to that of the HAVI or LAMI groups. The authors concluded that lifestyle interventions combining diet and exercise are effective for those individuals living with prediabetes, and that high volumes of moderate intensity exercise can be an effective method for improving glucose tolerance, whereas smaller volumes of exercise, and higher intensity exercise, are unable to improve any aspect of glycemic control, despite improvements in cardiorespiratory fitness (CRF). Therefore, not only is research investigating the benefits of exercise as an independent

treatment method for individuals living with prediabetes limited, but the results of available research are mixed. Given the low compliance to dietary lifestyle intervention, particularly in comparison to exercise-based interventions, future research investigating the independent effects of exercise is warranted to determine the potential utility in T2DM prevention (Lindahl et al., 2009).

Exercise to improve glycemic control in T2DM.

A plethora of high-quality studies have investigated the benefits of exercise as a method to improve glycemic control in individuals diagnosed with T2DM. Most notably, the Diabetes Aerobic and Resistance Exercise (DARE) and Heath Benefits of Aerobic and Resistance Training in individuals with type 2 diabetes (HART-D) trials were designed to investigate the benefits of aerobic training, resistance training, or a combination of the two for individuals with T2DM (Church et al., 2010; Sigal, 2007).

The DARE trial implemented a 26-week, single center, randomized control trial for 251 participants with HbA1c concentrations between 6.6 and 9.9% (Sigal, 2007). Participants were randomized to one of four groups, each differing in training modality. The control group was asked to maintain pre-trial activity levels; the aerobic exercise group exercised on treadmills or cycle ergometers three times a week, progressing from 15 to 20 minutes at 60% of maximum heart rate per session to 45 minutes at 75% maximum heart rate; the resistance training group exercised three times a week, performing two to three sets of seven exercises at a weight that could be lifted seven to nine times; and the combined group completed the full aerobic program plus the full resistance training program each week. HbA1c concentrations were significantly reduced by both the aerobic (-0.51; 95% Confidence Interval [CI]: -0.87 to -0.14) and resistance (-0.38%; 95% CI: -0.72 to -0.22) exercise programs when compared to the controls. The

combined program produced an additional 0.46 (95% CI: -0.83 to -0.09) improvement compared to the aerobic program, and an additional 0.59 (95% CI: -0.95 to -0.23) improvement compared to the resistance training program. While these data certainly show the ability of exercise training to improve HbA1c, the authors decision to combine the aerobic and resistance training programs without adjusting for volume makes it difficult to differentiate if the additional benefit experienced by the combined group was due in part to completing both types of exercise, or simply due to the overall increased volume (as this group completed twice the amount of activity).

The HART-D trial was designed to address the question of exercise volume introduced by DARE, by comparing the independent benefits of aerobic, resistance, and combined training programs while maintaining similar weekly training volumes (Church et al., 2010). Here, 262 participants with an HbA1c concentration between 6.5 and 11.0% were randomized to one of four, nine month training interventions. The control group was offered weekly stretching and relaxation classes, and instructed to maintain current activity levels. The three exercise group programs were standardized to participant body weight, with the estimation that 150 minutes of moderate intensity exercise per week was equivalent to 10 – 12 kcal/kg of body weight. As such, the aerobic exercise group completed 12 kcal/kg per week at an exercise intensity from 50 – 80% of maximal oxygen consumption. The resistance training group exercised three days per week, with each session consisting of two sets of four upper body exercises, three sets of three lower body exercises, and two sets of abdominal exercises. Each set consisted of 10 to 12 repetitions, with weight increasing once the participant was able to complete 12 repetitions for each set of a provided exercise. The combined group completed 10 kcal/kg/week of aerobic activity at 50 – 80% of maximal oxygen consumption, and two resistance training sessions

per week, completing one set of each of the exercises completed by the resistance training group. The results of the HART-D study provide support for the findings of the DARE trial, in that the combination training group experienced the greatest HbA1c improvement. The degree of the improvement however, was much smaller. Combination training led to a 0.34% (95% CI: -0.64 to -0.03) improvement in HbA1c compared to controls, whereas neither the aerobic or the resistance training groups experienced significant improvements. The authors hypothesized the differences in improvement were due to two main factors: 1) differences in the study population, as the HART-D participants had a longer duration of diabetes (7.1 vs 5.4 years), included more women (63% vs 36%), and had a higher prevalence of participants who were visible minorities (47% vs 8%); and 2) differences in the handling of medications, as the DARE trial excluded participants who were treated with insulin and minimized changes in medication, whereas the HART-D trial allowed participants who were treated with insulin (18.3% of participants) and left medication decisions to the discretion of participants and their physicians (this led to substantial changes in medication across groups). It also warrants noting that the difference in HbA1c between the combination exercise and control groups exists in the HART-D trial even though the control group increased the use of diabetes medication, and the combination training group decreased medication use. In summary, while improvements in HbA1c are seemingly consistent following combined exercise training, the DARE and HART-D trails (despite being two of the highest quality trails investigating this relationship) leave many questions regarding the optimal prescription parameters unanswered.

Fortunately, the quantity of trials investigating the ability of exercise to improve glycemic control in T2DM is high, resulting in several systematic reviews and meta-

analyses designed to establish the preferred prescription parameters. One such analysis from Boulé, et al. (2001) analysed 14 trials representing 504 participants living with T2DM. Post-intervention HbA1c measurements were significantly lower among exercise groups when compared to controls (7.65% vs 8.31%; SD: -0.66%), with similar reductions stemming from aerobic exercise (-0.67%; 95% CI: -1.04 to -0.30) and resistance training (-0.64%; 95% CI: -1.29 to 0.01). Neither exercise intensity nor volume were associated with the degree of HbA1c reduction experienced by participants. Snowling & Hopkins, (2006) included an analysis of combined exercise training in their analysis of 27 studies varying in length and study design. Aerobic training (-0.7%, 90% CI: -1.0 to -0.4), resistance training (-0.5%, 90% CI: -1.0 to -0.1), and combined training (-0.8%, 90% CI: -1.3 to -0.2) were all found to reduce HbA1c to a similar level. Snowling and Hopkins, (2006) also investigated the potential influence of program duration on changes in HbA1c, noting the mean effect of all three exercise modes was greater in programs lasting longer than 12 weeks (compared to those lasting less than 12 weeks), in line with the expected turnover time of red blood cells. A more recent meta-analysis conducted by Schwingshackl et al. (2014) differs from that of Snowling and Hopkins (2006), in that the authors detected additional benefit in participants completing a combination of aerobic and resistance exercise when compared to either type alone. In this analysis, 14 randomized control trials including 915 participants with T2DM were aggregated. A reduction in HbA1c was more pronounced following aerobic training when compared to resistance training (-0.20%, 95% CI: -0.32 to -0.08), with combination training resulting in additional reductions compared to both aerobic (-0.17%, 95% CI: -0.31 to -0.03) and resistance training (-0.62%, 95% CI: -0.95 to -0.30) regimens. A final meta-analysis conducted by Umpierre et al. (2011) was designed to assess the association of structed

training regimens and physical activity advice on changes in HbA1c. The authors included 47 randomized control trials (23 implementing structured exercise programs and 24 only providing exercise advice) totaling 8,538 patients with T2DM who engaged in an exercise intervention for at least 12 weeks. Structured exercise led a 0.67% (95% CI: -0.84 to -0.49) reduction in HbA1c compared to controls, with aerobic training regimens leading to a 0.73% (95% CI: -1.06 to -0.40) reduction, resistance training leading to a 0.57% (95% CI: -1.14 to -0.01) reduction, and combined exercise leading to a 0.51% (95% CI: -0.79 to -0.23) reduction. Moreover, programs structed to achieve more than 150 minutes of aerobic activity per week led to 0.89% (95% CI: -1.26 to -0.51) reductions in HbA1c, whereas programs less than 150 minutes per week led to a 0.36% (95% CI: -0.50 to -0.23) reduction. Moreover, the authors found providing physical activity advice alongside dietary advice led to a 0.58% (95% CI: -0.74 to -0.43) reduction in HbA1c concentration. Taken together, the research suggests exercise can be a successful mechanism for reducing HbA1c in individual living with T2DM. Aerobic and combined exercise modalities have often been found to produce larger reductions when compared to primarily resistance training programs, however each type can benefit patients. Given the apparent inconsistencies in the magnitude of change produced by the various exercise modalities, it is likely the degree of change is associated with parameters of the exercise prescription.

High Intensity Interval Training

Given the intensity-dependent action of the aforementioned AMPK enzyme and Ca^{2+}/calmodulin complexes, exercise intensity may be a vital parameter when using exercise to produce changes in glycemic control. However, neither Boulé et al. (2001) nor Snowling and Hopkins (2006) were able to identify a meaningful impact of exercise intensity on glycemic control, each referencing a paucity of high-quality research

investigating such a relationship. More recent research has started to investigate the ability of high-intensity exercise and high-intensity interval training (HIIT) as methods to improve glycemic control. Little et al. (2011) were among the first to investigate HIIT in a sample of eight individuals living with T2DM. Participants completed 6 HIIT sessions (10 bouts of cycling at approximately 90% of maximal heart rate with 60 seconds of active rest in each session) over the course of two weeks, averaging approximately 75 minutes of exercise per week. The authors reported a significant reduction in average 24-hour blood glucose concentrations (as measured by continuous glucose monitors) from 7.6 ± 1.0 mmol/L to 6.6 ± 0.7 mmol/L as a result of the two weeks of HIIT, also observing increases in overall mitochondrial protein content, and a 369% increase in GLUT4 protein content, thereby becoming one of the first groups to confirm the benefits of low volume, high intensity training as a beneficial exercise option for individuals with T2DM. Terada et al. (2013) followed up the results of the short-term investigation from Little et al. (2011), investigating the feasibility of T2DM patients completing a 12-week HIIT program compared to a moderate intensity, continuous aerobic exercise program. Fifteen participants were randomly allocated to a HIIT or continuous exercise program, and were supervised while exercising 5 times per week, for twelve consecutive weeks. The programs were matched for exercise duration, frequency, and relative intensity via VO_2 Reserve (VO_2R). The continuous exercise group performed exercise at 40% VO_2R for the duration of each session, and the HIIT group completed 1-minute intervals at 100% VO_2R with 3-minute recovery intervals at 20% VO_2R as many times as possible during the allotted time for each session four times per week, with one session of the continuous exercise protocol per week. The authors concluded that the HIIT did not negatively impact exercise adherence or retention compared to the more traditionally used continuous

exercise program, suggesting HIIT completed over a longer period of time could be a viable training method for those living with T2DM. Støa et al. (2017) subsequently investigated if HIIT was a superior training strategy when compared to moderate intensity continuous exercise in terms of reducing risk factors in individuals living with T2DM. Thirty eight people with T2DM were allocated to either a HIIT program (four sets of 4 minutes running at 85-95% of peak heart rate with 4 minutes of active rest between each), or a continuous exercise program (approximately 60 minutes of continuous walking or running at 70-75% peak heart rate), and exercised three times per week for 12 weeks. Participants in the HIIT program experienced a 0.58 ± 0.55% reduction in HbA1c, which was determined to be significantly greater than the non-significant 0.02 ± 0.30% change observed in the continuous training group.

While the results from Støa et al. (2017) certainly suggest an additional benefit when partaking in HIIT, this may not always be the case. A narrative review conducted by Wormgoor et al. (2017) summarized much of the current literature investigating the benefits associated with HIIT on glycemic control and cardiometabolic risk factors in those with T2DM; while the benefits associated with medium term (4-26 week) HIIT protocols certainly provide benefit, most studies comparing HIIT to continuous exercise protocols fail to illicit superior benefits in glycemic control. Additionally, the authors highlighted many of the limitations currently restricting the proliferation of HIIT as a recommended training method, as inconsistencies across much of the literature including participant heterogeneity, variation in training program design (such as work : rest ratios), the inclusion of non-HIIT exercise as part of HIIT programs, and varied levels of supervision have limited the ability to determine the true effectiveness of HIIT as a suitable exercise intervention for individuals living with T2DM.

1.6 Precision Exercise Prescription [1]

Health organizations provide exercise recommendations aimed at reducing chronic disease and premature mortality (Bull et al., 2020; Piercy et al., 2018; Tremblay et al., 2016). While regular exercise is generally associated with health benefits, studies dating back to the 1980s report the magnitude of change in a given outcome varies widely between individuals, to the degree that some are seemingly unable to garner the expected benefits (Lortie et al., 1984; Prud'homme et al., 1984). The seminal HEalth, RIsk factors, exercise Training and Genetics (HERITAGE) Family Study was among the first to demonstrate heterogeneity in the observed responses following a standardized aerobic exercise training intervention (Bouchard et al., 1995; Bouchard et al., 1999). A recent review by Williamson et al. (2017) critiqued these findings mainly because the HERITAGE Family Study lacked a control group and referred to short-term reliability – a limitation discussed in more detail in the next section. Following in the footsteps of HERITAGE, the number of reports investigating heterogeneity in observed responses has constantly grown; many of which reflect the limitations outlined by Williamson et al. (2017) (Avila et al., 2017; Bouchard et al., 2012; Bouchard & Rankinen, 2001; Despres et al., 1984; Hamel et al., 1986; Hrubeniuk et al., 2021; Koch & Britton, 2017; Prud'homme et al., 1984; Simoneau et al., 1986; Walsh et al., 2019).

[1] The contents of sections 1.6 to 1.12 were published in *International Journal of Sports Medicine.*

Hrubeniuk, T. J., Bonafiglia, J. T., Bouchard, D. R., Gurd, B. J., & Sénéchal, M. (2021). Directions for Exercise Treatment Response Heterogeneity and Individual Response Research. *International Journal of Sports Medicine.* https://doi.org/10.1055/a-1548-7026

A by-product of investigating exercise treatment response heterogeneity has been a more clinically applicable focus on the individuals who struggle to experience the anticipated benefits, typically referred to as 'non-responders'. Accurate interpretation of an individual's ability to experience the targeted benefits – or not – from a prescribed exercise program would allow clinicians to make an informed decision and adapt the exercise program parameters or implement a different treatment regimen. Moreover, identifying the mechanisms contributing to an individual's ability to benefit from an exercise program may provide insight to the true effectiveness of exercise and allow for personalized exercise prescriptions, moving beyond the standard recommendation of achieving current physical activity guidelines in a clinical setting (Buford et al., 2013; Ross et al., 2019).

It is important to recognize that investigating the influence of exercise training on treatment response heterogeneity, and determining if a participant responded to an intervention (or not) are two distinct analytical approaches, designed to answer different questions. Conflating the two may lead to inappropriate interpretation of results. Common errors include interpreting improvements in the group mean as an exercise intervention increasing the 'response rate' or associating higher response rates with reduced treatment response heterogeneity (Atkinson et al., 2019; Bonafiglia, Preobrazenski, Islam, et al., 2021). Moreover, as the desire to understand exercise treatment response heterogeneity and individual response has grown, the number of proposed methods for conducting such research has significantly inflated. Accordingly, there is an ongoing debate on the most appropriate, rigorous and feasible techniques (Atkinson et al., 2019; Atkinson & Batterham, 2015; Bonafiglia et al., 2018; Bonafiglia et al., 2019; Hecksteden et al., 2015, 2018; Hopkins, 2015; Ross et al., 2019; Swinton et al., 2018; Williamson et al., 2017).

Various questions and concerns have emerged, including the ability to truly isolate the impact of exercise training, the nature of individual responses in relation to mean group changes, and the utility of individual response research (Atkinson et al., 2019; Del Giudice et al., 2020; Islam et al., 2019, 2020; Lindholm et al., 2016).

Here, we will first discuss the strengths and limitations associated with current methods for quantifying the contribution of exercise to observed treatment response heterogeneity. Second, current methods used to categorize participants based on their response to exercise will be outlined, as well as proposed mechanisms to identify factors that contribute to response variation. Finally, current issues at the forefront of individual exercise response research will be outlined.

1.7 Sources of Variation Contributing to an Individual's Observed Response

Prior to discussing exercise treatment response heterogeneity or individual response categorizations, it is important to understand that individual observed changes following an exercise intervention are the product of some combination of random variation, within-subject variation, and the subject-by-training interaction.

Random Variation

Random variation is comprised of the error introduced by the measurement instrument(s) (technical error) and day-to-day biological variation. When multiple measures are taken over a period of time within which the true value is not expected to change, the noise introduced by random variation will result in a cluster of observed scores that are normally distributed around the true value. Using the average value of multiple measurements for analysis can reduce the influence of random variation (Hopkins, 2000). Likewise, random variation can be estimated by collecting repeated measurements on a

group of individuals and calculating the typical error of the measurement (TE_M) (Hecksteden et al., 2018; Hopkins, 2000; Swinton et al., 2018).

Within-Subject Variation

Within-subject variation is inconsistent variance introduced by changes in the environment or behaviour unrelated to the intervention (e.g., short-term changes in eating patterns, seasonal changes influencing behaviour or mood) (Williamson et al., 2017). Theoretically, if the same individual were provided the same intervention at a different time, within-subject variation would be responsible for much of the variance in the observed difference in the change scores, if random variation was removed. The impact of within-subject variation on a participant change score may be dependent on the duration of the intervention, with longer duration trials expected to increase its influence (Bonafiglia et al., 2019).

True Responses to Exercise Training

The true response to exercise represents the 'trainability' of an individual, or the consistent, repeatable changes experienced in relation to the provided intervention. Although genetic endowment may contribute to an individual's trainability, stable characteristics or traits such as lived experiences, lifestyle habits (e.g., exercise, diet), and epigenetic modifications also influence the ability of an individual to respond to the training stimulus (Bouchard & Rankinen, 2001; Hecksteden et al., 2015, 2018). The subject-by-training interaction refers to the degree to which true responses to training (i.e. trainability) differs across a group of participants.

1.8 Methods for Quantifying Exercise Treatment Response Heterogeneity

Exercise treatment response heterogeneity exists when the true training-induced changes experienced across a sample of participants differ to a degree that can be

considered *meaningful* (Atkinson et al., 2019; Bonafiglia et al., 2019). Quantifying exercise treatment response heterogeneity requires the subject-by-training interactions to be isolated from within-subject and random variation (Hecksteden et al., 2015; Senn, 2016; Senn et al., 2011), necessitating a crossover trial with multiple intervention and control periods, each separated by an adequate washout (Senn et al., 2011). The true value of the subject-by-training interaction can then be calculated using a linear mixed model approach (Hecksteden et al., 2015). While this study design may be possible in certain research areas (Goltz et al., 2019), conducting such a trial using an exercise intervention presents several limitations: high operating costs, heavy resource requirements, significant time investments, and challenges with participant recruitment and compliance. Moreover, the carry-over effects of an initial training intervention are not well enough understood to accurately suggest an adequate washout period between phases (Williamson et al., 2017).

Alternatives for estimating exercise treatment response heterogeneity have been proposed, each of which must complete two steps to increase accuracy. First, the observed heterogeneity among participant change scores must be shown to be attributable to exercise training *per se*, and therefore not primarily a product of random or within-subject variation. Second, the magnitude of heterogeneity throughout the sample should be contextualized in relation to the chosen outcome measure (Hopkins, 2015). Contextualizing the magnitude of the heterogeneity helps to determine if the variance introduced by exercise is meaningful in relation to the anticipated variation associated with the measurement technique. Table 1 outlines the various statistical methods proposed for estimating treatment response heterogeneity, the subject-by-training interaction, random variation, and within-subject variation. The following sub-sections will provide additional detail for some of the notable methods.

Table 1. Assessment of variation with different trial designs*

Method	Statistical Approach	Outcome	Potential Limitations
Repeated measurements at individual timepoint	TE_M ($TE_M = SD_{diff} / \sqrt{2}$)	Estimate of random variation	Does not account for within-subject variation
Replication of a cross-over trial	Linear mixed model Fixed Effect: Training Group Random Effect: Subject Identity	Determines individual subject-by-training interaction	Feasibility Unknown wash-out duration
Comparator Group: Control Group	$SD_{IR} = \sqrt{(SD_{EXP}^2 - SD_{CON}^2)}$	Standard deviation of individual responses; Group-based estimate of the variance across participants' subject-by-training interaction	Potential differences in variation between the control and training groups
	TE_Δ ($TE_\Delta = SD_{diff} / \sqrt{2}$)	Estimate of within-subject variation.	May also contain random variation
Comparator Group: Reliability Data	$SD_{IR} = \sqrt{(SD_{EXP}^2 – [\sqrt{2} * TE_M])}$ or $SD_{IR} = \sqrt{(SD_{EXP}^2 – [\sqrt{2} * CV])}$	Standard deviation of individual responses; Group-based estimate of the variance across participants' subject-by-training interaction	Transferability of sample used to calculate the reliability data Duration of previous trial
Repeated measurements throughout the intervention	Linear mixed model Fixed effect: measurement number Random effect: subject ID-by-measurement number interaction Dependent variable: measured value	Individual estimates of subject-by-training interaction	Increased demand on participants and resources Potential influence of accumulating tests

*Interpreted based on Table 3 from Hecksteden et al., 2015 and Table 2 from Ross et al., 2019.
TE_M = typical error of a measurement; SD_{diff} = standard deviation of the difference score; SD_{IR} = standard deviation of individual responses; SD_{EXP} = standard deviation of the change scores from the experimental group; SD_{CON} = standard deviation of the change scores from the experimental group; TE_Δ = typical error of a change score; CV = coefficient of variation.

Control group designs: SD_{IR} method

If exercise training meaningfully contributes to treatment response heterogeneity, exercising participants will display greater variation in their pre-post difference scores than a non-exercising control group (Hopkins, 2015). As the control group did not participate in the intervention, it is assumed variance among the difference scores is a product of random and within-subject variation. Conversely, the intervention change scores also include variance introduced by individual responses to training (i.e., subject-by-training interactions). Therefore, the magnitude of variation introduced by participating in the exercise program can be estimated by subtracting the variance of the control group change scores from the variance of the intervention group changes (Bonafiglia et al., 2019; Hopkins, 2015; Swinton et al., 2018). The resulting value is referred to as the standard deviation of individual responses (SD_{IR}), which estimates the influence of individual responses to exercise training on overall response heterogeneity, accounting for the influence of random and within-subject variation (Atkinson & Batterham, 2015; Bonafiglia et al., 2019; Hopkins, 2015; Williamson et al., 2017). If the standard deviation of the changes in the intervention group are not substantially larger than the control group, theoretically the exercise training has not contributed to the observed variance (Atkinson & Batterham, 2015; Hopkins, 2015; Williamson et al., 2017).

The SD_{IR} method relies on the assumption that larger variance among the change scores in the experimental group, when compared to controls, is sufficient to estimate the magnitude of treatment response heterogeneity attributable to exercise training. To improve the accuracy of the SD_{IR}, steps should be taken to improve estimates of within-subject and random variation. Ensuring the control group follows the same time interval as the intervention group (Williamson et al., 2017), and taking multiple measurements at every timepoint (for both the control and intervention groups) can reduce these influences

(Hopkins, 2000). Simply stated, researchers should follow proper randomized control trial practices to ascertain the impacts of participating in the provided intervention (Atkinson et al., 2019).

A number of additional assumptions and limitations require consideration when using the SD_{IR}. Most notably, it is important to consider that the SD_{IR} relies on the assumption that the combined effect of random and within-subject variation is equal between the intervention and control groups (Bonafiglia et al., 2019). Even with randomized allocation to control and intervention groups, an inability to calculate within-subject variation across each group leaves the potential for its influence to differ. Accordingly, this assumption should be reported as a limitation whenever the SD_{IR} is used.

Despite a necessary reliance on the assumptions associated with implementing randomized control trials in exercise science (Bonafiglia et al., 2019), the SD_{IR} remains the preferred method for estimating the influence of exercise training on observed treatment response heterogeneity. This is in large part due to the SD_{IR} being, to our knowledge, the only method able to estimate the magnitude of confounding sources of variation in parallel-arm randomized control trials. Nonetheless, it is important to recognize there are many statistical methods designed to compare the equality of variance across groups. For example, Leifer et al. (2016) compared variability in observed responses between exercise and control groups using Levene's test. We find the SD_{IR} to be preferred over such tests as it estimates the magnitude of treatment response heterogeneity in units of the measured outcomes rather than relying on the interpretations of a *p*-value. However, to maximize confidence in the utility of the SD_{IR}, potential threats to major assumptions need to be avoided, and if present, reported.

Using reliability data

If a control group is not available, using data from a relevant reliability study (i.e., test, re-test) has been proposed as an alternative (Hecksteden et al., 2015, 2018; Hopkins, 2015). When using reliability data, it is suggested the SD_{IR} can be estimated by subtracting the variance of test, re-test change scores from the variance in change scores following exercise training. However, 'replacing' a control group should not be done without concern, as the limitations when using reliability data to calculate the SD_{IR} far outweigh the benefits. Data from a relevant reliability trial will solely allow for an estimate of random variation, meaning within-subject variation *remains unaccounted for*. Accordingly, the estimate of what would have happened to intervention participants had they not participated in the intervention is no longer valid; meaning the SD_{IR} cannot distinguish variability in true changes attributable to exercise training from the changes resulting from behavioural and/or environmental factors. Additionally, differences between the intervention participants and the reliability group can significantly impact the results. As such, we recommend against using reliability data to calculate the SD_{IR}.

Repeated measures design

Hecksteden et al. (2015) introduced a longitudinal approach using the collection of repeated measurements throughout the duration of an intervention as an alternative to calculating the SD_{IR}. The concept has been subsequently demonstrated on two occasions (Bonafiglia et al., 2019; Hecksteden et al., 2018). When using the repeated measurement design, alternative tools for detecting exercise treatment response heterogeneity become available. Namely, true response estimates are derived from the slope of each individual's regression line of the measured values throughout the duration of the intervention. As opposed to calculating the SD_{IR} based on the variance among the change scores from the intervention and control groups or reliability trials, taking repeated measures allows for

the SD_{IR} to be estimated by calculating the between-subject standard deviation of individual slopes or by using a linear mixed model. Importantly, and in line with any single-group design, this method cannot account for the counterfactual, and therefore cannot discern whether the variance introduced was the product of exercise training or behavioural/environmental changes that occurred during the intervention, *per se*. Moreover, this method assumes that responses generated over time will be linear, which may not be the case for certain physiological variables (*e.g.* cardiorespiratory fitness) (Bonafiglia, Ross, et al., 2019). Frequent testing may also introduce learning effects, carry-over effects or performance biases, masking results. Therefore, using a control group to calculate the SD_{IR} remains the preferred method.

Contextualizing the magnitude of exercise treatment response heterogeneity

Once the SD_{IR} has been calculated, its magnitude should be contextualized to determine if the variance introduced by exercise is meaningful. This can be done via standardization, or by comparing the SD_{IR} to a predetermined threshold value. Standardization consists of dividing the SD_{IR} by the standard deviation of all subjects at baseline, and comparing them to threshold values of 0.1, 0.3, 0.6, 1.0, and 2.0 (representing small, moderate, large, very large, and extremely large effects) (Hopkins, 2015; Smith & Hopkins, 2011). Alternatively, the SD_{IR} can be viewed in relation to a predetermined threshold such as the minimal clinically important difference, or the smallest worthwhile difference (Hopkins, 2000; Swinton et al., 2018).

Summary

Understanding the contribution of exercise to the observed heterogeneity following an intervention can aid researchers in interpreting the effects of exercise. Currently, there are a number of limitations restricting the ability to accurately quantify

exercise treatment response heterogeneity. While multiple methods have been proposed to provide estimates of the influence of exercise training on the observed variance, the SD_{IR} remains the preferred metric. It is important to emphasize that a negative SD_{IR}, or a suggestion that treatment response heterogeneity was not only a product of exercise training; does not preclude the possibility of responders and non-responders being identified (Walsh et al., 2019). A negative SD_{IR} could suggest the observed heterogeneity was largely influenced by other factors than participation in the prescribed exercise training. Alternatively, negative SD_{IR} values may reflect sampling errors in estimates of observed variability due to small sample sizes, which remains a major challenge for exercise training studies aiming to investigate treatment response heterogeneity.

1.9 Categorization of Participants as Responders or Non-responders

Categorizing participants as responders or non-responders speaks to the ability of each individual to improve beyond a threshold value for a selected outcome, as a result of participating in a specific exercise intervention. Such a categorization requires a consideration and comparison to a control condition. It is important to clearly define what being categorized as a 'responder' means for the current investigation, prior to conducting an analysis. Categorization may occur in a variety of ways, each requiring a response threshold to be selected, and a method to account for the variance limiting the ability to directly quantify an individual's true response (Hecksteden et al., 2018). The method used to categorize individuals should be carefully selected to answer the research question and be constructed in a way that accounts for the desired sources of variance. Categorizations may be made based on estimates of random variation (see below), and it can be argued these participants did experience benefit. However, without comparison to a control group the observed changes cannot be assigned to the exercise intervention, *per se*. Accordingly,

we suggest participants only be categorized as responders/non-responders when a control condition is part of the design and considered when making the categorization. If a control group is not considered, participants can only – at best – be categorized as experiencing a benefit, or not experiencing a benefit.

Various types of response thresholds have been used throughout the literature, including: (1) zero change as a fixed value, (2) the upper limit of observed differences expected as a result of variation, and (3) the lower limit of clinically or practically meaningful differences. Each threshold type differs in if, and to what degree, a method of accounting for the variance masking an individual's true change score is intrinsically applied. If an estimate of the potential influence of variance is not built into the threshold, additional steps should be taken to ensure the accuracy of a response estimate prior to the response categorization. Moreover, a threshold which is too permissive to answer the research question may result in inaccurate response categorizations, and a threshold which is too conservative may overstate the non-response rate (Hecksteden et al., 2018). Regardless of the method used, the threshold will always remain arbitrary and debated (Schulhauser et al., 2020). The following section will outline the thresholds used to categorize participants, and the methods which may be applied to account for the variance limiting the accuracy of an individual response estimate.

Zero change as a fixed value

Here the response threshold is set at zero change, defining non-response as a difference from pre- to post-intervention as zero or less (Figure 2A) (Bouchard & Rankinen, 2001; Sisson et al., 2009). While straightforward, using zero change as a threshold does not account for the limited accuracy of a response estimate, allowing random and/or within-subject variation to bias the categorization. To improve the

accuracy of the categorization, an individual confidence interval for each participant's change score can be calculated using an intervention-specific estimate of error (Bonafiglia et al., 2018; Swinton et al., 2018). Individuals can then be categorized as successful or not based on whether the confidence interval for the true change lays across or beyond the set threshold. Using a zero-based threshold, individuals can be categorized as having a positive response, a negative response, or an uncertain response, dependent on the interval laying entirely above, below, or crossing zero, respectively.

The interpretation of said categorization will be highly dependent upon the estimate of error used to calculate the confidence interval. Error estimates based on repeat baseline tests (TE_M) can be used if the goal is to categorize participants based on changes beyond an estimate of random variation. Accordingly, these participants should be referred to as having 'experienced benefit' or not. Conversely, if the goal is to more confidently categorize responders based on changes beyond both random variation and within-subject variation – thereby increasing the likelihood that observed changed resulted from participation in the provided exercise intervention – a time-matched control group should be used to estimate the combined influence of random and within-subject variation by calculating the typical error of the change score (TE_Δ) (Hecksteden et al., 2018; Swinton et al., 2018; Williamson et al., 2017), and using it to estimate the influence of error. Subsequently, participants can be categorized as responders or non-responders to the intervention.

Swinton et al., (2018) provides adjusted multiples that can be used to calculate the width of the confidence interval. The width of the confidence interval is at the discretion of the user, understanding that larger widths increase the risk of making type 2 errors (incorrectly categorizing an individual as uncertain when they are likely to be responders

or non-responders), whereas smaller widths increase the risk of making type 1 errors (incorrectly categorizing as a responder or non-responder).

Thresholds based on estimates of variation

The aim when using an estimate of variation is to set the threshold at the highest possible change that may occur as a result of extraneous variation. Similar to using confidence intervals, the interpretation of response categorizations will depend upon the estimate of error used to set the response threshold (Figure 2B) (Astorino & Schubert, 2014; Bonafiglia et al., 2016; Gurd et al., 2015; Lannoy et al., 2017; Montero & Lundby, 2017).

The first step when using an estimate of variation to set a response threshold is to estimate the influence of variation on the observed changes. Therefore, a decision needs to be made regarding what sources of variation will be accounted for by the threshold value. Again, the TE_M can be used to estimate the influence of random variation on a single measure. However, a change score is composed of two independent measurements, each subject to random variation. To account for this, the estimate should be multiplied by a factor greater than one prior to setting the response threshold, to increase the level of confidence in subsequent categorizations (Hecksteden et al., 2018; Swinton et al., 2018). Again. it must be emphasized that individuals categorized using this method only experienced a change beyond an estimate of random variation. This change cannot be attributed to participation in exercise (or any other source) *per se*; all that is known is a change greater than what was expected to occur due to random error has occurred, and categorized as having experienced benefit, or not. Alternatively, a time-matched control group can be used to estimate the combined influence of random and within-subject variation by calculating the typical error of the change score (TE_Δ) (Hecksteden et al.,

2018; Swinton et al., 2018; Williamson et al., 2017). By replicating the measurement schedule of the intervention, the TE_{Δ} estimates the variance that may be introduced due to within-subject variation in the absence of the prescribed exercise, while also capturing the influence of random variation (Swinton et al., 2018; Williamson et al., 2017). Utilizing a well-structured randomized control trial to set a threshold using the TE_{Δ} means those individuals categorized as responders were likely to have experienced a beneficial change as a result of the provided intervention.

Once the influence of extraneous variation is estimated, the threshold can be set. Although the TE_{Δ} theoretically estimates the majority of variance introduced throughout the duration of an intervention, some suggest this estimate should also be multiplied by a factor greater than one to increase the level of confidence in response categorizations (Hecksteden et al., 2018; Swinton et al., 2018). However, multiplying the TE_{Δ} may inappropriately increase the threshold to a value which inaccurately categorizes individuals as non-responders. Despite the estimate of variance being empirically defined, the factor used to set the limits for response introduces a potential limitation. As the chosen factor can only be legitimized by convention and/or recommendation across the scientific community, disagreement will lead to a variety of factors being implemented and inconsistent thresholds throughout the literature. As a result, comparing results or responder prevalence across trials can pose a great challenge.

Lower limit of practical relevance

A practically relevant response threshold exists at the border between a trivial and a meaningful difference. The preferred method for setting a threshold at the lower limit of practical relevance is to use a well-established minimal clinically important difference. While using the smallest worthwhile difference (0.2 multiplied by the standard deviation

of baseline values) is an acceptable alternative, the calculated value will be sample-specific and restrict generalizability. An example of categorizations made based on the lower limit of practical relevance can also be seen in Figure 2B (Bonafiglia, Ross, et al., 2019; Walsh et al., 2019).

Similar to using zero change, a threshold based on practical relevance has no inherent ability to account for the limited accuracy of a single response estimate. As such, an individual confidence interval for each participant's observed change score should be calculated with the aforementioned considerations and interpretations in mind (Swinton et al., 2018).Assuming the utility of a control group to construct the confidence intervals, individuals can then be categorized as having a clinically meaningful positive response (*responder*; confidence interval lays completely beyond the threshold in the positive direction), a meaningfully negative response (*adverse responder*; confidence interval lays completely beyond the threshold in the negative direction), a non-response (*non-responder*; confidence interval lays completely below the positive threshold and above the negative threshold), or uncertain (confidence interval partially overlaps the threshold) (Figure 2C) (Bonafiglia et al., 2018; Swinton et al., 2018).

Repeated measurements to calculate individualized confidence intervals

As an alternative to using group-based estimates of error to calculate individual confidence intervals, Hecksteden et al. (2018) outlines how to produce individualized response estimates based on repeated measurements taken throughout a longitudinal intervention. This method eliminates the need to assume equal variance throughout the sample, permitting a more personalized analysis. Response estimates are calculated as the slope of the individual's regression line of observed values vs. time, with the scatter of the observed values around the individual regression line (TE_{SLOPE}) providing a method to

calculate the uncertainty. These values can then be used to calculate individualized confidence intervals.

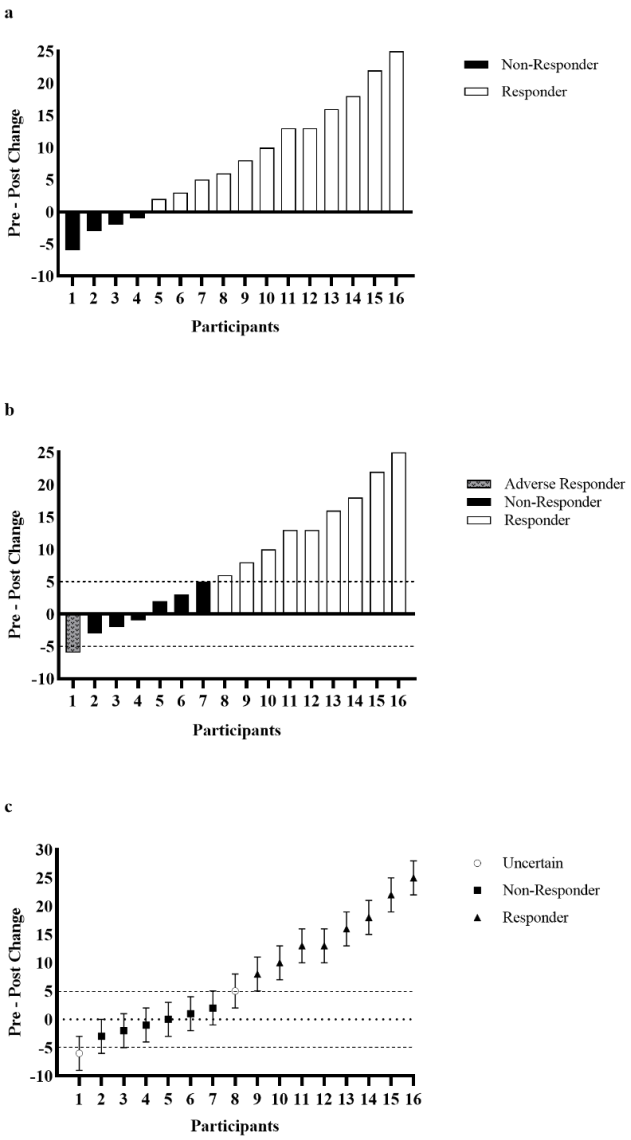


Figure 2. Participants categorized based on (a) zero change as a fixed value, (b) estimates of variation or clinical relevance, and (c) individual confidence intervals.

Summary

Undeniably, there are numerous options available for setting response thresholds and accounting for degrees of variance. The decision of which threshold to apply or which sources of variance to take into account will significantly impact both the categorization

of numerous participants and the interpretation of the results. Importantly, if the goal is to attribute a response categorization directly to the provided exercise intervention, a high-quality randomized control trial design must be used. As such, decisions regarding how response categorizations will be interpreted must be made prior to study initiation, as post-hoc decision making can lead to interpretation errors.

1.10 Methods for Investigating Factors Influencing Response Variation

An important component to investigating exercise treatment response heterogeneity and individual response is to determine factors contributing to the differences in response. Several reviews have discussed factors which may influence response heterogeneity following exercise (T. N. Mann et al., 2014; M. D. Roberts et al., 2018; Vellers et al., 2018). Here, we will outline the methods commonly used to identify the moderators and mediators of exercise treatment response heterogeneity and individual responses.

Moderators of the SD_{IR}

As described in a series of articles from Atkinson and Batterham (2015), Hecksteden et al. (2015), and Hopkins (2015), any variable influencing treatment response heterogeneity would logically impact the magnitude of the SD_{IR}. As such, Atkinson and Batterham (2015) proposed a method to determine the SD_{IR} and identify its moderators using a modelling approach and adjusting for identified co-variates at baseline. Using a linear mixed model the study arm (intervention or control) is entered as the fixed effect, an additional binary "dummy" variable is entered as a random effect (explained as allowing for extra variance in the change scores in one group versus the other), and the baseline value of the outcome entered as a covariate. The SD_{IR} may then be derived from the parameter estimate. Subsequently, potential moderators can then be tested by

including them in the model and interpreting the resultant changes in the SD_{IR}. The authors recommend consulting with a statistician to ensure models are properly applied.

The Atkinson and Batterham (2015) method was subsequently implemented by Hammond et al. (2019) who, despite large effect sizes, were unable to detect any statistically significant predictors of exercise induced treatment response heterogeneity. However, the authors provided meaningful commentary on numerous limitations associated with this method. Most prominently, the utility of a linear mixed model – while in line with good analytical practice – will likely require large sample sizes to find statistically significant results. As an example, the authors referred to their inadequate power with 181 participants, calculating that 504 participants were required to achieve statistical significance. Although samples of that size may pose limitations to individual research groups, it is important to note a requirement of large sample sizes is not unique to this modelling approach; small sample sizes are a challenge for all methods estimating SD_{IR} values and/or moderators treatment response heterogeneity. High-quality analytical approaches are necessary, to accurately elucidate moderators of exercise treatment response, meaning successful collaborative efforts, or innovative, practical alternatives should be pursued.

Categorization of "high" and "low" responders

Numerous authors have instead opted to divide their sample into groups of "high" and "low" responders before identifying moderators and/or mediators contributing to the observed differences in the magnitude of change (M. D. Roberts et al., 2018). The two key steps to this method are deciding how to divide the sample, and choosing a statistical method to identify the factors contributing to the differences in the observed changes.

A common method used to separate participants into categories of high and low responders is to break the sample into quartiles or quantiles, based on the magnitude of each individual's observed change (Morton et al., 2018; Raleigh et al., 2018; Sénéchal et al., 2013, 2015). Selecting a fixed proportion of participants with the highest (or lowest) differences as the high (and low) responders provides balanced groups with easily identifiable differences in response. Alternatively, K-means clustering has been used (Bamman et al., 2007; Petrella et al., 2008; Stec et al., 2016). While these methods are common, it is important to consider that breaking participants into predetermined groups will not adequately account for the limited accuracy of a response estimate and is only meaningful to the current sample. As a result, it remains possible that participants in the "high responder" group may have not truly responded to the intervention, or that participants in the "low responder" group did have a meaningful response to the intervention.

Once divided, various techniques have been used to identify key characteristics contributing to the differences in change scores, including regression analyses (Sénéchal et al., 2013, 2015) and ANOVA (Bamman et al., 2007; Petrella et al., 2008; Raleigh et al., 2018; Stec et al., 2016). Alternatively, one group has utilized Principal Component Analysis (Morton et al., 2018). It is important to reiterate that these approaches do not consider the influence of random or within subject variability when categorizing individuals, nor do they quantify the magnitude of observed treatment response heterogeneity, or attempt to clarify the contribution of exercise, per se. Therefore, while these approaches have been used previously and can indicate potential moderators or mediators for the response categorizations, the observed changes may be influenced by variation, or only be truly representative of the current intervention.

Summary

A primary purpose of individual analyses is to identify factors contributing to an individual's response categorization. However, in line with many aspects of this research field, conducting such analyses requires a great deal of assumptions. Likewise, researchers who choose to investigate these outcomes should be prepared to experience a number of challenges. While the prospect of identifying moderators and mediators of exercise response is intriguing, identifying rigorous study design and analytical methods for doing so represents one of the areas for future development within treatment response heterogeneity and individual response research.

1.11 Current Questions Facing Exercise Treatment Response Heterogeneity and Individual Response Research

Can we move beyond a categorical approach when describing individual responses?

There are advantages to identifying individuals who significantly benefit, and seemingly struggle to benefit, from an exercise trial and categorizing them accordingly. Doing so can provide clear cut points from which subsequent analysis can occur; such as investigating the underlying mechanisms contributing to these differences, or potentially working towards a future with personalized exercise prescriptions. However, categorizing individuals as responders or non-responders following a single trial comes with notable limitations. First, any categorization only holds true in the context of the provided exercise intervention, the selected response threshold, and the outcome of interest. Adapting the exercise protocol, choosing an alternative response threshold, or focusing on a different outcome can result in a different categorization (Bonafiglia et al., 2016; Bouchard et al., 2012; Hecksteden et al., 2018; Marsh et al., 2020; Montero & Lundby, 2017; Walsh et al., 2019). As such, the generalizability of findings may be severely limited. Second,

categorizing an individual fails to consider the continuous nature that probabilities of response may provide (Bonafiglia et al., 2018; Swinton et al., 2018). As a result, individuals with a high likelihood of response may be classified as non-responders simply due to their inability to improve beyond a subjectively chosen threshold, and an individual who only slightly surpassed the response threshold is considered equal to an individual who surpassed the threshold five-fold.

Swinton et al. (2018) proposes a method to address the limitations imposed by the categorical approach and move towards likelihood-based classification, which were used by Bonafiglia et al. (2018). It should be noted that these methods make use of the Magnitude-Based Decision Making technique (Hopkins, 2000), which has received much criticism regarding the likelihood of statistical error masking results (Aisbett et al., 2020; Barker & Schofield, 2008; Borg et al., 2018; Curran-Everett, 2018; Lohse et al., 2020; Sainani, 2018; Sainani et al., 2019; Welsh & Knight, 2015). However, these critiques are aimed at the group-level utility of these procedures, with no current debate regarding the application of these methods on individual analyses. Nonetheless, research attempting to transition towards an accepted, reliable mechanism for likelihood-based decision making is warranted.

Are we truly able to identify exercise-training related changes on an individual level?

One of the most important assumptions associated with individual analyses is that the true response to exercise training is an identifiable, consistent, reproducible trait. The origins of this assumption stem from studies using selectively bred rats, monozygotic twins, and nuclear families, highlighting a genetic component to the changes experienced following exercise training, particularly in reference to measures of cardiorespiratory fitness (Avila et al., 2017; Bouchard et al., 1999; Despres et al., 1984; Hamel et al., 1986;

Massett et al., 2009; Sarzynski et al., 2017). While these studies suggest some degree of reproducibility in the true response to exercise, evidence of this reproducibility remains limited. Lindholm et al. (2016) detected poor correlations for individual changes in exercise performance following two identical training sessions separated by a washout period, Islam et al. (2019) reported poor reproducibility among acute changes in gene expression following repeated application of exercise, Islam et al. (2020) outlined non-significant correlations among skeletal muscle adaptations in individuals who repeatedly completed an identical training regimen, and Del Giudice et al. (2020) found changes in VO_2max and time to fatigue were not reproducible and led to some participants whose response categorization changed following identical four-week high-intensity training regimens, separated by a three-month washout period. There are several potential explanations for these findings, each with different repercussions for individual response research.

First, it is possible the implemented washout periods were unable to account for potential carry-over effects from the initial training phase, or that participant behaviour was different prior to each of the training interventions. Although some authors report similar performance metrics at the initiation of each training phase (Del Giudice et al., 2020; Islam et al., 2020), it remains possible that undetected physiological alterations influenced the observed adaptation in subsequent training periods. Improved understanding of the carry-over effects following exercise training (including both a more holistic physiological outlook across various outcomes and a better understanding of the duration of these effects) would allow for more accurate washout lengths. Regardless, participants experiencing differences in response following subsequent, identical training

periods highlights that a response categorization is highly specific to the provided exercise intervention.

Second, it may hold true that the true response to exercise is a constant, repeatable trait, and the current methods for separating random and/or within-subject variation from the true response are not sensitive enough to fully account for their influence. As such, our ability to isolate the subject-by-training interaction may be inadequate. Regardless of the threshold used, current methods for categorizing an individual as a responder or non-responder neglect to account for what would have happened if that *individual* had not participated in exercise, making it impossible to definitively know if an individual responded to the exercise *per se* (Atkinson et al., 2019; Senn, 2016). Proposed mechanisms for setting response thresholds or calculating confidence intervals provide *estimates* for extraneous variation, but we currently cannot be certain that these influences are entirely accounted for. This explanation would suggest a need for more accurate estimates of the true response to exercise training, or improved methods for accounting for random and/or within-subject variation. Doing so would provide a more accurate indication of the influence of exercise training on individuals. A better understanding of the carry-over effects of an exercise trial and collaboration across research labs may improve the feasibility of conducting high quality cross-over trials to address this concern. Until that time, it may be wise to reconsider the 'exercise responder' terminology. We recommend shifting away from categorizing participants as responders or non-responders to exercise, and re-phrasing these determinations to who responded beyond an estimate of random or within-subject variation.

Lastly, these findings may suggest there is true intra-individual variation in response to exercise training, meaning the true response to exercise training is not a stable,

reproducible trait. This would pose a great challenge for the future of personalized exercise prescription, and emphasizes the importance of not categorizing individuals following a single trial. Instead, it may be more worthwhile for research to focus on identifying the factors contributing to higher and lower change scores among participants. Moreover, as opposed to individualizing exercise prescription, practitioners may instead focus their attention on those who do not benefit from an initial training intervention and adapt exercise to garner improvements in the future (Marsh et al., 2020).

It is important to discern the true nature of the true response to exercise training, and our ability to accurately identify it. Notably, much of the research questioning the identifiability of the subject-by-training interaction has focused on outcomes related to fitness or muscle health in relatively young, healthy men. Future investigations should aim to include various outcomes and populations to confirm these findings and move the field forward.

Are response rates reflective of the individual, or truly a group statistic?

The vast majority of research reporting response rates do so by counting the total number of responders throughout the sample (Astorino & Schubert, 2014; Gurd et al., 2015; Lannoy et al., 2017; Montero & Lundby, 2017; Ross et al., 2015; Sisson et al., 2009). These numbers are often used to compare interventions and determine the preferred method for reducing the quantity of non-responders. Results often show higher volumes of exercise leading to reduced non-response rates, or suggest increases in training volume reduce treatment response heterogeneity and eradicate non-response (Astorino & Schubert, 2014; Lannoy et al., 2017; Montero & Lundby, 2017). Atkinson et al. (2019) challenge this assertion and argue responder counts are highly sensitive to changes in the group mean; concluding that these metrics are truly representative of changes throughout

the group – rather than individualized analyses – and should be treated as such. Subsequent analyses conducted by Bonafiglia et al. (2021) supported this argument highlighting how 'response rates' are reflective of differences in mean group changes, not in treatment response heterogeneity or true individual responses. Recent studies have hypothesized that, compared with exercising at relative intensities (*e.g.* a percentage of VO_{2max}), exercising above physiological thresholds reduces heterogeneity in metabolic stress and thus decreases interindividual variability in observed responses to exercise training (Seward et al., 2019; Weatherwax et al., 2019; Wolpern et al., 2015). Although these studies reported that threshold-based prescriptions increased response rates compared with relative-intensity prescription, they did not statistically compare the variability in observed response between groups. It is therefore unclear whether larger response rates following threshold-based prescription are explained by larger mean changes in the absence or presence of reduced interindividual variability (Bonafiglia, Preobrazenski, Islam, et al., 2021). Future work should adopt a statistical test (e.g., Levene's test) to compare variability in observed responses to exercise training prescribed at a relative and threshold-based intensity.

Atkinson et al. (2019) suggest avoiding response counts when comparing interventions, instead recommending an approach described by Swinton et al. (2018) to estimate the proportion of responders in the population of interest. Here, the SD_{IR} is used as a parameter for the distribution of true responses around the mean treatment effect. The proportion of individuals predicted to be above or below the selected response threshold is then estimated using the characteristics of a normal distribution. Simulations run by Atkinson et al. (2019) outline the superior accuracy of this method to reflect the proportion of responders following an intervention. The authors recommend future researchers use

the Swinton method to estimate the proportion of response and infer to a population of interest to reduce the influence of bias associated with response categorizations.

Estimating the proportion of response can help remove the influence of mean changes when comparing interventions and may provide a more accurate representation of how many individuals will benefit from a provided intervention. However, this method poses practical application limitations. Specifically, the ability to consider the implications of an intervention at the individual level have been removed. As such, individual non-responders cannot be identified, meaning subsequent decision making or exercise prescription adaptations cannot be completed. Therefore, prior to selecting the analytical method, the purpose of the analysis and utility of the outcomes must be considered, as these two streams of research (individual analysis vs. group-based analysis) propose different theoretical approaches.

Can multiple outcome measures be simultaneously considered?

Human physiology is complex. As such, categorizing an individual as a 'universal' responder or non-responder based solely on the changes experienced in a single outcome measure following an exercise intervention does not adequately reflect the complexity of the physiological response. Current response categorizations are specific to the selected outcome measure and the provided intervention. However, studies have shown intraindividual variance and inconsistency across response categorizations when numerous outcomes are considered (Bouchard et al., 2012; Phillips et al., 2017; Walsh et al., 2019). Moreover, the current method of categorizing individuals using an 'outcome by outcome' basis does not allow for conceptual outcomes, in which several outcomes are considered simultaneously (such as physical function, frailty, or metabolic syndrome), to be utilized. Therefore, methods which allow for the consideration of numerous outcomes

simultaneously should be investigated. This would allow for more global categorizations of responders and non-responders.

What degree of confidence should we use when categorizing individuals?

The confidence with which response catego rizations are made is highly varied, including categorizations made based solely on estimates of variation (Lannoy et al., 2017; Schulhauser et al., 2020; Seward et al., 2019; Wolpern et al., 2015), using 50% confidence intervals (Bonafiglia et al., 2018; Schulhauser et al., 2020), and 90% confidence intervals (Bonafiglia et al., 2018; Hrubeniuk et al., 2021). Generalizing the confidence of response categorizations will likely be difficult, as it will be highly influenced by the desired threshold value and the variance the researcher or clinician wants to account for, the outcome measure being focused on, and the acceptable degree of risk associated with an error in the categorization. Additional commentary on the acceptable degree of confidence is necessary, but will always be contended. Currently, we proposed future research provide a complete justification for the selected level of confidence, and outline the associated strengths and limitations.

What are the economic costs of 'precision medicine'?

Throughout this review a number of recommendations and limitations associated with assessing variance and analyzing on an individual level have been noted, including larger sample sizes, taking multiple measures at each time point, and conducting repeated crossover trials with extensive washout periods. Addressing these recommendations and limitations will require significant resources and financial support. While we believe conducting these trials is worthwhile, and results can be directly transferred into practice, the economic costs are not trivial. To the best of our knowledge, there is minimal evidence for, nor has a cost benefit analysis been conducted, suggesting implementing personalized

exercise prescriptions will provide superior, financially responsible outcomes compared to the current 'mean improvement' based exercise prescription model.

Understandably, cost benefit analyses and longitudinal trials comparing the effects of precision exercise prescription to mean improvement-based prescription cannot be completed until previous questions are answered and optimal procedures are accepted. However, resource requirements and financial needs should be taken into consideration while attempting to develop and implement these models.

What should be done once a response categorization is made?

A major question often left unanswered is what should be done with individuals following a response categorization. The answer will likely depend on the setting within which the categorization is made (i.e., clinical or research). A potential course of action for a clinical setting will be described in the subsequent section. From a research perspective, a decision on how to progress following response categorizations should be made prior to the initial analysis. As individual responses are highly specific to the outcome of interest, selected response threshold, and provided intervention (Hecksteden et al., 2018), and reporting 'response rates' based on responder counts has been shown to more accurately reflect mean group changes (Atkinson et al., 2019; Bonafiglia, Preobrazenski, Islam, et al., 2021), it is hard to justify simply reporting individual responder and non-responder categorizations as generalizable, novel, or helping advance the field. Therefore, we propose future research should look beyond categorizing and look to advance the field. Such approaches could include investigating any one of the questions provided throughout this section, investigating the proportion of responders produced following an exercise intervention and comparing it to alternate interventions using the Swinton method (Atkinson et al., 2019; Swinton et al., 2018), with the goal of improving

the likelihood of participants experiencing beneficial changes, attempting to identify the root causes of heterogeneity across the sample, or exploring if subsequent/alternative exercise interventions may improve the response categorization of individuals categorized as non-responders and generate beneficial adaptations within the targeted outcome (Hrubeniuk et al., 2021; Marsh et al., 2020). These are topics worthy of additional attention, allow for a more thorough analysis beyond the response categorization, and may help move us closer to precision exercise prescriptions.

1.12 Translating Treatment Response Heterogeneity and Individual Response Research to Practice

It is worth outlining how research investigating treatment response heterogeneity and individual responses to exercise training could improve the application of exercise. Currently, exercise is prescribed based on broad guidelines, designed to provide a mean improvement to various aspects of overall health. The goal of the methods described throughout this review is to provide clinicians a method for implementing a targeted, personalized approach when prescribing exercise, while recognizing the complexity of human physiology implies benefits will extend beyond a single outcome.

The utility of treatment response heterogeneity and individual response research differ; however, they may be applied in unison when prescribing exercise. Understanding treatment response heterogeneity and subsequently estimating the proportion of response (as directed by Swinton et al. (2018) and Atkinson et al. (2019)) will allow clinicians to prescribe exercise based on the likelihood of an individual to experience a change greater than a selected threshold (Atkinson et al., 2019). This means the clinician may be able to target a specific outcome of importance for the patient (e.g.: cardiorespiratory fitness,

glycated hemoglobin concentration, or systolic blood pressure), a desired degree of improvement, and prescribed exercise intensity, modality, and mode based on which combination would provide the greatest likelihood of experiencing the targeted improvement. Subsequently, individual response research may allow for clinicians to more accurately interpret the individual's ability to experience the targeted benefits – or not – following the prescribed exercise, meaning the clinician can react appropriately at follow-up. If the individual was determined to be a non-responder following the provided intervention, the prescription could be adapted, or an alternative prescription could be provided based on the estimated likelihood of success. It is our view that these methods provide an alternative, and potentially more beneficial, approach to the current model of prescribing exercise.

As research progresses and the factors contributing to an individual response categorization are better understood, the accuracy of an initial prescription or subsequent adaptations may improve. Moreover, the aforementioned questions facing treatment response heterogeneity and individual response research must be addressed for such a future to become reality. Nonetheless, we believe it is a worthwhile pursuit to advance the utility of exercise.

1.13 Research Aims and Overview

Methods used to evaluate treatment response heterogeneity and individual responses have been developed with contributions from a plethora of disciplines, including genetics, biostatistics, medicine, human bioenergetics and exercise physiology (Atkinson et al., 2019; Atkinson & Batterham, 2015; Bonafiglia et al., 2018; Bonafiglia, Ross, et al., 2019; Bouchard, 2012; Bouchard et al., 1999; Hecksteden et al., 2015, 2018;

Ross et al., 2019; Senn, 2016; Williamson et al., 2017). Despite the breadth of knowledge available, it is still common to observe exercise physiology researchers interchangeably using the terms ‘treatment response heterogeneity’ and ‘individual responses’. Likewise, the methods used to conduct individual response research often utilize designs and analytical techniques which neglect previously identified best practices, such as choosing to implementing a mechanism to estimate the influence of exercise on the observed response heterogeneity, setting an individual response threshold that is clinically relevant, and/or accounting for the influence of random variation, within-subject variation, or the subject-by-training interaction. The extent of this issue was recently highlighted by Bonafiglia et al. (2021). In their systematic review, the authors found that despite the majority of research focusing on individual responses has been published from 2015 onward, only 9.5% (8/84) studies published since 2017 used a statistical mechanism to estimate treatment response heterogeneity. Likewise, of the reviewed articles categorizing individuals as responders or non-responders 31.9% (37/116) did not include a mechanism to account for the error in an observed change or set the threshold for response at a lower limit of clinical or practical relevance, leaving findings vulnerable to a high degree of type 1 (a non-responder being incorrectly categorized as a responder) or type 2 (a responder being incorrectly categorized as a non-responder) error.

Interestingly, Bonafiglia et al. (2021) also highlight that despite a knowledge of individual categorizations, few authors have taken the time to clearly describe or consider why categorizing individuals is important in the first place. Undeniably, the field appears to be at a stand-still despite a clear need for continued evolution. The vast majority of the literature remains focused on simply reporting response rates (Alvarez et al., 2017; Álvarez et al., 2018; Astorino & Schubert, 2014, 2014; Bouchard & Rankinen, 2001;

Lannoy et al., 2017; Ross et al., 2015; Scharhag-Rosenberger et al., 2012; Sisson et al., 2009), despite evidence that these works are highly specific to the study sample and provide minimal information targeting individuals (Atkinson et al., 2019; Bonafiglia, Preobrazenski, & Gurd, 2021; Hecksteden et al., 2018). What is needed are further attempts to answer the pertinent methodological and dissemination questions that currently prevent progress and restrict the transferability of findings.

This dissertation is designed to outline how research investigating treatment response heterogeneity and individual responses to exercise training can be designed and implemented to improve the clinical application of exercise for individuals living with prediabetes or T2DM. The aims of this dissertation are to: 1) Identify if prescribing high intensity exercise to youth at risk of T2DM increases the likelihood of experiencing the targeted benefits (responding) to exercise, and; 2) Investigate if increasing exercise intensity can be used as a method to adapt an exercise prescription to improve the response categorization for individuals living with prediabetes or T2DM who were previously identified as non-responders.

To accomplish this, the dissertation is divided into two studies. The first study is an analysis of a randomized controlled trial designed to examine the impact of exercise training intensity on several T2DM risk factors. This analysis explored the proportion of treatment response heterogeneity attributable to exercise training among individuals at risk of T2DM and attempted to decipher if the contributions differ between moderate and vigorous exercise intensity, and if individuals who exercise high intensity are more likely to experience benefits from exercise training when compared to those who train at moderate intensity. The second study is an attempt to explore if increasing the intensity of exercise training completed by individuals living with prediabetes or T2DM will help

those previously identified as non-responders to experience the targeted improvements in HbA1c. Lastly, a concluding chapter provides an overview of the potential implications stemming from these works and future research avenues emerging from the findings.

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Chapter 2.0: Manuscript One

Interindividual variation in cardiometabolic health outcomes following 6 months of endurance training in youth at risk of type 2 diabetes mellitus

2.1 Abstract

This study determined the interindividual variation in the cardiometabolic response to 6-months of moderate or vigorous intensity exercise training (ET) among youth at risk for type 2 diabetes mellitus. Youth were randomized to moderate intensity ET (45-55% heart rate reserve; n= 31), vigorous intensity ET (70-85% heart rate reserve; n= 37), or control (n= 36). Only those attending ≥70% of ET sessions were included. Cardiometabolic measures included insulin sensitivity, hepatic triglyceride content, visceral adipose area, and cardiorespiratory fitness. The contribution of ET to interindividual variation was determined using the standard deviation of individual responses (SD_{IR}) and considered meaningful if the SD_{IR} surpassed the smallest worthwhile difference (SWD), calculated as 0.2 * the standard deviation of the control group baseline values. ET meaningfully contributed to the interindividual variation among changes in VO_{2peak} following moderate (SD_{IR}: 2.04) and vigorous (SD_{IR}: 3.43) ET (SWD: 1.17 ml·kg-FFM^{-1}·min^{-1}), body fat percentage and hepatic triglyceride content following moderate-intensity ET (SD_{IR}: 1.64, SWD: 1.05%; SD_{IR}: 10.08, SWD: 1.06%, respectively), and visceral fat mass following vigorous ET (SD_{IR}: 11.06, SWD: 7.13 cm^2). Variation in the changes in insulin sensitivity were not influenced by ET. The contribution of ET to

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interindividual variation appears to be influenced by the desired outcome and prescribed intensity.

Key words:

Cardiometabolic health, individual response, interindividual variation, exercise intensity, diabetes, prediabetes, obesity

2.2 Introduction

Interindividual variation in the observed cardiometabolic response to exercise training (ET) is a well-established phenomenon (Ross et al. 2019). However, identifying the independent influence of ET on overall variation requires consideration of all potential sources of variance. Interindividual variation may be the result of individual biological day-to-day variation in an outcome measure and the technical error associated with the measurement device, collectively referred to as typical error. It may also result from physiological responses to changes in behaviour and/or the environment the individual is exposed to during ET (within-subject variation). Lastly, the true individual physiological response to the ET regimen could differ between participants (interindividual variation), reflected as a subject-by-training regimen interaction (Hecksteden et al. 2015; Atkinson and Batterham 2015; Hopkins 2015; Bonafiglia et al. 2019). Understanding the contribution of ET to overall interindividual variation in the observed changes in cardiometabolic health (i.e., the subject-by-training interaction) can provide additional insight to the effectiveness of training, and may have important implications for the future of personalized exercise prescription (i.e., precision ET) (Atkinson and Batterham 2015; Williamson et al. 2017).

Our group has described the individual cardiometabolic responses to moderate and vigorous intensity ET among youth at risk for type 2 diabetes mellitus (T2DM), and its determinants; however, we did not dissect training effects from other sources of variation (Sénéchal et al. 2015b). The standard deviation of individual responses (SD_{IR}) is a metric that isolates the variance attributable to ET from other sources of variance, representing the magnitude of interindividual variation associated with a prescribed training protocol (Atkinson et al. 2019; Bonafiglia et al. 2019). Walsh et al. (2019) recently used this approach to quantify the impact of six months of aerobic exercise, resistance training, or a combination of both on the observed variance in the cardiometabolic responses among youths living with obesity. Despite significant interindividual variation across all responses to training, ET was a meaningful determinant of the variation in only 33% of the measured outcomes. To the best of our knowledge, this novel work was the first attempt to describe the independent contribution of ET across various exercise modalities on interindividual variation among cardiometabolic outcomes in youth. However, the influence of ET on the observed variance for youth at an increased risk for T2DM, particularly at different exercise intensities remains unknown.

Evidence suggests performing ET at higher intensities may elicit greater improvements in cardiometabolic risk factors, compared to moderate intensity ET, and thereby increase the likelihood of being classified as a responder (Ross et al. 2015). Yet it remains unclear if increasing ET intensity solely influences an individual's ability to respond, or if it produces comprehensive changes in the effects of ET on observed interindividual variation, per se. Given the value of ET in T2DM prevention (Church et al. 2010; Umpierre et al. 2011) and the importance of positive ET experiences in youth at

risk of T2DM (Thompson et al. 2003), clarifying this gap in the literature is worthwhile to provide precise and effective ET prescriptions for this population.

The POWER trial was designed to examine the impact of ET intensity on several T2DM risk factors (Hay et al. 2016). The primary objective of this secondary analysis of the POWER trial data was to build on our previous work on interindividual variation in the response to ET (Sénéchal et al. 2015b) and to identify the proportion of interindividual variation that was attributable to ET, for several cardiometabolic risk factors in youth at risk of T2DM. The primary hypothesis was that a meaningful portion of the variance in the observed change scores among youth at an increased risk for T2DM will be attributable to ET across both moderate and vigorous intensities. The secondary objective was to estimate the proportion of responders for each of the cardiometabolic risk factors following both moderate and vigorous intensity ET programs. Our secondary hypothesis was that a larger proportion of individuals from the vigorous intensity ET group will be estimated to respond to training when observed against the moderate intensity ET group for each cardiometabolic risk factor.

2.3 Materials and Methods

Study Design and Population

We performed an exploratory, secondary analysis of the POWER trial (Hay et al. 2016). Between May 2008 and July 2012 youth between the ages of 13 and 19 were recruited and randomized to vigorous ET (70 – 85% of heart rate reserve; n = 37), moderate-intensity ET (40 – 55% of heart rate reserve n = 31), or a control group (n = 36) for six months (Clinical Trials Identifier: NCT0075554). For the purpose of this analysis only ET participants with ≥70% attendance and controls were included, meaning 15

participants remained in the vigorous group, and 11 in the moderate intensity group. The ≥70% attendance threshold was selected based on previous works investigating ET in individuals living with T2DM (Johannsen et al. 2013; Sénéchal et al. 2015a). While this requirement caused a large reduction in sample size, differences in attendance throughout the sample would produce differences in the applied training stimulus, which would almost certainly increase the observed variation. The magnitude of variance introduced by differences in attendance cannot be accounted for using the SD_{IR}, and would restrict the ability to accurately determine the magnitude of influence ET has on the observed interindividual variation if not controlled (Bonafiglia et al. 2019). Therefore, the reduction in sample size was a necessary step to answer our research question without compromising the data.

Participants were eligible if they were classified as overweight or obese based on age and sex-specific body mass index percentiles, and displayed at least one additional risk factor for T2DM: (1) a family history of T2DM, (2) member of an ethnic group at higher risk for T2DM (i.e., First Nation or South Asian), (3) fetal exposure to gestational or pre-gestational diabetes, (4) evidence of non-alcoholic fatty liver disease (peak hepatic triglyceride to water ratio >5.5%) or (5) elevated liver enzymes (>30 UI-1). Participants were excluded if they had/were: (1) previously received a diagnosis of T2DM or impaired glucose tolerance, (2) severe obesity or an injury that would prevent them from exercising, (3) experienced significant weight loss in the previous six months or presently enrolled in a weight loss program, (4) taking medications known to impact metabolism, or (5) were pregnant. All participants and parents provided written informed consent. The study was approved by the University of Manitoba Biomedical Research Ethics Board and performed according to the Declaration of Helsinki.

Primary Exposure

The intervention consisted of structured ET offered three times per week for six months at YMCA locations in Winnipeg, Manitoba, Canada. Participants were supervised throughout the duration of each session and self-selected the exercise modality; however, walking/running was encouraged and either stationary cycling or treadmill activity was selected in over 80% of the training sessions. ET was performed for 30 – 45 minutes at either 40 – 55% (moderate intensity) or 70 – 85% (vigorous intensity) of heart rate reserve. The duration of exercise at each session was adjusted to match caloric expenditure between the two exercise groups at ~350kcal per session. ET intensity was monitored and recorded throughout each session using a Polar heart rate monitor (Polar Electro, Kempele, Finland) by the supervising research assistant.

Outcome Measures

Protocol overview. Each participant was asked to come to the Children Hospital Research Institute of Manitoba for three visits to confirm phone screening and perform the baseline assessment. For the first visit, an oral glucose tolerance test was performed after a 12-hour fast. In addition, anthropometric measures, body composition, and cardiorespiratory fitness assessment were assessed. Participants were given the opportunity to consume a light snack/beverage prior to starting the cardiorespiratory fitness assessment. In the second visit, insulin sensitivity was assessed after a 12-hour fast. The final visit was performed at the National Research Council during a subsequent day or evening (depending on MRI availability) in a non-fasted state to quantify visceral adiposity and hepatic triglyceride content. All post-intervention measurements were repeated 72 hours following the final ET session.

Anthropometric measures. Body weight was measured to the nearest 0.1 kg on a calibrated scale. Height was obtained with a standard stadiometer. Body mass index (BMI) was calculated as: body weight (kg)/height (m2). Both measurements were taken in accordance with Canadian Society for Exercise Physiology protocols (Canadian Society for Exercise Physiology 2013). Absolute BMI was converted to a BMI percentile using nationally representative age and sex-specific data (Cole et al. 2000). Waist circumference was measured to the nearest 0.5 cm at the highest point of the iliac crest, using a flexible measuring tape (Canadian Society for Exercise Physiology 2013). All anthropometric measures were taken in duplicate with the mean of the two measures used in the final analysis.

Body composition. Total fat mass and percent body fat were measured using dual-energy X-ray absorptiometry (Hologic, Bedford, MA).

Visceral fat mass. Adipose tissue volumes were quantified from a high-resolution magnetic resonance image acquired between the third and fifth lumbar vertebrae using 1.5 (GE Medical Systems, Milwaukee, WI) or 3.0 Tesla (Trio, Siemens, Oakville, ON, Canada) whole-body magnets, as previously described (Wicklow et al. 2012). The total volume was quantified off-line using Slicer3 software (version 3.21; Boston, MA).

Insulin sensitivity. Insulin sensitivity was determined using a modified frequently sampled intravenous glucose tolerance test (Wicklow et al. 2012). Glucose and insulin kinetics were modeled using the Bergman Minimal Model (MINMOD) to quantify insulin sensitivity (Matthews et al. 1985; Pacini and Bergman 1986).

Hepatic triglyceride content. Hepatic triglyceride content was determined using proton magnetic resonance spectroscopy using 1.5 (GE Medical Systems, Milwaukee, WI) or 3.0 Tesla (Trio, Siemens, Oakville, ON, Canada) whole-body magnets, as

previously described (Wicklow et al. 2012). LM Model software was used to quantify peak lipids and water.

Cardiorespiratory fitness. Cardiorespiratory fitness was assessed as the peak oxygen uptake recorded during the final minute of an exhaustive graded exercise test completed on a cycle ergometer. Participants began the test at a cadence of 60 revolutions per minute against a workload of 30 watts. The workload increased by 30 watts every two minutes until a respiratory exchange ratio or > 1.0 was achieved, at which point the workload was increased by 30 watts every minute until exhaustion (Wittmeier et al. 2012). Indirect calorimetry was used to measure and record peak oxygen uptake (Parvomedics True One; Parvo Medics, Sandy, UT). Cardiorespiratory fitness was expressed relative to kilograms of fat-free mass.

Statistical Analysis

To estimate the influence of exercise on the interindividual variation observed across each of the outcome variables, the standard deviation of individual responses (SD_{IR}) was calculated as:

$$SD_{IR} = \sqrt{(SD_{\Delta INT})^2 - (SD_{\Delta CON})^2}.$$

Here, the standard deviation of the observed change scores in the control group ($SD_{\Delta CON}$) is subtracted from the standard deviation of the observed change scores in intervention group ($SD_{\Delta INT}$; completed individually for each intervention group). As extraneous variation introduced by changes in behaviour and/or the environment (within-subject variation), as well as variation from the measurement device and daily fluctuations in motivation, wellness, etc. (typical error), are present in both SD_{INT} and SD_{CON}, any remaining variance (SD_{IR}) is likely to have been a result of the ET intervention (i.e. the subject-by-training interaction). As first proposed by Hopkins (2015), and recently

implemented by Walsh et al. (2019), upper and lower 90% confidence intervals were calculated for each SD_{IR}. The observed variation was considered to be meaningfully attributable to exercise when the SD_{IR} surpassed the smallest worthwhile difference (SWD). The SWD was calculated as 0.2 * the standard deviation of the baseline value of the control group for each outcome variable (Hopkins 2015), thereby representing a meaningful, albeit small effect size. This method has been previously recommended as the preferred method for interpreting the magnitude of interindividual variation (Atkinson and Batterham 2015; Williamson et al. 2017; Walsh et al. 2019). In some cases, the $SD_{\Delta CON}$ was greater than the $SD_{\Delta INT}$. As a negative value does not have a true square root, the SD_{IR} could not be calculated for these outcomes. In such a circumstance, it was assumed the ET did not contribute to the observed interindividual variation. Therefore, the SD_{IR} equation was rearranged to represent the homogenizing effect of exercise in comparison to the controls (Walsh et al. 2019).

The identification of responders has previously been completed through the simple method of counting how many individual participants' observed change surpassed a predetermined threshold (Hecksteden et al. 2015, 2018). However, this method has received scrutiny due to the influence that changes in the group mean may have on the raw number of responders, an inability to adequately identify a true subject-by-training interaction, and the influence of within-subject variation (Atkinson et al. 2019). Atkinson et al. (2019) suggests providing an estimate of the expected proportion of responders based on the SD_{IR}, as described by Swinton et al. (2018). Based on the assumption that the true score change follows a normal distribution centered on the mean observed change, the SD_{IR} provides a parameter for the distribution of true responses. A response threshold (i.e. the SWD) is then be set, and the proportion of responders is estimated as the percentage

of participants calculated to be above (or below, where applicable) said threshold using the characteristics of a normal distribution.

2.4 Results

The 62 youth included in this analysis (Control n = 36; Moderate Intensity n = 11; High Intensity n = 15) were 15.2 ± 1.7 years of age, 68% female, and 58% Caucasian. Participants had an average VO_2peak of 41.5 ± 5.6 ml•kg-FFM^{-1}•min^{-1} (24.2 ± 4.1 ml•kg-FFM^{-1}•min^{-1}) at baseline, and BMI was on average in the 97th percentile based on age and sex standards. Baseline participant characteristics separated by group allocation are presented in Table 2. Youth randomized to the vigorous intensity group maintained an average of 67.2 ± 0.1% of heart rate reserve throughout the ET program, whereas youth randomized to the moderate intensity group maintained an average of 53.7 ± 0.1% of heart rate reserve.

Table 2. Baseline characteristics by group allocation.

	Control n = 36	Moderate intensity n = 11	Vigorous intensity n = 15
Age (years)	15.2 ± 1.8	15.2 ± 1.9	14.9 ± 1.6
Female n (%)	23 (63.9)	8 (72.7)	11 (73.3)
Caucasian n (%)	19 (52.8)	5 (45.5)	11 (73.3)
Height (centimeters)	167.5 ± 7.8	161.9 ± 5.2	161.7 ±7.2
Weight (kilograms)	92.9 ± 17.4	86.7 ± 11.5	86.8 ± 16.3
BMI (kg/m^2)	32.9 ± 5.4	33.1 ± 4.6	33.0 ± 4.4
BMI percentile	97.2 ± 3.1	97.4 ± 2.5	97.1 ± 4.0
Waist circumference (cm)	107.6 ± 13.6	106.1 ± 10.8	105.3 ± 13.6
Systolic BP (mmHg)	116.2 ± 13.5	111.2 ± 8.5	116.0 ± 7.2
Diastolic BP (mmHg)	63.4 ± 7.9	63.4 ± 7.5	65.3 ± 5.4
Body fat percentage	39.1 ± 5.3	38.8 ± 6.2	40.5 ± 4.2
Visceral fat mass (cm^2)	84.4 ± 35.7	93.2 ± 45.1	84.3 ± 27.9
Cardiorespiratory fitness ($ml \cdot kg\text{-}FFM^{-1} \cdot min^{-1}$)	40.7 ± 5.9	41.7 ± 5.9	43.3 ± 4.5
Si ($mU\ kg^{-1}\ min^{-1}$)	3.1 ± 1.6	3.3 ± 1.4	4.2 ± 5.1
Hepatic TG content (% F/W)	5.2 ± 5.3	5.8 ± 4.4	3.7 ± 3.1

Data presented as mean ± SD or n (%); BMI: body mass index, Si: insulin sensitivity, BP: blood pressure, TG: triglycerides, kg: kilograms, m: meters, cm: centimeters, ml: millilitres, FFM: fat free mass, min: minute, F/W: fat/water.

Interindividual variation

The SWD and SD_{IR} (with associated 90% confidence limits), stratified by group allocation, are presented for the observed changes in body fat percentage, visceral fat mass, cardiorespiratory fitness, insulin sensitivity, and hepatic triglyceride content in

Table 3. Regardless of intensity, ET meaningfully contributed to the variance in the observed changes in cardiorespiratory fitness, as expressed by the SD_{IR} for both moderate intensity (SD_{IR}: 2.04, 90% Confidence Interval: -16.96 to 21.03) and vigorous intensity (SD_{IR}: 3.43, 90% CI: -16.79 to 23.65) ET, surpassing the SWD ($ml \cdot kg\text{-}FFM^{-1} \cdot min^{-1}$). While training contributed to the observed variation among changes in body fat percentage for both moderate and vigorous intensity groups the SD_{IR} for the moderate intensity group (SD_{IR}: 1.64, 90% CI: -3.20 to 6.48) surpassed the SWD (1.05%); whereas the SD_{IR} for the vigorous training group did not (SD_{IR}: 0.95, 90% CI: -2.21 to 4.11), indicating the contribution of vigorous intensity ET was not considered meaningful. Regardless of training intensity, the SD_{IR} for insulin sensitivity was negative. Such a result indicates the variance was larger amongst the control participants when compared to the intervention, suggesting training did not inflate the observed variation and had no impact on the observed variance. The influence of ET on the variation observed among changes in visceral fat mass and hepatic triglyceride content differed between moderate and vigorous intensity training groups. Changes in visceral fat mass were not influenced by moderate intensity ET, but were meaningfully influenced by vigorous ET (SD_{IR}: 9.71, 90% CI: -653.49 to 675.61), passing the SWD (7.13 cm^2). In contrast, changes in hepatic triglyceride content were meaningfully influenced by the moderate intensity training program (SD_{IR}: 10.08, 90% CI: -82.69 to 102.85), surpassing the SWD (1.06% fat/water) but were not at all influenced by vigorous training.

Table 3. Interindividual variation and estimated proportion of responders following 6-months of aerobic exercise.

	Moderate intensity n=11	Vigorous intensity n=15
Body fat percentage		
SWD	1.05	
SD_{IR} (90% CI)	1.64 (-3.20 to 6.48)*	0.95 (-2.21 to 4.11)
Visceral fat mass (cm^2)		
SWD	7.13	
SD_{IR} (90% CI)	**16.27 (-516.25 to 548.79)**	11.06 (-653.49 to 675.61)*
Cardiorespiratory fitness ($ml \cdot kg\text{-}FFM^{-1} \cdot min^{-1}$)		
SWD	1.17	
SD_{IR} (90% CI)	2.04 (-16.96 to 21.03)*	3.43 (-16.79 to 23.65)*
Insulin sensitivity ($mU\ kg^{-1}\ min^{-1}$)		
SWD	0.31	
SD_{IR} (90% CI)	**1.50 (-0.88 to 3.88)**	**1.05 (-1.66 to 3.76)**
Hepatic TG content (% F/W)		
SWD	1.06	
SD_{IR} (90% CI)	10.08 (-82.69 to 102.85)*	**4.16 (-0.80 to 4.58)**

Bolded text indicates when the SD_{IR} was negative and equation was reversed.
* indicates meaningful contribution of exercise training to observed interindividual variation.
SWD: smallest worthwhile difference, SD_{IR} (90% CI): standard deviation of the individual responses and 90% confidence interval. TG: triglycerides, kg: kilograms, m: meters, cm: centimeters, ml: millilitres, FFM: fat free mass, min: minute, F/W: fat/water.

Proportion of responders

The estimated proportion of responders to ET is provided in Figure 3. Within the moderate and vigorous intensity ET arms, 69.2% and 62.3% of youth were considered responders based on improvements in cardiorespiratory fitness beyond the SWD (1.17 $ml \cdot kg\text{-}FFM^{-1} \cdot min^{-1}$) (Figure 3A & 3B). Likewise, 47.0% and 50.1% of youth in the

moderate intensity and vigorous intensity arms were considered responders based on a greater than a 1.05% reduction in body fat percentage (Figure 3C & 3D). Lastly, 35.8% of youth in the moderate intensity arm were considered responders based on reductions in hepatic triglyceride (Figure 3E), and 50.4% of youth in the vigorous ET arm were considered responders based on reductions in visceral fat mass by at least 7.13 cm2 (Figure 3F).

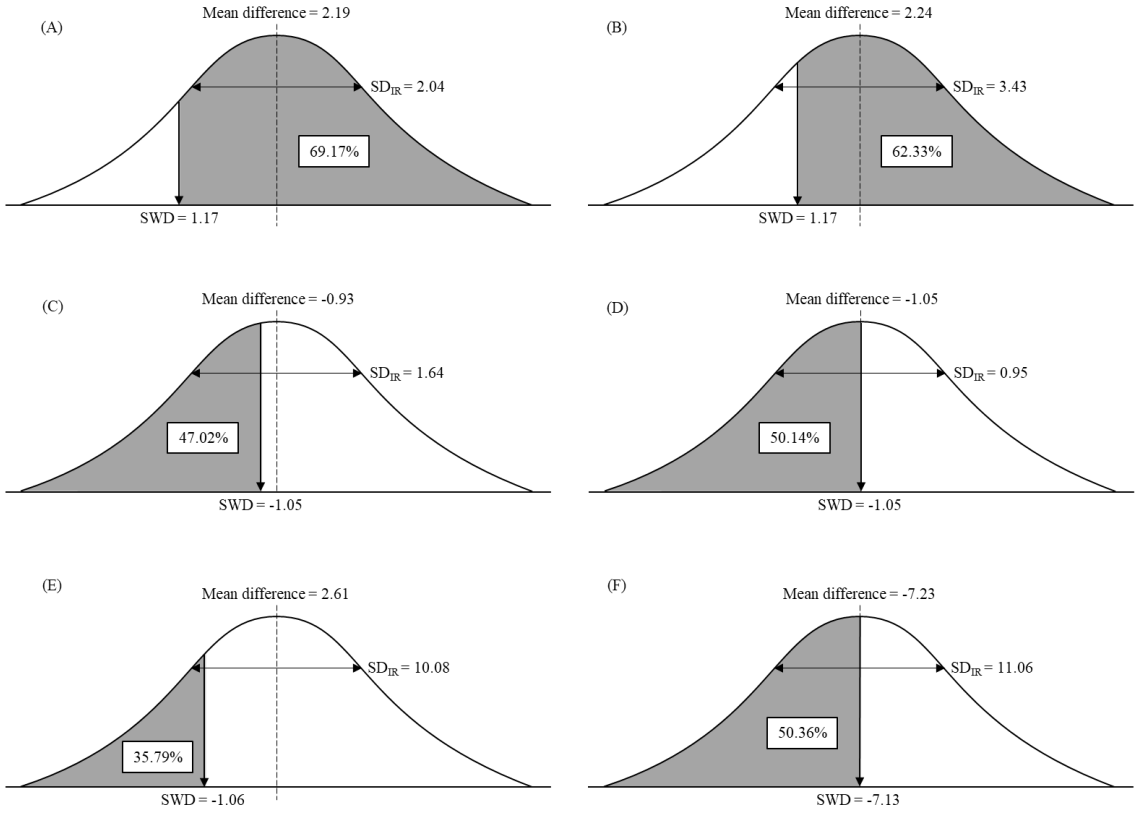

Figure 3. Estimated proportion of response for cardiorespiratory fitness following moderate (A) and vigorous intensity (B) training; body fat percentage following moderate (C) and vigorous intensity (D) training; hepatic triglyceride content following moderate intensity training (E); and visceral fat mass following vigorous intensity training (F). Shaded portions represent the estimated proportion of responders. SD_{IR} = standard deviation of individual responses, SWD = smallest worthwhile difference

2.5 Discussion

The primary hypothesis of this analysis was that a meaningful portion of the variance in the observed change scores among youth at an increased risk for T2DM will be attributable to ET across both moderate and vigorous intensities. The secondary hypothesis was that a larger proportion of individuals from the vigorous intensity ET group would be estimated to respond to training when observed against the moderate intensity ET group for each cardiometabolic risk factor. The main findings of this study provide insight into the influence of ET and ET intensity on interindividual variation among changes in cardiometabolic outcomes in youth at risk of T2DM. Following six months of moderate or vigorous intensity ET, heterogeneity throughout participant changes was meaningfully influenced by ET (the subject-by-training interaction) in 50% of scenarios (5 outcomes x 2 intensities, as described in Table 3). The degree to which variance among changes in body fat percentage, visceral fat mass, and hepatic triglyceride content were affected by ET differed based on the intensity of training. Conversely, interindividual variation among changes in cardiorespiratory fitness was consistently impacted by ET, regardless of intensity. Where applicable, the proportion of youth estimated to respond spanned from 36% to 69%. This study provides preliminary evidence to suggest the influence ET has on interindividual variation in youth at risk for T2DM differs based on the chosen outcome and ET intensity, and highlights the importance of assessing ET response heterogeneity when reporting changes in cardiometabolic health outcomes in youth at risk for T2DM.

These data are in line with those from Walsh et al. (2019), who found similar inconsistencies in the contribution of ET to interindividual variation in youth living with obesity. Those authors found the contribution of ET differed based on the exercise

modality and the outcome measure, with variation meaningfully influenced by exercise in only 33% of scenarios. The combined findings highlight the importance of using the SD_{IR} to estimate the contribution of ET to the observed interindividual variation, prior to classifying participants as responders or non-responders. Numerous publications have outlined the incidence of non-response to ET, or the determinants of a non-responder phenotype, using various methods and outcome measures (Bouchard and Rankinen 2001; Sisson et al. 2009; Sénéchal et al. 2015b; Ross et al. 2015; Alvarez et al. 2017; Lannoy et al. 2017; Álvarez et al. 2018). However, none of these attempts used the SD_{IR}, or any alternative, to indicate if variation is attributable to the influence of ET. This is concerning as without using the SD_{IR}, the authors should not assume observed heterogeneity in participant changes scores is primarily the product of ET (Atkinson and Batterham 2015; Williamson et al. 2017; Atkinson et al. 2019; Bonafiglia et al. 2019). Resultant response categorizations may therefore be highly influenced by error, or should lead to non-response rates being interpreted as reflecting variance introduced by extraneous factors, as opposed to an inability to benefit from ET.

Interindividual variation among cardiometabolic health outcomes

Our findings suggest that following six months of ET, the variance among changes in insulin sensitivity in youth at risk for T2DM are unlikely to be the result of either moderate or vigorous ET. Therefore, variation was likely a product of typical error and/or within-subject variation rather than individual differences in the subject-by-training interaction. To date, few studies have investigated the components of interindividual variation in changes in glucose and insulin kinetics, particularly within those at increased risk for T2DM (Solomon 2018). Álvarez et al. (2017 & 2018) have conducted studies attempting to outline exercise response rates among youths at risk for T2DM following

high-intensity interval training. Non-response rates for measures of glucose and insulin kinetics ranged from 25.0% to 94.1%. Although the physiological changes following training were undoubtedly varied the authors did not determine the true source of variance, meaning the interpretations of individual responses may have been the product of extraneous variation Álvarez et al. (2017 & 2018). The data presented here challenges those from Álvarez et al. (2017 & 2018), suggesting any interindividual variation among changes in insulin kinetics were more likely to be the result of random or within-subject variation (as opposed to differences in the subject-by-training interaction), and categorizing participants as responders or non-responders to the ET protocol is inappropriate. However, as research investigating the influence of ET on the heterogeneity among changes in glucose and insulin kinetics is limited, additional research is necessary to confirm our results.

The current findings provide support to the existing data showing that ET has a substantial influence on interindividual variation among changes in cardiorespiratory fitness (Bonafiglia et al. 2018; Hecksteden et al. 2018). However, to the best of our knowledge this study is among the first to do so within a sample of youth at an increased risk of T2DM. Moreover, interindividual variation among changes in body fat percentage also appear to be influenced by both moderate and vigorous intensity ET. These data work in concert with those from Walsh et al. (2019), who reported a consistent influence of ET on interindividual variability among changes in body fat percentage, across numerous ET modalities. As such, it appears ET may consistently contribute to the interindividual variability among observed changes in body fat percentage in youth at risk of T2DM, regardless of ET intensity or modality. It is unknown if such an occurrence is limited to

youth represented within or sample, or if it extends to youth outside of the inclusion criteria used for this work.

Estimated proportion of response

Approximately 50% of instances analyzed in our study displayed greater variance among the controls (SD_{CON}) when compared to intervention participants (SD_{INT}), suggesting interindividual variation was not primarily attributable to the influence of ET. In these instances, an estimate of the proportion of responders was not possible. Among instances where an estimate could occur, the proportion of youth estimated to experience a meaningful change in cardiorespiratory fitness was found to be similar following moderate and vigorous intensity training. This result was unexpected, as some data suggests increasing exercise intensity may help increase the proportion of responders following ET. In particular, Ross et al. (2015) assigned 192 adults to 24 weeks of training in one of three groups: (1) low-volume, low-intensity; (2) high-volume, low-intensity; or (3) high-volume, high-intensity. The authors found doubling the training volume (group 1 vs. 2) led to a 50% decrease in non-response, whereas increasing the intensity and volume (group 3) eradicated the non-responder phenotype (Ross et al. (2015). The results from Ross et al. (2015) suggest that while increasing ET volume increases the likelihood for beneficial changes, increasing ET may provide additional benefit. Although our sample differs, our study is the first to utilize a randomized control group when analyzing the influence of ET intensity on interindividual variation, prior to estimating response rates. Our results suggest that increasing the intensity of exercise while matching volume does not substantially influence cardiorespiratory fitness response rates in youth at risk for T2DM. Similar trends were observed for adiposity measures, as increased ET intensity did not produce substantial changes in response rates based on body fat percentage, and

only 50% of youth were estimated to experience changes in visceral fat mass following the vigorous ET protocol. As such, increasing ET intensity beyond moderate intensity does not appear to be a comprehensive method for reducing non-response to ET in youth at risk of T2DM.

Differences between our findings and those from Ross et al. (2015) are likely explained by the conflicting methods used to reflect response rates. Ross et al. (2015) chose to use individual response counts which likely reflect the influences of random and within-subject variation on individuals as opposed to true response heterogeneity (Atkinson et al. 2019). Moreover, the reduction in individually counted non-responders in the high volume/high intensity group (Group 3) of the Ross et al. (2015) trial may be the result of an increase in the mean change following the increased ET volume and intensity, when compared to Groups 1 & 2. The increased group mean may have led to a lower number of participants who were negatively impacted by the influences of random and within-subject variation, meaning more individuals were perceived as responders. Conversely, the estimated proportion of response reported in our study is based on the SDIR, which theoretically applies a parameter for the distribution of true changes free of the influence of random and within-subject variation. This method potentially allows for a more accurate representation of the true proportion of responders while minimizing the influence of mean group changes (Atkinson et al. 2019).

Strengths and Limitations

The current study has limitations that need to be acknowledged. First, the small sample size was a self-imposed limitation. The decision of including participants who attended ≥70% of the prescribed ET sessions may have reduced our sample but was necessary to ensure the proper implementation and interpretation of the SD_{IR}. However,

there are other external limitations which may compromise the validity of the SD_{IR} (Bonafiglia et al. 2019). Of particular relevance to the current analysis, not blinding the control participants to their group allocation may have led to a change in their habitual behaviour (Halpern 2003), producing inaccurate estimates of random and within-subject variation and influencing the SD_{IR}. It is also worth noting the difference in sample sizes between the control and intervention groups. Having a larger control sample may naturally reduce heterogeneity and contribute to an inflated SD_{IR}; however Levene's test for equality of variances suggests the variance observed across the three groups was equal for most outcomes (with the exception of insulin sensitivity).

A second limitation requiring consideration when interpreting our results is the lack of a tightly controlled, standardized ET stimulus. When evaluating interindividual variation and exercise response, a primary assumption is that all participants are being evaluated following an identical ET program. Prescribing ET intensity using a percent of heart rate reserve (Mann et al. 2013), allowing for a 15% range in ET intensity, and permitting participants to select the ET modality (treadmill, cycle ergometer, etc.) may have introduced heterogeneity that was otherwise unaccounted for in our analyses.

Moreover, current recommendations suggest 60 minutes of moderate-to-vigorous physical activity to maintain or improve cardiometabolic risk factors (among other health benefits) (Davis et al. 2012; Ho et al. 2013; Tremblay et al. 2016). Therefore, it is possible that the ET stimulus provided here was insufficient to produce changes, thereby limiting the variance introduced due to exercise and hampering the ability to detect a meaningful contribution of the interindividual variation to the observed change. Lastly, participants in the vigorous intensity group did not maintain the targeted intensity of 70% of heart rate reserve across all sessions. However, the average intensity of 67.3% of heart rate reserve

achieved by this group is still considered vigorous, according to guidelines used by the Canadian Society for Exercise Physiology and American College of Sports Medicine (Garber et al. 2011).

Despite these limitations, the study was strengthened by the inclusion of a randomized control group. Having change scores from a randomized, time-matched control group allows us to use the SD_{IR} to isolate the effect of exercise (i.e. the subject-by-training interaction) from the variation introduced by typical error and within-subject variation, and increase our certainty in understanding the individual responses to ET. Additionally, participant dropout was relatively minimal, and consistent across all groups (1 moderate intensity, 1 vigorous intensity, and 4 control). This is important, as difference in participant compliance and/or drop out across groups may introduce unknown variance, influencing the SD_{IR} (Bonafiglia et al. 2019). Moreover, many of the measurement tools used are considered highly reliable, gold standard methods of evaluation. Using these methods help reduce the influence of measurement error in our analysis and increase the certainty in the SD_{IR} calculation.

2.6 Conclusion

In conclusion, this secondary analysis of the POWER trial outlines an exploratory attempt to estimate the influence of ET on the interindividual variation among changes in cardiometabolic health outcomes in youth at increased risk for T2DM. The results of this study suggest the influence of ET on the observed interindividual variation differ across cardiometabolic health outcomes and ET intensity. These findings provide additional insight to the effectiveness of training, and may contribute to the future development of personalized, precision ET prescription.

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Chapter 3.0 Manuscript Two

Increasing training intensity fails to improve the glycemic response in people living with prediabetes or type 2 diabetes mellitus: The INTENSITY Trial

3.1 Abstract

Introduction: Some individuals living with prediabetes or type 2 diabetes mellitus (T2DM) who engage in exercise training will not experience the anticipated improvements in glycemic control, referred to as non-responders. Some studies suggest exercise training performed at higher intensity may lead to improvements in responder status. However, it is unclear if increasing exercise intensity for non-responders with prediabetes or T2DM would enhance their responder status.

Objective: The purpose of this two-phase quasi-experimental trial was to 1- identify responders and non-responders based on changes in glycated hemoglobin (HbA1c) in individuals living with prediabetes or T2DM following 16 weeks of aerobic exercise, and 2- investigate if increasing exercise intensity can change the status of non-responders.

Methods: During phase one, participants performed 16 weeks of aerobic exercise at an intensity of 4.5 metabolic equivalents (METs) for 150 minutes per week. Participants were then categorized as responders, non-responders or unclear based on the 90% confidence interval (CI) laying above, below, or crossing a 0.3% reduction in HbA1c. During phase two, participants were randomized to a maintained intensity (4.5 METs), or increased intensity (6.0 METs) group for 12 additional weeks of aerobic exercise, and subsequently re-categorized.

Results: Following phase one, two (4.1%) participants were categorized as responders, four (8.2%) as non-responders, and 43 (87.7%) as unclear. Twenty-six participants were

randomized to the increased intensity group and 23 were randomized to the maintained intensity group. Following phase two, two participants randomized to the increased intensity group and one participant randomized to the maintained intensity group experienced an improvement in response categorization.

Conclusion: Our results suggest that increasing exercise intensity does not appear to improve the response categorization for people living with prediabetes or T2DM.

3.2 Introduction

Exercise is recommended for individuals living with prediabetes or type 2 diabetes mellitus (T2DM) to minimize the likelihood of progression towards T2DM and improve glycemic control (Church et al., 2010; Diabetes Prevention Program Research Group, 2009; Glechner et al., 2018; Schwingshackl et al., 2014; Sigal, 2007; Xiao-Ren et al., 1997, p.). Despite knowledge of the potential health benefits associated with exercise, heterogeneity exists among the improvements experienced by each participant. Individual participants often do not experience the targeted health benefits despite improvements in the group mean. These individuals are generally referred to as 'non-responders', whereas those who benefit are referred to as 'responders' (Atkinson & Batterham, 2015; Hecksteden et al., 2015, 2018; Hopkins, 2015; Hrubeniuk, Bonafiglia, et al., 2021; Marsh et al., 2020; Ross et al., 2019; Swinton et al., 2018; Williamson et al., 2017). Recent advancements in the methods used to categorize individual exercise responses provide further contextualization and expand upon the binary nature of categorization (Bonafiglia et al., 2018; Hrubeniuk, Bonafiglia, et al., 2021; Swinton et al., 2018). As a result, those observed to be negatively impacted by an intervention are referred to as 'adverse responders', and those who cannot be categorized within a selected degree of confidence are referred to as 'unclear' (Bonafiglia et al., 2018; Bouchard et al., 2012; Hrubeniuk, Bonafiglia, et al., 2021; Swinton et al., 2018).

There is a growing body of literature attempting to identify characteristics that predispose individuals to respond favourably to an exercise intervention (Bamman et al., 2007; Petrella et al., 2008; Raleigh et al., 2018; Roberts et al., 2018; Sénéchal et al., 2015; Stec et al., 2016). However, these attempts often neglect to consider much of the error associated with an individual response estimate (Hrubeniuk, Bonafiglia, et al., 2021).

Moreover, categorization decisions can be highly variable, as they rely on the selected outcome measure, the variance associated with the measurement technique, and the desired level of confidence in the decision (Hecksteden et al., 2018; Ross et al., 2019; Walsh et al., 2018). Likewise, there are attempts to identify exercise training protocols that produce the highest 'response rates' (Alvarez et al., 2017; Álvarez et al., 2018; Astorino & Schubert, 2014; Gurd et al., 2015; Lannoy et al., 2017). One such study from Ross et al. (2015) allocated adults at risk of T2DM to one of three groups for 24 weeks of exercise to improve cardiorespiratory fitness: (1) low-volume, low-intensity; (2) high-volume, low-intensity; or (3) high-volume, high-intensity (18). The authors found a higher training volume led to a 50% decrease in non-response, whereas a higher training intensity only produced responders. These findings were interpreted as suggesting an increase in intensity may increase the likelihood of an individual responding to the intervention. However, we have to be cautious when interpreting this data. When choosing to compare response rates between groups based on the raw counts of responders and non-responders, the authors are more accurately comparing differences in the respective group means rather than the true variation among individual responses (Atkinson et al., 2019). This is due to the natural tendency of observed changes to distribute normally, resulting from the effects of random and within-subject variation. Alternative approaches have been proposed to isolate the influence of exercise training on individual response variation (accounting for the effects of random and within-subject variation), providing a more accurate estimate of response rates (Swinton et al., 2018). However, these methods are limited in their ability to address an individual, and do not allow for direction in a clinical setting.

It is important to emphasize that a non-responder categorization does not imply an individual cannot benefit from engaging in exercise (Hecksteden et al., 2018; Marsh et al., 2020; Montero & Lundby, 2017). Rather, a non-responder categorization suggests the individual did not experience a benefit from the currently prescribed program based on the targeted outcome. It remains possible that a non-responder will benefit from an alternative program with different prescription parameters (i.e., adapting volume, modality, or intensity) or experience secondary benefits. Therefore, it may be beneficial to identify the effectiveness of adapting exercise interventions to assist previously identified non-responders in achieving improvements in the targeted outcome. Recent findings from Marsh et al. (2020) displayed how an individual categorized as a non-responder can subsequently experience a response by changing exercise modality. Using a randomized cross-over trial their data suggests non-responders to an aerobic exercise intervention are likely to respond to a subsequent resistance training intervention, and vice versa. Moreover, Montero and Lundby (2017) showed increasing volume to a minimum of 180 minutes per week improved the response categorization for all non-responders. However, it is worth noting these trials were conducted with healthy adults free of chronic disease and response categorizations were made based on fitness related outcomes.

Despite growing evidence suggesting high intensity exercise can be beneficial for those living with prediabetes or T2DM (Little et al., 2011; Støa et al., 2017; Terada et al., 2013), few studies have investigated if increasing exercise intensity can successfully improve the response categorization of previously identified non-responders. Likewise, it remains unknown if 1) increasing exercise intensity would translate to specific improvements in individuals previously categorized as non-responders, and 2) if increasing exercise intensity would improve the response categorization among non-

responders living with prediabetes or T2DM, specifically based on improvements in glycemic control.

The objectives of the INTENSITY trial were to:

1. Identify the number of non-responders, based on the observed changes in glycated hemoglobin (HbA1c), across individuals living with prediabetes or T2DM following 16 weeks of supervised continuous aerobic exercise.
2. To investigate if increasing the intensity of the supervised continuous aerobic exercise for an additional 12 weeks will improve the response categorization of those individuals previously categorized as non-responders.

It has been estimated that approximately 20% of individuals with T2DM will fail to improve their metabolic health following a standardized exercise intervention (Stephens & Sparks, 2014). Accordingly, it was hypothesized at least 20% of participants will be categorized as non-responders following the initial exercise program, based on an inability to improve HbA1c beyond the minimal clinically important change (MCIC) of 0.3%. It was also hypothesized that increasing exercise intensity will successfully improve the response categorization of previously identified non-responders.

3.3 Methods and analysis

The INTENSITY trial was conducted in Fredericton, New Brunswick, Canada, with all experimental procedures approved by the University of New Brunswick Research Ethics Board (REB: 2018-168). Oral and written consent was obtained from each participant prior to participation in the study. Comprehensive details and a rationale for the study design and procedures can be found in the protocol paper (Hrubeniuk, Bouchard, et al., 2021) and ClinicalTrials.gov study registration (NCT03787836). Due to the

COVID-19 pandemic, the previously published protocol was amended. A summary of those changes is provided below.

Participants

Between April 2019 and November 2020, we aimed to recruit 60 participants for the INTENSITY trial using a convenience sampling method. Advertisements were placed in public locations and on social media. To be included, participants were required to be:

1. Adults aged 19 years or older;
2. Living independently;
3. Currently living with prediabetes or T2DM as diagnosed by a physician and confirmed by an HbA1c value of 5.7% or above, as verified by duplicate testing;
4. Not currently partaking in a self-reported regular exercise regimen, defined as consistent participation in running or jogging activity, attending exercise classes on a weekly basis, or averaging 10,000 steps per day or more over the course of seven days;
5. Not currently have an injury that would prevent safe participation in the intervention.

Exclusion criteria were:

1. A self-reported diagnosis of low iron concentrations, anemia, or being treated for these conditions;
2. Being diagnosed with any red blood cell altering condition (i.e., sickle cell anemia, poikilocytosis);
3. Currently living with any cardiovascular disease which would impact the ability to safely participate in exercise;

4. Currently prescribed any medication which would impact the ability to use a heart rate monitor to accurately track intensity.

Study Design

Participation in the INTENSITY trial took place in two phases (Figure 4). Phase one of the INTEISTY trial was used as a lead-in phase and used to complete objective one. Phase two was a parallel group randomized trial designed to complete objective two. All participants met with the research staff for analysis six times: twice at the time of enrollment for baseline assessment, twice between phase one and phase two for mid-point follow up and randomization, and twice following phase two for post-testing.

Phase One

Eligible participants were assigned to either a control or an intervention group, based on the time of recruitment. The first 11 participants were assigned to the control condition, with all subsequent participants assigned to the intervention. Allocation was chosen in favour of randomization during phase one, as data from the control group is required to estimate measurement variance and allow for the categorization of intervention participants prior to randomization in phase two. All control participants were expected to complete participation prior to finishing recruitment of all intervention participants. Participants allocated to the control group received no exercise advice or instruction and were instead instructed to maintain current lifestyle habits. All 11 control participants completed phase one and attended midpoint re-assessment. Participants allocated to the intervention group participated in treadmill-based aerobic exercise for 16 weeks at an intensity of 4.5 metabolic equivalents (METs). An absolute measure of intensity was chosen in favour of a relative measure of intensity to equalize energy expenditure across all participants. Following baseline aerobic testing, participant METs and heart rate values

were reviewed, and the heart rate associated with 4.5 METs was identified. This heart rate was used to prescribe and monitor participant intensity during subsequent training sessions, until cardiorespiratory fitness was re-evaluated. Intervention participants were eased into the program using a four-week progression, completing 80 minutes of exercise in week one, 100 minutes in week two, 120 minutes in week three, and 135 minutes in week four. For each of the remaining 12 weeks participants completed 150 minutes of exercise. All sessions were supervised by research staff in a private facility to ensure compliance. Following each session, participants were asked to report their perceived exertion using a Borg Rating of Perceived Exertion Scale (Borg, 1982) on a scale from 6 (no exertion) to 20 (maximal exertion). To account for improvements in cardiorespiratory fitness each participant was re-evaluated every four weeks.

If a participant was unable to achieve the required time allotment for three consecutive weeks, or for a total of four weeks *during phase one*, they were considered non-compliant, removed from the trial, and replaced. Participants were not replaced if this happened during phase two. If a participant was absent from the trial for a full week (e.g., due to illness, vacation, family emergency), an additional week was added at the end of the phase for each week missed. A maximum of three additional weeks throughout the totality of the trial was allowed for each participant. If surpassed, the participant was excluded from further participation and considered a drop out. If this occurred during phase one, the participant was considered non-compliant, and replaced. Fourteen participants allocated to the intervention group were non-compliant during phase one and replaced. After recruitment was completed in December 2019, one participant was deemed to be non-compliant to the program, but not replaced. As a result of COVID-19

interruptions, scheduling issues, and illness or injury unrelated to the INTENSITY study, it took 16.7 ± 0.8 weeks for intervention participants to complete phase one.

Response Categorization

For the purpose of this analysis, a responder was defined as any individual who experienced a decrease in HbA1c beyond the MCIC while accounting for the variation-induced changes in HbA1c experienced by the time-matched control group (thereby unrelated to participation in the exercise program). Based on the observed changes in HbA1c following the 16 weeks of exercise, each participant in the intervention group was categorized as a responder, non-responder, adverse responder, or unclear responder. Individual 90% confidence intervals (CI) around the observed change in HbA1c were calculated for each participant, with participants whose upper bound of the 90% CI lay below the selected response threshold categorized as responders, and those whose lower bound of the 90% CI lay above the response threshold categorized as non-responders. If the lower bound of the 90% CI lay above the response threshold in the opposite direction (indicating a rise in HbA1c), the participant would be categorized as an adverse responder, and if the CI for a participant crossed the threshold for response they were categorized as an unclear responder.

Blinding and Randomization

All participants, outcome assessors, and research staff who supervised exercise training were blinded to all follow-up measures of HbA1c and response categorizations until all participants completed phase two of the trial. A laboratory staff member unrelated to the project was responsible for gathering measures of HbA1c and categorizing participants. For the sole purpose of randomization for phase two, participants categorized as adverse or unclear following phase one were grouped with the non-responders. The

response categorization was then communicated to a research team member who had no interaction with participants (DRB), who entered the categorization into a random number generator (SPSS version 22.0) to allocate participants for phase two. Randomization occurred in blocks of 10 (five per group) based on participant response status (responder vs. non-responder and unclear). Group allocation was then communicated to TJH and implemented for phase two.

Phase Two

Participants in the control group were instructed to maintain current lifestyle habits for 12 weeks. Nine control participants completed phase two and attended post-testing. Participants in the intervention group were blocked based on response status and randomly allocated to either a maintained group, or an increased intensity group. Participants in the maintained group continued the supervised, treadmill-based aerobic exercise for 150 minutes per week at an intensity of 4.5 METs, for 12 weeks. Participants in the increased intensity group increased the intensity of the supervised, treadmill-based aerobic exercise to 6.0 METs, for 150 minutes per week. Supervision and recording of perceived exertion followed the same methods as applied during phase one. Likewise, cardiorespiratory fitness was re-evaluated every four weeks. If a participant was found to be non-compliant to the study protocols during phase two, they were allowed to continue participation but considered drop-outs for the current analysis. As a result of COVID-19 interruptions, scheduling issues, and illness or injury unrelated to the INTENSITY study, it took 12.5 ± 1.1 weeks for participants to complete phase two.

Changes to the study protocol and impacts of the COVID-19 pandemic

Following initial trial registration, inclusion and exclusion criteria were amended. Age criteria were expanded from 19 – 65 years to any community-dwelling adults aged

19 years or older to expand the potential participant pool. A confirmation of HbA1c being 5.7% or above as measured in the laboratory was required to ensure all participants were, at the time of enrollment, living with an HbA1c value above the diagnostic cut-off for prediabetes. Similarly, self-reported and objectively measured physical activity levels prior to participation were added to ensure participants were not regularly active prior to the trial. Exclusion criteria were expanded and specified to ensure participants were not currently living with any condition which may impact the ability to accurately measure HbA1c, and to confirm the participants could safely participant in physical activity.

Due to ethical considerations and facility closures related to the COVID-19 pandemic, all recruitment and participation was put on hold from March to August 2020. When the intervention resumed additional cleaning, social distancing, and personal protective equipment protocols – in line with local COVID-19 regulations – were in place.

All control participants had completed their participation prior to the interruption. Four participants who were in phase two of the trial in March 2020 chose not to return, and dropped out of the trial (Figure 5). Seven participants had completed phase one and were enrolled in phase two of the trial at the time of shutdown. They also chose to return at re-opening. These participants all completed an additional round of midpoint testing and restarted phase two after the five-month delay. Participants remained in their previously allocated arm (maintained or increased intensity). Upon re-opening local COVID-19 outbreaks led to two additional shutdowns lasting one week each (January 2020 and April 2020). Two participants in phase two of the trial dropped out as a result of these shut downs. The remaining participants added one week to whichever phase of the trial they were currently enrolled in to make up for the missed time.

Outcomes and instrumentation

Primary outcome

The primary outcome of the INTENSITY trail is HbA1c, analyzed using a DCA Vantage Analyzer (Siemens, Germany). The DCA Vantage Analyzer has been shown to provide accurate, valid measures of HbA1c when compared to laboratory measurements (Mardis & Foohey, 2017; Sánchez-Mora et al., 2011; Szymezak et al., 2008). To further increase reliability HbA1c was measured twice at each timepoint, separated by less than seven days, with the mean value used in all analyses.

Participant characteristics

At baseline research staff recorded participant demographics, family history of metabolic disease, and current medication use. Changes in medication use were confirmed at each testing time point. To confirm baseline exercise patterns and ensure eligibility, participants completed the Physical Activity and Sedentary Behaviour Questionnaire (Canadian Society for Exercise Physiology, 2013), and were sent home with a Piezo Rx pedometer (StepsCount, Deep River, ON, Canada) following the initial visit. Each participant wore the pedometer for seven consecutive days prior to starting the trial, excluding sleep time.

Secondary outcomes

At each timepoint physiological and anthropometric measurements were taken over the span of two days, separated by less than one week. Participant height, systolic and diastolic blood pressure, and waist circumference were measured in accordance with Canadian Society for Exercise Physiology protocols (Canadian Society for Exercise Physiology, 2013). Body mass, fat mass, and fat free mass were estimated using the BODPOD (COSMED; Rome, Italy) following a 12-hour overnight fast. In our laboratory,

the coefficient of variation (calculated across 11 men (n = 6) and women (n = 5)), is 3.5% for body fat percentage and 0.8% for fat-free mass.

Cardiorespiratory fitness ($VO_{2\ peak}$) was evaluated using an amended version of the Balke and Ware treadmill test protocol (Balke & Ware, 1959; Hrubeniuk, Bouchard, et al., 2021). Briefly, each participant walked at 3.4 miles per hour (mph) at 0% grade on a treadmill. While speed remained constant, treadmill grade was increased to 5% after 2 minutes. Thereafter, grade was increased by 1% every minute until 15.0% incline was reached. If the participant did not reach maximal capacity, the grade was maintained and speed was increased by 0.5 mph each minute until volitional fatigue. Gas exchange and heart rate values were continuously recorded using a TrueOne 2400 Metabolic Cart (ParvoMedics, Salt Lake City, UT, USA) and Polar FT1 heart rate monitor (Polar, Kempele, Finland), respectively. $VO_{2\ peak}$ was identified as the highest oxygen consumption achieved over a 15-second average over the course of the last minute of testing.

Cardiorespiratory fitness re-evaluation

Every four weeks throughout each phase, a submaximal aerobic test was performed to account for changes in cardiorespiratory fitness and movement economy. Prior to a typical session, participants replicated the typical five-minute warm-up with gas exchange and heart rate measures being recorded. Treadmill grade and speed were gradually increased until the desired MET value (4.5 or 6.0 METs) was achieved and maintained in a steady state. The target heart rate identified during the fitness re-evaluation was used for all subsequent training sessions, until the next re-evaluation.

Statistical analysis

The primary purpose of the control group was to provide insight to the anticipated variance and changes in HbA1c among individuals not participating in the intervention. Accordingly, a key assumption when calculating individual CIs is that the two groups are similar. Therefore, Mann-Whitney U tests were used to test for differences between the control and intervention participants at baseline. Independent sample t-tests were used to test for differences between the increased intensity and maintained intensity groups at mid point. Likewise, when individual responder counts are extrapolated to describe trends among a group, they are known to be influenced by changes in the group mean. Therefore, although the trial was designed to analyze individual participant changes, Friedman Tests were run to identify group changes in HbA1c across each timepoint, for each group. Likewise, split-plot ANOVAs were conducted to compare the main effects of group allocation (increased intensity vs. maintained intensity) and time point (mid-point vs. post-intervention), as well as the interaction effect between group allocation and time point, on the secondary outcomes.

There were two objectives of the INTENSITY trial. Objective one was to identify the number of responders, non-responders, unclear responders, and adverse responders based on the observed changes in HbA1c, across individuals living with prediabetes or T2DM following 16 weeks of continuous aerobic exercise. Objective two was to investigate if increasing the intensity of the supervised continuous aerobic exercise for an additional 12 weeks will improve the response categorization of those individuals previously categorized as non-responders, based on observed changes in HbA1c.

Objective 1:

Individuals were categorized as responders if the observed change in HbA1c was confidently assumed to be beyond the MCIC, while accounting for the variation-induced

changes experienced by the time-matched control group. In line with the Federal Drug Agency and the European Medicines Agency, an MCIC of 0.3% for HbA1c was used (Center for Drug Evaluation and Research, 2008; Committee for Medicinal Products for Human Use, 2012). Accordingly, an individual 90% CI for each participant was calculated using the following equation (Swinton et al., 2018):

$$\text{Individual CI} = (\text{Observed score}_{MID} - \text{Observed score}_{BASELINE}) \pm (\text{CI multiplier x typical error}).$$

Here, the typical error is calculated as $SD_{diff}/\sqrt{2}$ and allows for potential variation introduced in the absence of the intervention to be considered when constructing each CI (Swinton et al., 2018). The SD_{diff} is calculated as the standard deviation (SD) of the difference scores from the control group's HbA1c measurements at midpoint and baseline. As the sample size of the control group may influence the certainty of the CI, the CI multiplier was adjusted for a control sample size of 10 individuals (CI multiplier = 1.83) (Swinton et al., 2018). Based on the results from the control group, the typical error was 0.446. To estimate if the variance among observed responses to the intervention was a product of participating in the intervention, the standard deviation of individual responses (SD_{IR}) was calculated as:

$$SD_{IR} = \sqrt{(SD_{INT}^2 - SD_{CON}^2)}.$$

Here, the SD_{INT} represents the standard deviation of change scores from the intervention group (INT) and the SD_{CON} represents the standard deviation of change scores from the control group (CON).

Objective 2:

Following the completion of phase two, the categorization procedure conducted for Objective One was repeated for all previously identified unclear and non-responders.

The individual CIs were calculated based on the observed HbA1c measurements taken at midpoint and follow-up testing. Likewise, the typical error was re-calculated with the SD of the difference scores from the control group using HbA1c measurements taken at midpoint and follow-up post testing. This allows for the CIs to represent the potential variation-induced changes experienced by the time-matched control group across the second, 12-week period for Objective Two. Based on the results from the control group, the typical error for Objective Two was calculated as 0.386. To estimate if the variance among observed responses to either the maintained or increased intensity interventions was a product of participating in the aforementioned intervention, the standard deviation of individual responses (SD_{IR}) was calculated for each group.

Post-hoc analyses:

Completion of the trial and unblinding of investigators revealed the majority of participants were categorized as unclear responders following phase one. As outlined by Swinton et al. (2018), a high number of unclear responders suggests the standards for categorization were too restrictive. Here, the decision to utilize 90% CIs contributed to the high proportion of unclear responders. Therefore, the above analyses were also completed using 50% and 70% CIs to provide context and outline how categorizations may have changed.

3.4 Results

Baseline participant characteristics are shown in Table 4. Participants assigned to the intervention group were more aerobically fit, as measured using VO_{2peak}, at baseline than participants assigned to the control group. Forty-nine of 50 (98.0%) participants in the intervention group completed phase one and were randomized. Of those, 39 (79.6%)

participants (20 from the increased intensity group, 19 from the maintained intensity group) completed phase two (Figure 5). All but one intervention participant completed at least 95% of the total 4035 minutes of supervised aerobic exercise at the prescribed intensity.

Objective 1:

Following the completion of phase one, two participants (4.1%) were categorized as responders, four (8.2%) as non-responders, and 43 (87.8%) as unclear (Figure 6). All six participants who reported an increase in diabetes-related medication during phase one were categorized as unclear. The SD_{CON} for phase one was calculated to be 0.63. The SD_{INT} was calculated to be 0.62. As the SD_{CON} was larger than the $SD_{INT,}$ and the square root of a negative number cannot be calculated, the SD_{IR} was unable to be calculated for phase one. Mean effects of the intervention based on group allocation for phase one are provided on Table 5. There were no significant between or within group differences (control vs. intervention) throughout the intervention.

For phase two, twenty-six participants were randomized to the increased intensity group and 23 were randomized to the maintained intensity group, of which 20 and 19 completed the intervention, respectively (Table 6).

Objective 2:

Following the completion of phase two and the removal of the phase one responders, two participants (10.0%) randomized to the increased intensity group improved their response categorization, four participants (20.0%) in this group were categorized as non-responders, and 13 (65.0%) were unclear (Figure 7a). Four participants who reported an increase in diabetes-related medication at any point of the intervention were randomized to the increased intensity group. Of those, three were categorized as

unclear following phase two, and one experienced an improvement in response categorization. In the maintained intensity group one participant (5.0%) experienced an improvement in response categorization, one (5.0%) was categorized as a non-responder, one (5.0%) as an adverse responder, and 16 (84.2%) as unclear (Figure 7b). Five participants who reported an increase in diabetes-related medication at any point of the intervention were randomized to the maintained intensity group, all of whom were categorized as unclear following phase two.

The SD_{CON} for phase two was calculated to be 0.55. The SD_{INT} for the increased intensity group was calculated to be 0.99. Accordingly, the SD_{IR} for the increased intensity group was calculated to be 0.82. The SD_{INT} for the maintained intensity group was calculated to be 0.44 As the SD_{CON} was larger than the $SD_{INT,}$ and the square root of a negative number cannot be calculated, the SD_{IR} for the maintained intensity group was unable to be calculated. Mean effects of the intervention based on group allocation for phase two are provided on Table 7. There were no significant between or within group (maintained vs. increased intensity) differences in HbA1c throughout the intervention.

Post-hoc analysis:

Changes in response categorizations based on the desired level confidence are listed on Table 8. When 70% CIs were used, five participants (10.2%) were categorized as responders, six (12.2%) as non-responders, one adverse responder, and 37 (75.5%) as unclear after phase one. Subsequently, following the completion of phase two and the removal of the phase one responders, two (11.1%) participants randomized to the increased intensity group were categorized as responders and therefore improved the response categorization, five (27.7%) were categorized as non-responders, and 11 (61.1%) as unclear. Four participants randomized to the maintained intensity group were

categorized as responders and improved the response categorization (23.5%), three as non-responders (17.6%), and 10 (52.6%) as unclear.

When 50% CIs were used, ten (20.4%) participants were categorized as responders, 11 (22.4%) as non-responders, four (8.2%) as adverse responders, and 24 (48.9%) as unclear after phase one. Subsequently, following the completion of phase two and the removal of the phase one responders, an additional two (13.3%) participants randomized to the increased intensity group were categorized as responders and therefore improved the response categorization, four (26.6%) were categorized as non-responders, and 9 (60.0%) as unclear. Four (23.5%) participants randomized to the maintained intensity group were categorized as responders and therefore improved the response categorization, seven (41.2%) as non-responders, and six as unclear (35.3%).

3.5 Discussion

The first objective of the INTENSITY trail was to identify the number of non-responders, based on the observed changes in HbA1c, across individuals living with prediabetes or T2DM following 16 weeks of supervised continuous aerobic exercise. As a result of the initial 16 weeks of exercise, 4.1% to 20.4% of individuals were categorized as responders, dependent upon the desired level of confidence, whereas 8.2% to 22.4% of individuals were categorized as non-responders. However, the majority of individuals were categorized as unclear, ranging between 87.7% to 48.9% dependent upon the desired level of confidence. Taken together, these data suggest that once the variance in HbA1c observed throughout the control group was considered, it was not possible to confidently categorize the majority of individuals as responders or non-responders.

As a time-matched control group was used to calculate the typical error, the correct interpretation of these findings is that individuals categorized as uncertain or non-responders following phase one did not experience a reduction in HbA1c greater than what would have been expected as a result of the variation observed in the control group. It would be inappropriate to interpret these categorizations as an indication that uncertain and non-responders did not benefit from, or experience a change in HbA1c partially due to participation in, phase one of the intervention. Rather, we simply cannot distinctly and solely attribute the observed changes to participation in the 16 weeks of supervised aerobic exercise. The inability to calculate the SD_{IR} for phase one (due to the SD_{CON} being larger than the SD_{INT}) suggests the influence of exercise on the observed variance throughout phase one was minimal. As such, it is understandable that the majority of participants would not experience a change beyond the influences of variation experienced by the controls during phase one.

The second objective of the INTENSITY study was to explore if increasing exercise intensity for an additional 12 weeks would improve the response categorization of those individuals previously categorized as non-responders. Increasing exercise intensity improved the response categorization of two non-responders (10.5% to 13.3%, dependent upon the desired level of confidence), whereas maintaining intensity improved one (5.3% to 23.5% dependent upon the desired level of confidence). However, the majority of participants remained categorized as unclear across both groups. Interestingly, while the SD_{IR} for the maintained intensity group remained incalculable, the SD_{IR} for the increased intensity group suggests there was true response heterogeneity stemming from participation in the increased intensity training group. Taken together, these data suggest

while it is possible to improve the response categorization of previously identified non-responders by increasing exercise intensity, the likelihood of doing so is low.

As reported by Hecksteden et al. (2018), decisions regarding the degree of variance accounted for, the desired level of confidence when categorizing, and the threshold for response can significantly impact response categorizations. Moreover, Swinton et al. (2018) discusses the importance of setting realistic expectations. To accomplish this, practitioners must use typical error values, among other parameters, in such a way that variance estimates are not so large as to require unrealistic improvements for individuals to be considered responders. Here, we chose 90% CIs to allow for high confidence that participation in the intervention produced changes in HbA1c by accounting for as much variation-induced change experienced by the time-matched control group as possible. However, when 90% CIs were utilized, individuals who experienced reductions in HbA1c as high as 1.25% were classified as unclear responders at the end of phase one (Figure 3). Considering the chosen device to quantify HbA1c has been shown to be a valid and reliable measure (Hopkins, 2000; Mardis & Foohey, 2017; Sánchez-Mora et al., 2011; Szymezak et al., 2008), and the selected threshold reflects a well-established MCIC (Center for Drug Evaluation and Research, 2008; Committee for Medicinal Products for Human Use, 2012), there are likely two explanations as to why participants experiencing seemingly large improvements were not categorized as responders. First, it could be argued the *a priori* decision to set individual CIs at 90% using our measured typical error rates was too conservative, and we were inaccurately categorizing these individuals. The second is that the intervention had a minimal effect on the observed mean change in HbA1c, and that the variance experienced in the absence of the intervention could be the primary contributor to the observed changes. The close relationship between individual

response counts and the mean effects of an intervention are well understood (Atkinson et al., 2019). As the group changes in HbA1c were not statistically significant across either group (Table 5), it was highly likely that the number of true individual responders was low, unless the intervention itself can be shown to impact the magnitude of individual differences (response heterogeneity). If the intervention meaningfully contributed to response heterogeneity, it may be possible for a larger than anticipated number of individuals to have experienced a true change in HbA1c as a result of participation in the intervention, despite the group mean suggesting otherwise. However, an inability to calculate the SD_{IR} for phase one of the trial (as a result of the variance experienced by the control group being larger than that of the intervention group) indicates the intervention did not meaningfully influence response heterogeneity. Taken together, these data suggest our high threshold for response may have not been the primary contributor to our low number of responders. Rather, the intervention simply did not meaningfully contribute to the observed variance and, in large part due to the small mean effects, did not produce many responders.

Previous research investigating individual responses has implemented a variety of confidence limits when categorizing individuals. A number of studies have simply utilized estimates of variation to make categorizations, however both 50% and 70% CIs are common (Bonafiglia et al., 2018; Hrubeniuk, Bonafiglia, et al., 2021; Lannoy et al., 2017; Schulhauser et al., 2020; Seward et al., 2019; Wolpern et al., 2015). Here, a reduction from 90% to 70% CIs allowed for twice as many individuals to be categorized as either a responder or non-responder, and using 50% CIs allowed for approximately half of the participants to be categorized after phase one, with similar improvements throughout phase two. The question of what degree of confidence to use when categorizing

individuals will always be challenged, depending upon the outcome measure and the acceptable degree of risk associated with an error in the categorization (Hecksteden et al., 2018; Hrubeniuk, Bonafiglia, et al., 2021; Ross et al., 2019). Specific to the utilization of exercise as a treatment for T2DM or prediabetes, the vast majority of evidence suggests exercise to be a beneficial and safe lifestyle intervention (American Diabetes Association, 2019; Colberg et al., 2016; Diabetes Canada Clinical Practice Guidelines Expert Committee, 2018; Lindström et al., 2013). As such, we argue the potential negative health impacts associated with using 70% or 50% CIs and subsequently categorizing an unclear or non-responder as a responder are low, and subsequent categorizations would be sufficient to indicate if an implemented exercise program is beneficial for participants. Nonetheless, it is important to highlight the number of individuals improved following phase two remained similar between the increased and maintained intensity groups regardless of the CIs implemented. These data suggest some individuals with prediabetes or T2DM may simply experience changes slower than others, and not necessarily need to increase exercise intensity. However, for the majority of individuals, it would appear the exercise was simply not able to generate a response regardless of the assigned group.

When observed in a clinical setting, reductions of 1.0% in HbA1c are typically considered meaningful. A reduction of 0.3% is the threshold for evaluating pharmaceutical interventions (Center for Drug Evaluation and Research, 2008; Committee for Medicinal Products for Human Use, 2012) and reducing HbA1c by 1.0% has been associated with a decreased risk of diabetes-related mortality, myocardial infarction, and microvascular complications (Benhalima et al., 2011; Stratton et al., 2000). This likely highlights a potential limitation in the clinical application of individual response research. From a clinician and/or patient perspective, whether the observed

change was a product of exercise or an alternative lifestyle changes may not necessarily be important, nor are similar steps to account for every source of variance regularly taken. What is more relevant is the observed improvement and its potential ability to reduce complications of T2DM. However, our results would suggest a more cautious interpretation may be required. It is important to remember the uncertain or non-responder categorizations suggest an individual did not experience a reduction in HbA1c beyond what could be explained by the variation observed amongst the controls. While the clinician may observe a 1.0% reduction in HbA1c in an individual, our data suggest such a change could have been a result of inconsistent, non-repeatable variation (such as random measurement error, or the expected variation in the outcome over time), rather than a true repeatable change. By implementing a conservative response threshold, the clinician can be confident that any individual categorized as a responder experienced a reduction in HbA1c beyond that resulting from variance, suggesting the intervention had a true, meaningful effect. This is not to say research suggesting 1.0% reductions in HbA1c are associated with improvements in risk factors when observed across a large sample. Rather, we suggest that in a clinical setting it is important to consider the potential influences of variance when interpreting observed changes on an individual basis.

The inability of increased exercise intensity to improve the response categorization of more non-responders than maintaining intensity contradicts findings from Ross et al. (2015), which suggest training at high intensity (75% of VO_{2peak}) alongside high volume (600 kcal per session) eradicated non-response, and was superior to training at high volume and low intensity (50% VO_{2peak}). However, as shown in Table 5 and Table 7, we found no significant impact on HbA1c regardless of intensity. Previous research has provided support for high-intensity training as a method to improve glycemic control

(Little et al., 2011; Støa et al., 2017; Terada et al., 2013), which could translate to improvements in HbA1c. It is possible the prescribed intensity for both the maintained and increased intensity groups was not substantial enough to generate a meaningful difference in the number of individuals who experienced an improvement in response categorization. Despite the relatively low peak aerobic fitness of the participants (Canadian Society for Exercise Physiology, 2013), reported ratings of perceived exertion indicate a higher degree of intensity may have been tolerated by both groups (Table 9). However, doing so may have impacted participant adherence or drop-out rates. Likewise, the decision to prescribe exercise intensity based on absolute – rather than relative – values likely introduced a ceiling effect to the degree of improvement experienced by many of the participants; limiting changes in HbA1c. Moreover, some evidence suggests a combination of aerobic and resistance exercise training produces superior improvements in HbA1c to aerobic training alone (Church et al., 2010; Sigal, 2007). As such, future research aiming to reduce the number, or improve the categorization, of non-responders based on changes in HbA1c may experience different results by adapting how exercise intensity is prescribed, or by providing a combination of exercise modes.

Results from the current study should be interpreted while considering some important aspects. Exercise-based trials involving individuals living with T2DM are often difficult to control due to potential changes in medication and the resultant impact on HbA1c. No participant reported a reduction in their diabetes medication throughout the duration of the trial. Two control participants increased their diabetes related medication, indicating some degree of medication use was included in our variance estimate. Six participants reported an increase in their diabetes medications following phase one, none of which were categorized as responders (Table 4). Following phase two, six participants

reported an increase in their diabetes medication, one of which was considered to have had their response categorization improved by increasing exercise intensity (when evaluated using 90% CI), with another improved after maintaining intensity (when evaluated using 70% CI). It is possible these individuals may have only benefitted from the more aggressive treatment approach, reflecting a desire from their physician for tighter glycemic control. A second consideration should be the natural progression of glycemia throughout the lifespan. Given upwards of 50% of individuals living with prediabetes will progress to T2DM within five years, no change in HbA1c values could be considered a positive outcome (DiMenna & Arad, 2018; Zhang et al., 2010). In our study, seventeen participants began the INTENSITY study with a diagnosis of prediabetes, the remainder of which were diagnosed with T2DM. None of these individuals were categorized as responders, non-responders or, most importantly, adverse responders at either timepoint (regardless of the degree of confidence), which we interpret to be a positive outcome.

There are some limitations that need to be acknowledged. First, we started prior to COVID-19, were forced to pause, and finished while in the pandemic. It is possible that although no participants reported contracting COVID-19, other factors including mental health, lifestyle habits, social interaction, and stress may have influenced our outcomes. Specifically, all control participants completed their participation prior to the pandemic-related changes. Given our participants were considered to be at high risk of adverse effects for COVID-19, it is likely the lifestyle of control participants included more physical movement, social interaction, and less pandemic related stress than the intervention participants who were impacted by COVID-19. Moreover, the training environment was significantly changed as a result of COVID-19, meaning participants who completed the trial prior to COVID-19, and those who re-started the trial or were

recruited during the pandemic, were subject to different cleaning protocols, physical distancing, and social environments within the training facility, which may have impacted our results. Second, allocation to the control group was not random. While this was done to ensure the control group was completed prior to the intervention participants (to allow categorizations to be made), there may have been unidentified differences between these two groups due to the lack of randomization. Participants were also aware of their group assignment. Despite a request for control participants to maintain current lifestyle habits, these individuals were likely motivated and committed to a change in lifestyle. It is possible some of these participants made lifestyle changes which could have influenced HbA1c, thereby increasing the observed variance among the controls. Nevertheless, this study was strengthened by its complex, highly controlled, innovative design to categorize responders prior to implementing a randomized trial. It was further strengthened by the randomization of participants to the maintained or increased intensity groups, and by blinding all research staff and participants to the responder status. Lastly, participants were continuously under strict supervision throughout each exercise session, contributing to adherence and compliance rates above 95% among those participants who completed the trial.

3.6 Conclusion

Based on the observed changes in HbA1c, when analyzed individually very few participants living with prediabetes or T2DM responded to 16 weeks of aerobic exercise. Increasing or maintaining intensity for an additional 12 weeks improved the response categorization of a small number of participants, with no difference between the groups. Future research should investigate what elements of an exercise prescription should be

manipulated to optimize the likelihood of rescuing non-responders, particularly for individuals living with prediabetes, T2DM and other chronic conditions.

3.7 Tables and Figures

Table 4. Participant characteristics at baseline

	Control (n = 11)	Intervention (n = 40)	p-value
Age (years)	57.0 (45.0 – 66.0)	58.0 (52.0 – 66.0)	0.59
Sex (female)	6 (54.5)	18 (46.2)	0.12
Diabetes duration (months)	68 (12 – 156)	72 (24 – 171)	0.86
Family history of diabetes (yes)	9 (81.8)	24 (61.5)	0.04
Diabetes medications (total)	1 (1 – 3)	2 (0 – 2)	0.74
Systolic blood pressure (mmHg)	137.5 (126.5 – 151.5)	135.0 (126.0 – 142.0)	0.36
Diastolic blood pressure (mmHg)	85.5 (80.5 – 89.0)	83.0 (80.0 – 88.0)	0.35
Resting heart rate (bpm)	78.5 (67.0 – 91.5)	77.5 (65.0 – 82.0)	0.28
Height (cm)	168.5 (164.0 – 179.8)	173.0 (165.0 – 177.0)	0.76
Body mass (kg)	99.4 (93.5 – 113.1)	97.1 (82.9 – 110.4)	0.44
Body mass index (kg/m2)	34.9 (32.8 – 36.5)	32.4 (27.6 – 36.4)	0.19
Body fat (%)	43.5 (40.9 – 44.5)	40.4 (35.1 – 47.6)	0.33
Total cholesterol ($mmol \bullet L^{-1}$)	4.5 (4.0 – 4.7)	4.2 (3.6 – 4.8)	0.43
High density lipoproteins ($mmol \bullet L^{-1}$)	1.3 (1.1 – 1.3)	1.2 (1.1 – 1.4)	0.97
Low density lipoproteins ($mmol \bullet L^{-1}$)	2.3 (1.8 – 2.8)	2.0 (1.5 – 2.9)	0.38
Triglycerides ($mmol \bullet L^{-1}$)	1.5 (1.1 – 2.1)	1.7 (1.2 – 2.3)	0.39
HbA1c (%)	6.6 (6.2 – 8.1)	7.0 (6.0 – 7.2)	0.99
Steps (per week)	5848 (4055 – 8842)	6208 (4658 – 8115)	0.89
VO_2Peak ($ml \bullet kg^{-1}\ min^{-1}$)	18.6 (17.6 – 23.7)	23.7 (22.0 – 27.4)	0.01

Data presented as median (25^{th} – 75^{th} percentile) or n (%).

Table 5. Control vs. intervention HbA1c values

Group		Baseline	Mid point	Post	p-value
Control	HbA1c (%)	6.6 (6.2 – 8.1)	6.8 (6.2 – 8.6)	6.7 (6.1 – 8.4)	0.69
	HbA1c Change (%)		0.2 (-0.3 – 0.5)	0.1 (-0.3 – 0.4)	
Intervention	HbA1c (%)	7.0 (6.0 – 7.2)	6.8 (5.9 – 7.4)	6.7 (6.0 – 7.3)	0.16
	HbA1c Change (%)		-0.2 (-0.5 – 0.1)	0.1 (-0.3 – 0.4)	

Data presented as median (25^{th} – 75^{th} percentile).

Table 6. Intervention participant characteristics at midpoint and post-intervention

	Increased (n = 20)		Maintained (n = 20)	
	Midpoint	Post	Midpoint	Post
Systolic blood pressure (mmHg)	128.4 ± 8.6	132.3 ± 8.2*	130.8 ± 12.5	126.5 ± 11.3
Diastolic blood pressure (mmHg)	81.6 ± 5.6	81.7 ± 5.5	85.2 ± 7.3	82.1 ± 7.2
Resting heart rate (bpm)	73.4 ± 9.0	71.4 ± 12.5	77.8 ± 10.1	74.6 ± 10.5
Body mass (kg)	93.8 ± 17.0	92.9 ± 15.3	94.7 ± 19.1	93.1 ± 18.8
Body mass index (kg/m^2)	31.6 ± 5.6	31.3 ± 5.0	32.5 ± 6.1	31.8 ± 5.7
Body fat percentage	36.7 ± 8.1	36.8 ±8.2	41.6 ± 8.6	40.4 ± 8.8
Total cholesterol ($mmol \cdot L^{-1}$)	4.2 ± 1.1	4.2 ± 1.2	4.4 ± 1.0	4.1 ± 1.3
High density lipoproteins ($mmol \cdot L^{-1}$)	1.2 ± 0.2	1.2 ± 0.3	1.3 ± 0.3	1.4 ± 0.3
Low density lipoproteins ($mmol \cdot L^{-1}$)	2.1 ± 1.0	2.1 ± 1.1	2.2 ± 0.8	2.1 ± 0.9
Triglycerides (mmol•L-1)	2.0 ± 1.0	1.9 ± 1.5	1.9 ± 1.0	1.7 ± 1.0
VO2peak ($ml \cdot kg^{-1}\ min^{-1}$)	26.1 ± 5.3	27.9 ± 5.2*	26.4 ± 5.5	26.1 ± 4.9

Data presented as mean ± standard deviation. Significance set at p = 0.05. * indicates significantly different from midpoint; ▲ indicates significantly different between groups.

Table 7. Maintained vs. increased HbA1c values

Group		Baseline	Mid point	Post	p-value
Maintained	HbA1c (%)	7.0 (6.0 – 7.5)	6.7 (5.8 – 7.7)	7.0 (5.9 – 7.4)	0.21
	HbA1c Change (%)		-0.2 (-0.6 – 0.2)	0.1 (-0.3 – 0.3)	
Increased	HbA1c (%)	7.1 (6.1 – 7.2)	6.8 (5.9 – 7.3)	7.0 (5.9 – 7.4)	0.59
	HbA1c Change (%)		-0.3 (-0.5 – 0.3)	0.1 (-0.3 – 0.5)	

Data presented as median (25^{th} – 75^{th} percentile).

Table 8. Number of individuals categorized by level of confidence.

Group	Categorization	90% Confidence Interval	70% Confidence Interval	50% Confidence Interval
Phase one	Responders	2	5	10
	Non-responders	4	6	11
	Unclear	43 (6)	37 (6)	24 (6)
	Adverse responders	0	1	4
Phase two: Maintained*	Improved	1	4 (1)	4 (1)
	Non-responders	1	3	7
	Unclear	16 (5)	10 (4)	6 (4)
	Adverse responders	1	0	0
Phase two: Increased*	Improved	2 (1)	2 (1)	2 (1)
	Non-responders	4	5	4
	Unclear	13 (3)	11 (3)	9 (3)
	Adverse responders	0	0	0

Parentheses indicate number of individuals who increased diabetes medication. *Responders from phase one are removed from categorization for phase two.

Table 9. Exercise time and rate of perceived exertion

		Increased (n = 20)	Maintained (n = 19)
Phase One	Minutes completed	2235.0 (2235.0 – 2235.0)	2235.0 (2225.0 – 2235.0)
	Rating of perceived exertion	10.4 (9.5 – 11.7)	10.7 (9.4 – 11.7)
Phase Two	Minute completed	1800.0 (1800.0 – 1800.0)	1800.0 (1800.0 – 1800.0)
	Rating of perceived exertion	11.7 (10.6 – 12.5)	10.3 (8.0 – 11.3)

Data presented as median (25^{th} – 75^{th} percentile).

Figure 4. Study Design

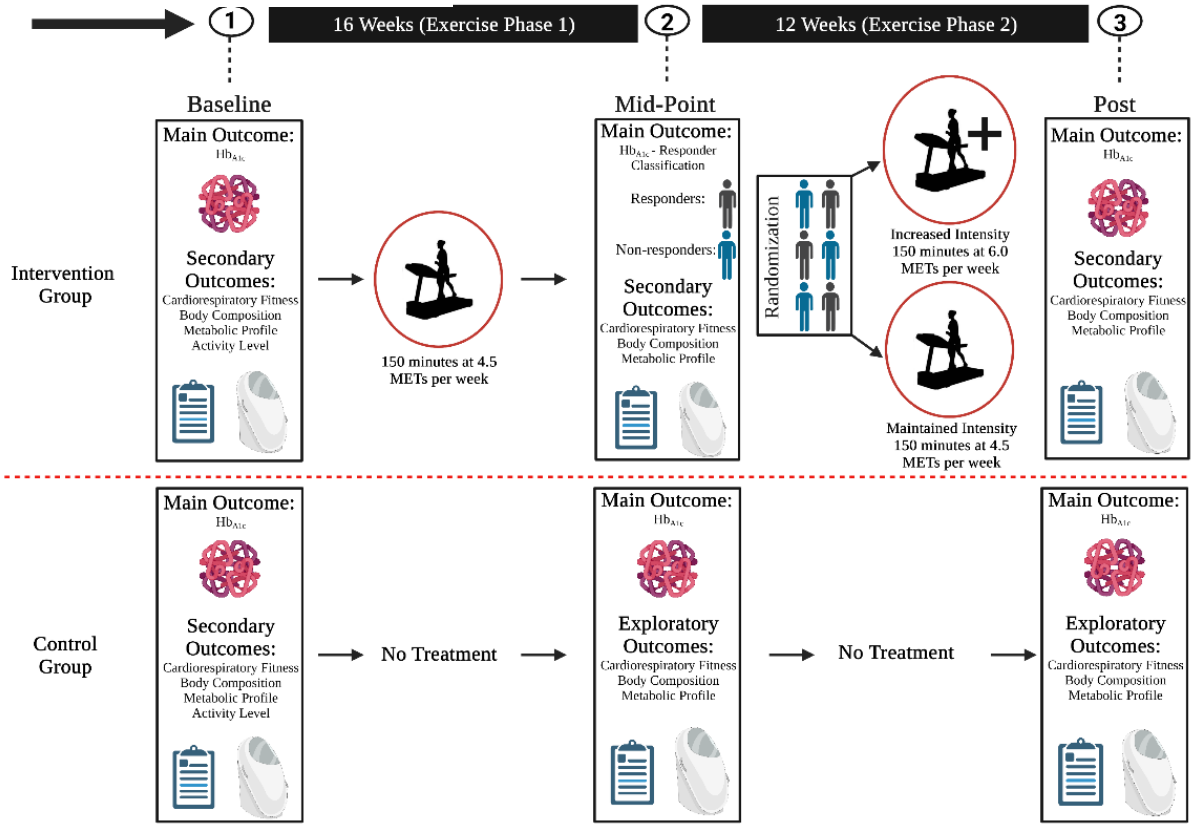


Figure 5. Participant flowchart

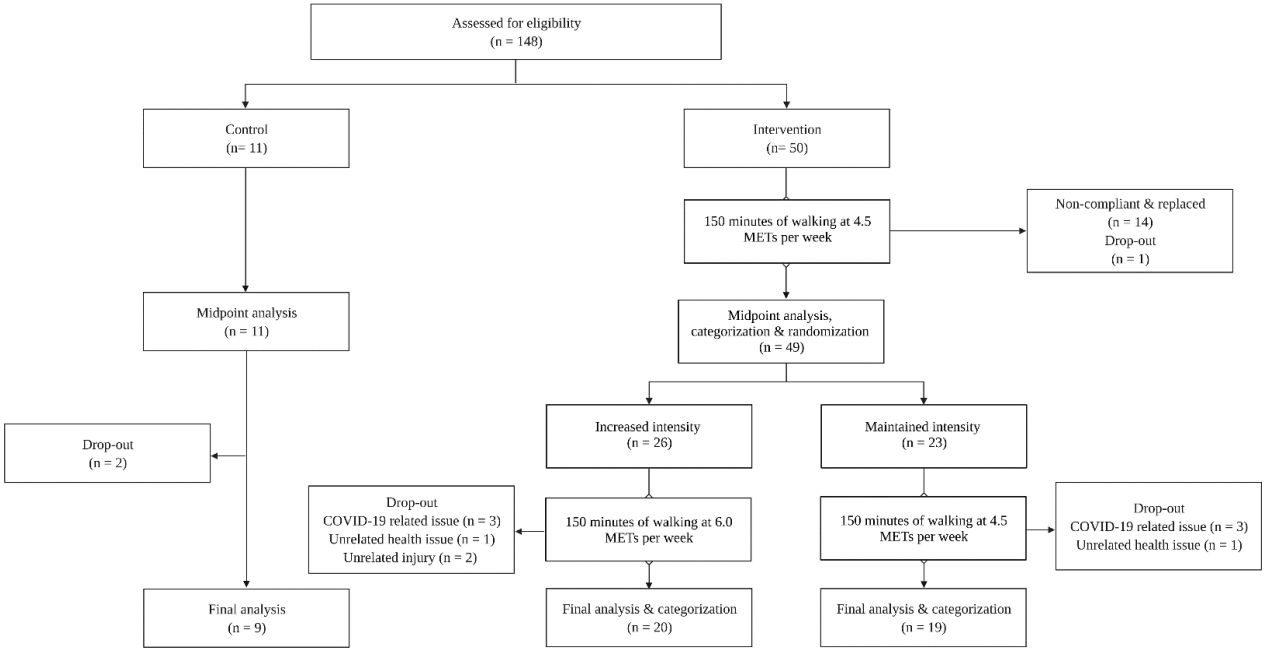


Figure 6. Participant changes in HbA1c from baseline to midpoint (90% individual confidence intervals)

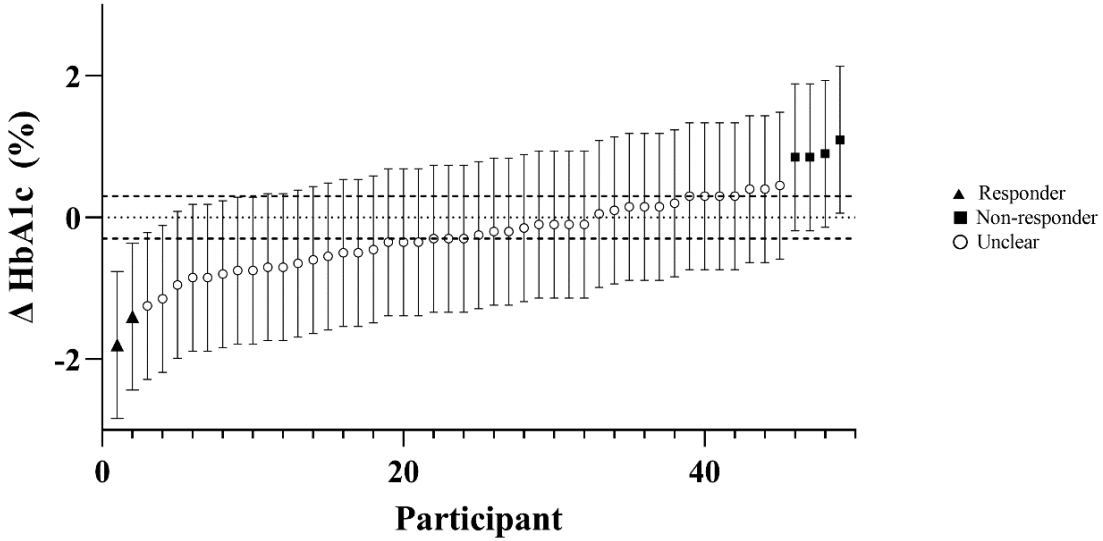
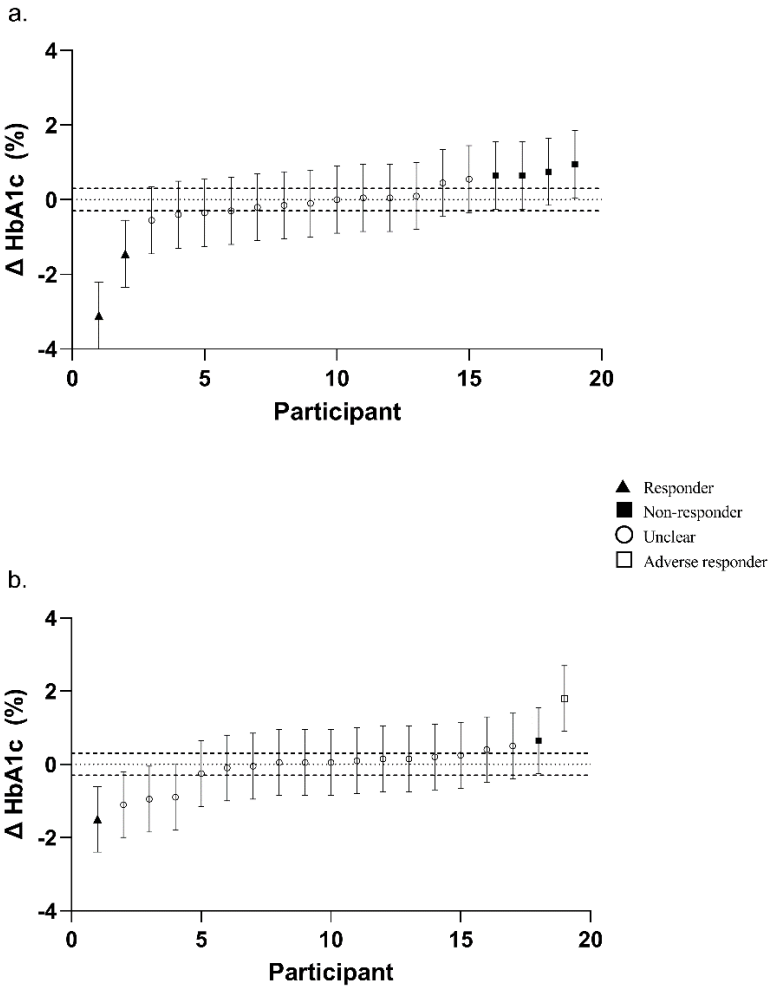


Figure 7. Participant changes in HbA1c after (a) increasing intensity or (b) maintaining intensity (90% individual confidence intervals)



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Chapter 4.0 Discussion Chapter

Overwhelming volumes of research indicate exercise is a key component in the prevention and treatment of prediabetes and T2DM. Despite this, we lack an ability to prescribe exercise training in a way that can target specific outcomes with consistent, repeatable results at an individual level, likely preventing exercise from being optimally implemented. In particular, without being able to prescribe exercise with the precision that pharmaceutical treatment options are prescribed, there lacks an ability to consistently, accurately identify, and subsequently adapt exercise prescriptions for those who don't experience the desired benefits following an initial prescription.

There have been numerous attempts to outline the incidence of non-response to exercise training, some of which have focused on outcomes related to prediabetes or T2DM (Alvarez et al., 2017; Álvarez et al., 2018; Bouchard et al., 2012; Lannoy et al., 2017; Leifer et al., 2016; Phillips et al., 2017). However, in most cases these findings more accurately reflect changes in the group mean, as opposed to providing a true analysis of individual participants (Atkinson et al., 2019; Bonafiglia et al., 2021). Moreover, studies reporting one exercise prescription as superior for 'reducing' or 'eliminating' non-responders by comparing group response rates are more accurately reporting a larger improvement in the group mean, leading to a higher proportion of individuals surpassing the arbitrarily set threshold value (Atkinson et al., 2019). Such analyses are not transferrable to samples beyond those observed. As such, the results from much of the previous literature do not provide relevant information for clinicians. As such, they cannot help improve the likelihood of success for initial exercise prescriptions, or provide advice for those who have been categorized as non-responders. For the utility of individualized

exercise prescription to move forward, a more comprehensive understanding of the appropriate methods, clarity on the strengths and weakness of differing analytical approaches, and a general consensus regarding the interpretation of results is needed. Subsequently, further attempts to implement these methods and provide direction for clinicians would allow for more practically applicable findings, with repeatable, transferable methods.

The aims of this dissertation were to: 1) Identify if prescribing high intensity exercise to youth at risk of T2DM increases the likelihood of experiencing the targeted benefits (responding) to exercise, and; 2) Investigate if increasing exercise intensity can be used as a method to adapt an exercise prescription to improve the response categorization for individuals living with prediabetes or T2DM who were previously identified as non-responders.

4.1 Summary and Impact of Findings

The first study was a secondary analysis of the Physical activity for OverWEight youth at Risk of type 2 diabetes (POWER) trial (Hay et al., 2016). Here, we aimed to identify the proportion of treatment response heterogeneity attributable to exercise training across several cardiometabolic risk factors in youth at risk for T2DM. Subsequently, for those outcomes whose response heterogeneity was influenced by exercise, we aimed to estimate the proportion of response and identify if proportions differed based on the intensity of exercise training. We found the influence of exercise training on treatment response heterogeneity to be inconsistent. While 50% of the scenarios studied indicated an influence of exercise on the observed heterogeneity, variation was *meaningfully* influenced (beyond a measure of the smallest worthwhile

difference) by exercise in 33% of scenarios. Throughout these scenarios, the proportion of youth estimated to respond spanned from 36% to 69%, with the estimated proportions being influenced by a combination of the intensity of exercise and the outcome of interest. Therefore, a practitioner looking to prescribe exercise intensity to a youth at risk for T2DM based on the greatest likelihood for success, would have to consider the primary outcome of interest. For example, while high intensity exercise training led to a higher proportion of response than moderate intensity when the target outcome was cardiorespiratory fitness (69.2% vs. 62.3%), moderate intensity exercise training was estimated to produce a higher proportion of responders than high intensity exercise when the targeted outcome was body fat percentage (50.1% vs. 47.0%).

These results are in line with a growing body of literature showing the influence of exercise on treatment response heterogeneity is highly dependent on the outcome of focus, the sample population, and the exercise prescription parameters (Hammond et al., 2019; Leifer et al., 2016; Steele et al., 2017; Walsh et al., 2019; Yu et al., 2021), as elegantly summarized by Bonafiglia et al (2021). Prior research has displayed this variance across a number of outcomes in adults (Hammond et al., 2019; Steele et al., 2017), older adults with chronic disease (Yu et al., 2021), and youth (Walsh et al., 2019), with both aerobic and resistance exercise modalities. Our data was the first to show similar inconsistencies across moderate and high exercise intensities for several outcomes in a sample of youth at increased risk for T2DM. Evidence continues to mount showing the influence of exercise – independent of the influences of random and/or within-subject variance – on treatment response heterogeneity is inconsistent. Accordingly, researchers in the field should consider the repercussions of these findings on the dissemination of trainability studies. It is increasingly clear that estimates of treatment response

heterogeneity should not be reported as transferable beyond the current sample, the outcomes observed, or the exercise prescription parameters. Instead, such analyses should be used as a descriptor for the study-specific conditions, outlining if variation among the observed responses to the prescribed exercise training regimen were discernibly a result of the exercise training *per se*, or a by-product of random or within-subject variation (Atkinson & Batterham, 2015; Bonafiglia et al., 2021; Dankel & Loenneke, 2020; Hecksteden et al., 2015, 2018). If treatment response heterogeneity is observed and calculable, an estimate of the proportion of response can then be made in line with the protocols outlined by Swinton et al., (2018) and Atkinson et al., (2019).

Rather than reporting response rates, we estimated the proportion of response (Atkinson et al., 2019; Swinton et al., 2018). By using a calculation of the SD_{IR} as a parameter for the distribution of true responses (in those outcomes where exercise was found to influence treatment response heterogeneity) around the mean treatment effect, we were able to predict the proportion of individuals who would experience changes above or below the response threshold for each outcome using the characteristics of a normal distribution. As outlined by Atkinson et al. (2019), regardless of the methods used to account for variation when categorizing individuals, raw counts of how many participants surpass a chosen threshold will closely reflect changes in the group mean. As a result, when comparing response rates between various interventions (when threshold values are identical), any intervention with a greater mean change will naturally produce a greater proportion of responders, regardless of individual response heterogeneity. By shifting away from a reliance on responder counts and implementing the methods outlined by Swinton et al. (2018), estimating the proportion of response accounts for random and within-subject variation. Doing so provides a clearer reflection of the heterogeneity

introduced by the intervention. Therefore, our estimates are less likely to solely reflect changes in the group mean, instead presenting a more accurate reflection of what proportion of similar individuals throughout the population may experience a true change attributable to the exercise intervention itself (Atkinson et al., 2019). For example, we can suggest that 69.2% and 62.3% of youth at risk for T2DM can be expected to improve cardiorespiratory fitness beyond 1.17 ml•kg-FFM^{-1}•min^{-1} (our selected threshold value) by following the moderate and vigorous exercise training protocols, respectively. It should be noted, however, that these methods are not without their own limitations. First, as these estimates are reliant on using a calculation of the SD_{IR}, they are only possible for those outcomes found to be influenced by treatment response heterogeneity, meaning we were limited in which outcome measures we can provide such estimates for. Accordingly, we were unable to provide an estimate of the proportion of responders based on an improvement in insulin sensitivity, regardless of the intensity of training. Second, these estimates may need additional contextualization when reported, as their interpretation differs from the prior (more common) reports. Prior research often reports response rates based on raw counts of the individual responders (e.g., 5 responders/10 individuals = 50% response), meaning without additional context, it is highly likely estimated proportions of response will be misinterpreted. Lastly, while this method may allow for a less biased, more transferrable estimate of the proportion of response, they are limited by an inability to account for additional confounding factors.

To the best of our knowledge, this was the first study attempting to investigate the influence of exercise on treatment response heterogeneity in youth at risk for T2DM. Likewise, it was the first attempt to estimate the proportion of response. While these data don't provide precision exercise prescriptions on an individual basis, or provide solutions

for those individuals who do not respond to the initial prescription, they offer a more accurate indication of the likelihood of improvement across a number of outcomes. Accordingly, as these methods are replicated and more data become available, clinicians can take the results into consideration and make more informed decisions when recommending an exercise regimen for similar individuals; hopefully optimizing the likelihood of success when attempting to use exercise training to prevent the onset of T2DM and its complications.

With an understanding of the limitations associated with providing group-based estimates of response, a need to highlight how categorizing individuals as responders or non-responders can be utilized to improve the prescription of exercise, and a desire to understand how best to aid those who do not respond to an initial exercise prescription, we conducted the second project, the INTENSITY study. Here, we aimed to first identify individuals living with prediabetes or T2DM who do not respond to a supervised aerobic exercise training program. Following which we explored if increasing exercise intensity can be used as a method to adapt the exercise prescription and improve the response categorization for individuals who were previously identified as non-responders (generate a subsequent change in HbA1c that would categorize them as responders). Participants were classified as responders, non-responders or unclear based on their individually calculated 90% CI laying above, below, or crossing the predetermined threshold value (a 0.3% reduction in HbA1c). After the initial exercise prescription, two participants (4.1%) were categorized as responders, four participants (8.2%) were categorized as non-responders, and 43 participants (87.8%) were unclear. Of those participants randomly selected to increase the intensity of exercise, two (10.0%) improved the response categorization, four (20.0%) were categorized as non-responders, and 13 (65.0%) were

unclear. Comparatively, one participant (5.0%) who maintained the originally prescribed intensity experienced an improvement in response categorization, one (5.0%) was categorized as a non-responder, one (5.0%) as an adverse responder, and 16 (84.2%) as unclear. These results were unexpected, as it was hypothesized that increasing the intensity of exercise would improve the response categorization for the majority of non-responders. Moreover, although these results may appear to contradict the common understanding of the benefits of exercising at increased intensity, we believe they highlight the importance of considering the influence of variance unassociated with the prescribed intervention when evaluating outcomes on an individual level. While doing so may require an individual to experience a larger observed change to be considered a responder, it allows for a higher level of confidence that the observed change was truly a product of the intervention, rather than a result of consistent variance. The clinician can then use these findings to make better informed decisions about adapting the exercise prescription, or continuing with the initial intervention.

As highlighted in the literature review and re-iterated by Bonafiglia et al., (2021), major questions facing individual response research include why we should be categorizing individuals in the first place, and how to best put these methods into practice. With the INTENISTY study we provided a proof of concept, outlining one way to clinically use individual categorizations and attempt to aid those who do not respond to an initial prescription, in line with the concept of rescuing non-responders coined by Marsh et al., (2020). To our knowledge, Montero & Lundby (2017) represent the only other attempt to amend an exercise training protocol following the initial prescription, with the goal of abolishing the non-responder categorization among a group of healthy, young adult males. Whereas our group focused on increasing exercise intensity, Montero

and Lundby (2017) chose to significantly increase exercise volume. In doing so, the authors reported a 100% success rate, having improved the response categorization for all non-responders (based on improvements in maximal power output) by increasing the initially prescribed training volume by 120 minutes per week.

At face value, our two investigations suggest drastically different success rates when attempting to improve the response categorization for non-responders. However, a number of factors likely contributed to the stark differences in the findings between the INTENSITY study and those from Montero & Lundby (2017). First, it must be stated that the two study samples represent very different populations (seemingly healthy vs. living with prediabetes or T2DM), with a focus on different outcomes (aerobic power vs. blood glucose), with vast differences in participant baseline fitness. It may be possible that the likelihood of success for rescuing non-responders differs based on the underlying characteristics of the population, however further research is needed to delineate this. Similarly, an additional factor we had to consider when analyzing our results was the potential influence of diabetes-related medications on our findings. Exercise-based trials involving individuals living with prediabetes or T2DM are often difficult to control due to potential changes in medication and the resultant impact on HbA1c. It is important to consider that two control participants increased their diabetes related medication, indicating some degree of medication change was included in our variance estimate. Six participants reported an increase in their diabetes medications following phase one of the INTEISITY study, none of which were categorized as responders. During phase two, six participants increased their diabetes medication. One of these individuals experienced an improvement in response categorization by increasing exercise intensity when evaluated using a 90% CI. A second participant experienced an improvement by maintaining

intensity when evaluated using a 70% CI. Although we believe we captured the influence of increasing diabetes medication within our estimate of variance (by way of having control participants who increased their medication), it is possible that without increasing medications, neither of these individuals would have improved their HbA1c enough to experience a positive change in response categorization through exercise training.

A key difference when interpreting the results of these two trials is which component of the exercise prescription was altered. Whereas Montero & Lundby (2017) chose to increase exercise volume with great success, we chose to increase exercise intensity based on numerous studies indicating the benefits of high-intensity exercise for glycemic control among a plethora of additional outcomes in those living with T2DM (Little et al., 2011; Rynders & Weltman, 2014; Støa et al., 2017; Terada et al., 2013). Moreover, an earlier trial from Ross et al., (2015) found training at high intensity (75% of VO_{2peak}) and high volume (600 kcal per session) produced a larger response rate when compared to training at "low" intensity (50% of VO_{2peak}) and high volume. While the results from Ross et al. (2015) were initially interpreted as an indication of the individual benefits stemming from training at a high intensity, it is now understood that the observed differences in the individual response rates more accurately reflect differences in the group means, rather than an improved likelihood for individual success (Atkinson et al., 2019). Regardless, we believed increasing exercise intensity could stand as a sound method to improve the response categorization for non-responders, and our unique study design would allow us to expand on the findings from Ross et al., (2015) to view the impacts of increasing exercise intensity on an individual level. Our data suggests individuals living with prediabetes or T2DM who do not respond to moderate intensity aerobic exercise can, but are unlikely to, experience an improvement in response categorization solely by

increasing the intensity of training. Moreover, unclear and non-responders who did not increase exercise training intensity and instead maintained the initial prescription appeared to improve their categorization at similar rates.

Although we were the first to analyze on an individual basis, we are not the first group to detect similar improvements in outcomes related to cardiometabolic health, glycemic control, or HbA1c among those living with prediabetes or T2DM following participation in moderate and high intensity exercise (Boulé et al., 2001; Hansen et al., 2009; Larsen et al., 1999; O'Donovan et al., 2005). Of particular note, Hansen et al. (2009) found similar, significant improvements in HbA1c among obese males living with T2DM following six months of supervised, continuous aerobic exercise at light/moderate intensity (50% of VO_{2peak} for 165 minutes per week) and high intensity (75% of VO_{2peak} for 120 minutes per week). However, as seen in Hansen et al. (2009), the majority of these interventions took the additional step of matching groups for total energy expenditure; whereas we did not. This is of particular significance to our results, as findings from Larsen et al. (1999) directly suggest total energy expenditure, as opposed to exercise intensity, is more closely related to glucose homeostasis and related outcomes. Therefore, it is possible that the 1.5 METs increase following phase one of the trial did not generate a large enough change in overall energy expenditure throughout phase two to produce changes in HbA1c for those unclear or non-responding individuals randomized to the increased intensity group. However, as suggested by Hansen et al. (2009) it is also worth considering that higher intensity aerobic interval training or anaerobic sprint interval training is more effective than continuous high intensity training at improving HbA1c in these populations (Little et al., 2011; Støa et al., 2017). As these methods of training have been shown to be tolerable in a similar sample Terada et al. (2013), future research

replicating our study design but implementing high intensity interval and/or sprint interval training should be conducted to determine if such methods can be used to improve the response categorization among non-responders.

A final, significant, factor to consider when comparing our results from those of Montero and Lundby is the impact of measurement variance, and the significantly different methods implemented by each research group to account for it. Montero and Lundby, (2017) used a raw estimate of the TE_M as the threshold for response. When used alone, this method attempts to solely account for the influence of random variation on the observed changes. Without taking steps to account for additional sources of variation, such as including the variance observed throughout a time-matched control group, the observed changes cannot be attributed to the exercise training (Atkinson et al., 2019; Atkinson & Batterham, 2015; Bonafiglia, Brennan, et al., 2019; Williamson et al., 2017), the authors cannot determine if alternate sources of variance contributed to the observed changes (Hecksteden et al., 2015, 2018; Senn, 2016; Williamson et al., 2017). In addition, there is no mechanism in place to ensure responders experienced a clinically meaningful change. As a result, relying solely on the TE_M to make categorization decisions has been shown to underestimate the true number of non-responders and categorize individuals who did not experience a true change as responders (i.e. type 1 error) (Bonafiglia et al., 2021; Hecksteden et al., 2018). It is likely that a key difference between the response rates reported by Montero and Lundby (2017) and our data could be explained by an overestimation of responders due to the methods they used to account for variance. Conversely, in the INTENSITY study we estimated error based on the observed changes in the control group, allowing us to consider both random and within-subject variation when calculating 90% CIs. Together, this provided us with a high degree of confidence

that individuals categorized as responders experienced a true change (beyond that which may have occurred as a result of the variance observed throughout the control group) following the prescribed exercise. Moreover, we implemented a MCIC as the threshold value meaning we have a high degree of confidence that individuals categorized as responders experienced a true, clinically important improvement in HbA1c. While our methods allow us to speak with more confidence when categorizing an individual as a responder, it is important to note that setting such a conservative threshold has been shown underestimate the number of responders, leading to some individuals being incorrectly categorized as unclear or non-responders (i.e. type 2 error) (Bonafiglia et al., 2021; Hecksteden et al., 2018). To account for this, we decided to re-analyze our results using 70% and 50% CIs. Results from these sub-analyses showed that more individuals were categorized as responders following the first phase of training. Yet there was little to no change in the total number of individuals who improved responder status by increasing exercise intensity.

All factors considered, we believe our findings, when considered in combination with those from Montero and Lundby (2017), suggest it is *possible* to improve response categorization for non-responders, however success will vary. Specific to the INTENSITY study, it appears the ability to aid unclear or non-responders living with prediabetes or T2DM by increasing exercise intensity by 1.5 METs has a low likelihood of success. Undoubtedly, further research is necessary to better understand the ability of amending exercise prescriptions to improve the categorization of non-responders. Nonetheless, it is important to re-iterate that the likelihood of success will be highly dependent upon the individual, the outcome of interest, the exercise prescription parameters, and how the research team and/or clinician chooses to define a responder.

4.2 Conclusion

As research in the field of exercise treatment response heterogeneity and individual responses to exercise training continue to expand, we may come to better understand factors that influence an individual's response to specific types of training, the interplay between specified outcomes and the likelihood of response, and how best to react when an individual does not respond to an exercise training program. The findings presented throughout this dissertation highlight the inconsistent impacts of exercise training across a variety of outcomes impacting treatment response heterogeneity, the estimated proportion of individuals who respond to exercise, and an individual's likelihood of improving their response categorization following an initial non-responder categorization. Taken together, these works provide a strong framework outlining how to best account for different sources of variations when conducting research in these fields for others to replicate, and identify numerous key topics for future research to focus on in order to move the field forward.

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Appendix 1: Curriculum Vitae

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Universities Attended:

University of Manitoba (2009 – 2014)
Bachelor of Kinesiology (with Distinction)

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Doctor of Philosophy

Publications:

1. Hrubeniuk TJ, Bonafiglia JT, Bouchard DR, Gurd BJ, Sénéchal M. "Directions for Exercise Treatment Response Heterogeneity and Individual Response Research." *International Journal of Sports Medicine*. 2022. doi: 10.1055/a-1548-7026

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