# Effects of a Diabetes Prevention Program

# Among Latino Youth with Prediabetes

by

Armando Peña

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Graduate Supervisory Committee:

Gabriel Q. Shaibi
Sonia Vega-López
Dorothy D. Sears
Stephanie L. Ayers
Micah L. Olson

ARIZONA STATE UNIVERSITY

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ABSTRACT

Latino youth are disproportionately impacted by obesity, prediabetes and type 2 diabetes (T2D). Pediatric obesity is characterized by abnormal increases in pro-inflammatory markers, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) and reductions in anti-inflammatory markers, high molecular weight adiponectin (HMW Adpn) and interleukin-10 (IL-10). Interleukin-1 receptor antagonist (IL-1ra) is an anti-inflammatory that is positively associated with obesity. IL-6, TNF-α, MCP-1 and IL-1ra have been associated with reduced insulin sensitivity and β-cell dysfunction, two central pathophysiologic mediators of glucose intolerance, while HMW Adpn and IL-10 have been associated with increased insulin sensitivity and β-cell function. The United States Diabetes Prevention Program (DPP) supported lifestyle intervention as the cornerstone approach for preventing T2D among adults with prediabetes, yet no studies to date have assessed the efficacy of an adapted DPP among Latino youth with prediabetes. In this dissertation, three studies were conducted. The first cross-sectional study among Latino youth with prediabetes and obesity (n=65) demonstrated that MCP-1 (β=-0.001, p=0.027; β=0.03, p=0.033), HMW Adpn (β=0.2, p<0.001; β=-2.2, p=0.018), and IL-1ra (β=-0.03, p=0.006; β=0.09, p=0.009) significantly predicted insulin sensitivity (measured by whole body insulin sensitivity index, WBISI) and glucose tolerance (measured by 2-hr glucose concentrations from an oral glucose tolerance test), respectively. Only HMW Adpn significantly predicted β-cell function, measured by oral disposition index, or oDI (β=0.6,

p<0.001). The second study was a randomized control trial that demonstrated the efficacy of lifestyle intervention (INT, n=79) for improving oDI among Latino youth with prediabetes and obesity, compared to a usual care control (UCC, n=38) group. No differences were found for changes in WBISI (Δ0.1, p=0.899) or 2-hr glucose (Δ-7.2, p=0.260) between groups. The third study was a secondary analysis (INT n=46, UCC n=29) that demonstrated no significant effects on IL-6, TNF-α, MCP-1, HMW Adpn, IL-10, or IL-1ra (all interactions, p>0.05).

# DEDICATION

I dedicate this dissertation to my mother and father, who have given me their unconditional love and support. This work is a reflection of the persistence and work ethic that they have instilled in me. This is also dedicated to my brothers and sister who are my number one support system.

# ACKNOWLEDGMENTS

This dissertation is a reflection of strong mentorship and support of individuals that have invested in my learning process as a scientist. I am forever grateful for the training opportunities that have been made available to me and will continue to foster strong learning environments for myself and for the next generation of scholars.

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Last but most certainly not least, I am extremely grateful for having my love, Jessica, by my side. She motivates me to pursue my career goals and provides me with her unconditional love and support.

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# CHAPTER 1:

# INTRODUCTION TO THE DISSERTATION

Latino youth are disproportionately impacted by prediabetes (Andes et al., 2020) and type 2 diabetes (T2D) (Lawrence et al., 2021). The Centers for Disease Control and Prevention (CDC) estimated that Latino youth have a 50% lifetime risk of developing T2D (Narayan et al., 2003). Lifestyle intervention is the cornerstone approach to preventing T2D among adults with prediabetes as demonstrated by the United States (U.S.) Diabetes Prevention Program (DPP) (Knowler et al., 2002), and these results have been replicated across DPPs that have been adapted in other clinical and community settings (Aziz et al., 2015). These findings have supported the implementation of the National DPP (NDPP) by the CDC which is a large-scale diabetes prevention effort to reach high-risk adult populations (Albright, 2012). Despite these efforts, less than 1% (~300,000 individuals) of adults with prediabetes in the U.S. have been reached through the NDPP (Ackermann & O'Brien, 2020). Moreover, scalable efforts among youth with prediabetes are lacking, likely due to only four other studies that we are aware of having adapted the DPP for youth with only one of these studies focusing exclusively on children and adolescents with prediabetes (Brown et al., 2013; Hingle et al., 2019; Savoye et al., 2014; Soltero et al., 2018). Tailoring interventions to the sociocultural context of Latino youth is key in developing effective diabetes prevention interventions (Castro et al., 2009). Therefore, studies are warranted that assess pragmatic DPP models

tailored to Latino youth that consider the sociocultural context of this specific ethnic population.

Pediatric obesity impacts approximately 20% of children and adolescents in the U.S. and is associated with prediabetes and T2D (Hales et al., 2017). Insulin sensitivity and β-cell function are two primary physiologic processes that work in conjunction to regulate blood glucose levels (Cerf, 2013). Insulin resistance, or decreased insulin sensitivity, is described by impaired insulin-mediated glucose uptake and increases the demand on β-cells to secrete more insulin, otherwise known as hyperinsulinemia, a phenomenon that is exacerbated among youth compared to adults (Arslanian et al., 2021). Failure to treat insulin resistance leads to an overcompensated β-cell, ultimately leading to β-cell failure—the hallmark pathophysiologic process of glucose intolerance which is currently used to diagnose T2D. Given that youth may progress more rapidly to overt T2D compared to adults (Barrett et al., 2020), there is an urgent need for diabetes prevention efficacy trials that are pragmatic and scalable to address the T2D disparities that impact Latino youth. Further, understanding the mechanisms by which diabetes prevention interventions reduce T2D risk will aid in the refinement of future interventions.

Chronic inflammation is a staple characteristic of pediatric obesity and has been associated with insulin resistance and β-cell dysfunction (Khodabandehloo et al., 2016). In obesity, adipose tissue is infiltrated by macrophages (M1 macrophages) that are characterized by a pro-inflammatory response. M2 macrophages, on the other hand, are

associated with an anti-inflammatory response; in obesity, these M2 macrophages undergo a polarization shift to M1 macrophage phenotypes (Lumeng et al., 2007). Thus, obesity is characterized by a disproportionate distribution of M1 and M2 macrophages (Lumeng et al., 2007). M1 macrophages produce pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), and chemokine, monocyte chemoattractant protein-1 (MCP-1). IL-6 and TNF-α are cytokines released by adipose tissue (i.e., adipokines) that may act locally in autocrine or paracrine fashion but may also be secreted systemically to have an endocrine effect (Engin, 2017). Hereafter, all cytokines of interest will be referred to as adipokines given their predominant origin in adipose tissue in obesity (Ahima, 2006; Lee & Lee, 2014), although it is appreciated that cytokines aside are not exclusively produced by adipose tissue (Lee & Lee, 2014; McLaughlin et al., 2014; Winer et al., 2014; Winer & Winer, 2012). MCP-1 is a chemokine known for its role in chemotaxis, which is the process by which monocytes infiltrate adipose tissue from the bloodstream as macrophages and has demonstrated metabolic effects associated with increased T2D risk (Kanda et al., 2006; Rull et al., 2010). Given that adipose tissue is biologically active (Ahima, 2006), it is believed that obesity increases T2D risk through the cross-talk of pro-inflammatory factors, such as IL-6, TNF-α, and MCP-1 from adipose tissue with other tissues including hepatic, skeletal muscle, and pancreatic tissues (Azzu et al., 2020; Biscetti et al., 2020).

Anti-inflammatory mechanisms are in place to reduce the damage posed by pro-inflammatory markers (Dayer et al., 2006; Tilg & Wolf, 2005). Adiponectin is an anti-

inflammatory adipokine that is almost exclusively produced by adipocytes. Aside from its anti-inflammatory properties, adiponectin is known as a potent insulin sensitizer (Liu et al., 2017) at hepatocytes and myocytes and stimulates insulin secretion in β-cells (Lihn et al., 2005). Adiponectin can also activate M2 macrophages to produce the anti-inflammatory adipokine IL-10 (Wolf et al., 2004) which has similar insulin sensitizing effects at skeletal muscle (Hong et al., 2009). Adiponectin and IL-10 are significantly reduced in pediatric obesity (Dorneles et al., 2016; Rambhojan et al., 2015). In addition to adiponectin and IL-10, interleukin-1 receptor antagonist (IL-1ra) is an anti-inflammatory adipokine that neutralizes pro-inflammatory pathways by competing with IL-1R1 receptor ligands (Dayer et al., 2006). Ironically, IL-1ra is significantly increased in obesity, likely due to its production by macrophages through the NF-KB pathway, which is the same pathway that upregulates IL-6 an TNF-α (Dayer et al., 2006).

Although associations have been examined between pro- and anti-inflammatory factors and T2D risk factors, there is a lack of representation of Latino youth in these studies. Furthermore, there is a predominant focus on adiponectin with less attention to other physiologically relevant inflammatory factors such as IL-10, IL-1ra and MCP-1. Lastly, β-cell function is understudied in the association with pro- and anti-inflammatory factors in pediatric obesity. Given that Latino youth have significantly elevated chronic inflammation compared to non-Hispanic White youth (Ho et al., 2005), there is a critical need to understand the associations of obesity-related pro- and anti-inflammatory risk

factors and T2D risk factors, including insulin sensitivity, β-cell function, and glucose tolerance in this specific ethnic population.

The DPP and adapted DPPs have demonstrated increases in adiponectin and reductions in IL-6 and TNF-α among adults with prediabetes (Gokulakrishnan et al., 2017; Mather et al., 2008; Miller et al., 2014). There are no studies to our knowledge that have examined the effects of a DPP-modeled lifestyle intervention on key pro- and anti-inflammatory markers among Latino youth with prediabetes. Despite this lack of research among high-risk youth with evidence of hyperglycemia, pediatric obesity prevention interventions not specifically modeled after the DPP that target increases in physical activity and dietary changes have demonstrated favorable effects on pro- and anti-inflammatory factors, including increases in adiponectin and reductions in IL-6 or TNF-α (Balagopal, George, Patton, et al., 2005; Balagopal, George, Yarandi, et al., 2005; Blüher et al., 2014; Cambuli et al., 2008; Chae et al., 2010; Gokulakrishnan et al., 2017; Hasson et al., 2012; Huang et al., 2014; Lee et al., 2010; Lira et al., 2011; Mather et al., 2008; Miller et al., 2014; Park et al., 2007; Rambhojan et al., 2015; Roberts et al., 2013; Roth et al., 2011; Rynders et al., 2012; Siegrist et al., 2013; Vos et al., 2011). However, these studies are predominantly quasi-experimental with no control groups and focus predominantly on the measurement of adiponectin. The next most studied adipokines are IL-6 and TNF-α and little to no research on other relevant adipokines or chemokines following lifestyle intervention among high-risk youth. Two randomized control trials demonstrated no significant effects on adiponectin compared to respective control groups

(Chae et al., 2010; Park et al., 2007). In contrast, another randomized control trial demonstrated significant increases in adiponectin with reductions in IL-6 and improvements in insulin sensitivity following lifestyle intervention (Balagopal, George, Patton, et al., 2005; Balagopal, George, Yarandi, et al., 2005). This study that demonstrated improvements in adiponectin and IL-6 was conducted in a pediatric obesity clinic where exercise was partially supervised throughout the week and an intensive caloric restriction diet was implemented to achieve weight loss (Balagopal, George, Patton, et al., 2005; Balagopal, George, Yarandi, et al., 2005). Although this study provides an evidence base for improvements in pro- and anti-inflammatory markers following lifestyle intervention among high-risk youth, its pragmaticism to address T2D disparities among Latino youth is questionable (Butler, 2017; Castro et al., 2009). For this reason, there is a need to fill gaps in the literature by developing and testing pragmatic DPP-modeled lifestyle interventions that can be implemented at scale in order to address the T2D disparities that exist among this key and underrepresented minority youth population. Furthermore, it is critical to understand the mechanisms by which such interventions reduce the risk for T2D, and obesity-related pro- and anti-inflammatory markers are prime candidates for investigation.

*STUDY PURPOSE*

Therefore, the overall purpose of this dissertation is to understand the associations between pro- and anti-inflammatory markers and T2D risk factors before and after a diabetes prevention lifestyle intervention among Latino youth with prediabetes and

obesity. In order to fulfill the purpose of this dissertation, three studies were conducted, each of which leveraged a NIH-funded trial (NCT02615353). Study I used cross-sectional data to examine the associations between pro- (IL-6, TNF-α, MCP-1) and anti-inflammatory (adiponectin, IL-10, IL-1ra) markers and T2D risk factors (insulin sensitivity, β-cell function, glucose tolerance) and to examine sex differences. Study II tested the efficacy of a culturally-grounded, community-based diabetes prevention program among Latino youth with prediabetes and obesity compared to usual care. Study III examined the effects of the diabetes prevention program on pro- and anti-inflammatory markers.

# CHAPTER 2:

# LITERATURE REVIEW

## *Type 2 Diabetes (T2D) Disparities among Latino Youth*

The marked rise in pediatric obesity in the last 30 years has been paralleled by an increased prevalence of type 2 diabetes (T2D) among youth (Hales et al., 2018; Ogden et al., 2016). Latino youth are disproportionately impacted by prediabetes (Andes et al., 2020) and T2D (Lawrence et al., 2021). The Centers for Disease Control and Prevention (CDC) estimated that Latino youth have a 50% lifetime risk of developing T2D (Narayan et al., 2003), which when developed in youth is associated with the premature risk of microvascular and macrovascular complications that increase mortality risk (Bjornstad et al., 2021). Given that Latinos are among the largest ethnic minority population in the United States (U.S.) (Jensen, 2021), there is a pressing need to develop and test effective diabetes prevention interventions that provide real-world frameworks to address the T2D disparities that burden Latino youth (Cruz & Granados, 2019).

Social determinants of health (SDoH) are the root cause of T2D disparities (Clark & Utz, 2014; Hill-Briggs et al., 2020). SDoH, such as low access to care, low socioeconomic status, and low education level have been associated with T2D among Latino youth and adults (Butler, 2017; Cartwright, 2021). In order to address the T2D disparities that burden Latino youth, it is important to consider the socioecological context that is operational on health behaviors among this specific ethnic group. The

expanded ecodevelopmental model is a framework that considers multiple levels of influence on an individual's health behaviors and health outcomes for T2D prevention among Latino youth (Castro et al., 2009). These levels include culture (e.g., familism, collectivism), community (e.g., community grocery stores and exercise facilities, community health norms), and family and peers (e.g., family exercise habits, food preferences, acculturation). Tailoring T2D prevention interventions that address the sociocultural contexts of Latino youth is key to developing effective interventions that may be translated at scale in order to address disparities at the population level among this specific ethnic youth group.

*Pathophysiologic Risk Factors of T2D*

The natural history of type 2 diabetes (T2D) among youth is less established but, like adults, is preceded by insulin resistance, or decreased insulin sensitivity, which results in β-cell compensation in the form of hyperinsulinemia per the degree of insulin sensitivity (Hannon & Arslanian, 2015). Pediatric obesity is a key risk factor for developing T2D and is associated with decreased insulin sensitivity and β-cell dysfunction (Gepstein & Weiss, 2019; Giannini et al., 2012; Lee et al., 2006). Nationally-representative data show that Latino youth are disproportionately impacted by obesity and insulin resistance compared to White youth (Lee et al., 2006; Ogden et al., 2018). Additionally, normal pubertal growth changes are accompanied by a temporary period of reduced insulin sensitivity which rebounds after puberty (Kelsey & Zeitler, 2016).

Therefore, being Latino and having prediabetes and obesity during adolescence poses an increased risk for developing T2D, thus warranting investigation of the mechanisms that contribute to reducing T2D risk following diabetes prevention interventions.

*Obesity-induced Changes in the Pro- and Anti-inflammatory Milieus*

Pediatric obesity is characterized by chronic inflammation (Chang et al., 2015). Obesity causes the infiltration of immune cells including macrophages, neutrophils, T-cells, and B-cells (Lee & Lee, 2014). Macrophages are the most extensively studied immune cells in the context of obesity and have generally been characterized as two main sub-types: M2 macrophages and M1 macrophages (Shapouri-Moghaddam et al., 2018; Winer & Winer, 2012). M2 macrophages are associated with an anti-inflammatory response, whereas M1 macrophages are associated with a pro-inflammatory response. In lean adipose tissue, concentrations of M2 and M1 macrophages within adipose tissue are proportionately distributed (Lumeng et al., 2007; Shapiro et al., 2011). However, during obesity, a polarization shift occurs from M2 to M1 macrophage activation, thereby causing a disproportionate increase in M1 macrophages in relation to M2 macrophages (Shapiro et al., 2011).

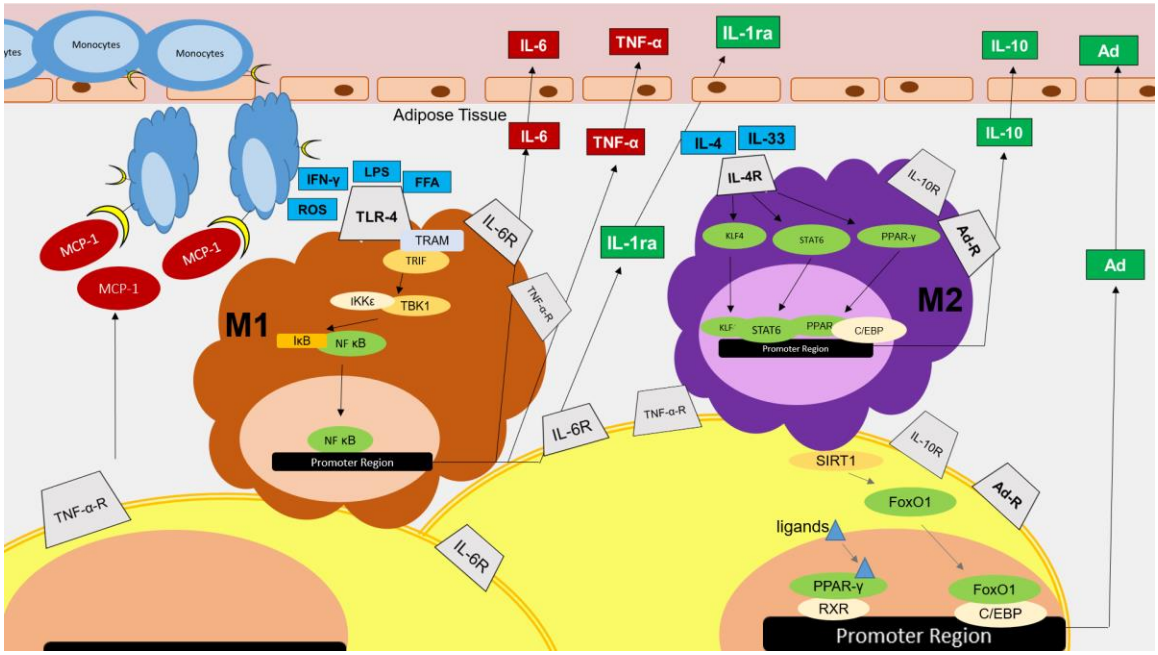
During the earliest phases of the expansion of adipocytes in obesity, adipose tissue becomes hypoxic which is caused by free-fatty acid (FFA) induced uncoupling of mitochondria oxidative metabolism (Lee et al., 2014) and reduced oxygen perfusion per

metabolic demands (Hosogai et al., 2007). Hypoxia increases the expression of hypoxia inducible factor-1-alpha which stimulates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB) pathway of M1 macrophages in adipose tissue. This NF-KB pathway is responsible for producing a robust pro-inflammatory response of chemokines and cytokines (Lawrence, 2009), as illustrated in Figure 1. In obesity, lipotoxic signals such as the endotoxin lipopolysaccharide (LPS) (Boutagy et al., 2016), reactive oxygen species (ROS, inducers of oxidative stress and signaling molecules) (McMurray et al., 2016), FFA (Reyna et al., 2008), and interferon-γ (IFN-γ) (Sindhu et al., 2019) are elevated. Each of these lipotoxic and inflammatory signals activate the toll-like receptor (TLR)-4 receptors on M1 macrophages in adipose tissue, leading to the production of pro-inflammatory factors through the NF-KB pathway (Aggarwal, 2000; Kim & Sears, 2010). Included in this pro-inflammatory response are cytokines, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) and chemokines, such as monocyte chemoattractant protein-1 (MCP-1), which bind to receptors on macrophages leading to their infiltration of adipose tissue in a process called chemotaxis (Morinaga et al., 2015). It should be briefly noted that IL-6 exhibits anti-inflammatory properties via non-NF-KB pathways in skeletal muscle during acute exercise.(Karstoft & Pedersen, 2016; Pedersen, 2017) However, IL-6 is upregulated by M1 macrophages and is chronically elevated during obesity;(Ottobelli Chielle et al., 2016) thus, IL-6 will be discussed as a pro-inflammatory marker moving forward whereby reductions in fasting levels of IL-6 are considered a healthy response to intervention.

The processes by which adipose tissue produces anti-inflammatory adipokines is also presented in Figure 1. Anti-inflammatory factors neutralize pro-inflammatory factors and their associated tissue damage / dysfunction (Akdis & Blaser, 2001; Lihn et al., 2005). Adiponectin is the richest adipokine in human plasma, is almost exclusively produced by adipocytes, and exerts anti-inflammatory effects (Choi et al., 2020). One study demonstrated that treating myocytes with adiponectin of wild-type mice led to reductions in LPS-induced expression of TNF-α (Jortay et al., 2010). Furthermore, a mouse adiponectin gene knockout model exhibited significantly elevated gene expression of M1 macrophage markers, including elevated IL-6, TNF-α, and MCP-1 following LPS stimulation, thereby supporting its role as an anti-inflammatory marker and potential therapeutic (Singer & Lumeng, 2017). Furthermore, treating human and mouse macrophages with adiponectin led to the upregulation of M2 macrophage markers, including the anti-inflammatory marker, interleukin-10 (IL-10) (Ohashi et al., 2010). IL-10 is produced by M2 macrophages and has demonstrated its anti-inflammatory properties through the downregulation of IL-6 and TNF-α in stimulated monocytes (Rossato et al., 2012; Smallie et al., 2010). In obese adipocytes, endoplasmic reticulum stress is known to impair post-translational modifications to adiponectin, thereby negatively influencing its secretion from adipocytes and potentially explaining, at least in part, its reduction in pediatric obesity (Liu & Liu, 2014; Orlando et al., 2019; Wang et al., 2008). As for IL-10, its concentrations are significantly reduced in obesity, possibly due to the polarization shift from M2 to M1 macrophages (Dorneles et al., 2016). Interleukin-

1 receptor antagonist (IL-1ra) is another anti-inflammatory marker that is produced by adipocytes, among other immune cells (Dayer et al., 2006; Westwell-Roper et al., 2015; Wolf et al., 2004). Interestingly, unlike adiponectin and IL-10, IL-1ra is positively associated with obesity (Seppä et al., 2018; Stoppa-Vaucher et al., 2012), likely due to its upregulation through the NF-KB pathway in macrophages (Darragh et al., 2010). IL-1ra exerts its anti-inflammatory effects by competing with IL-1β, a pro-inflammatory marker, for the IL-1R1 receptor (Böni-Schnetzler et al., 2018). Thus, it is possible that IL-1ra is increased as a compensatory mechanism to combat the damaging effects from the chronic inflammation posed by obesity. Like IL-6, IL-1ra release from skeletal muscle is increased during acute exercise (Dorneles et al., 2016; Karstoft & Pedersen, 2016), but reductions in IL-1ra concentrations following intervention are considered a healthy response in the context of obesity. These alterations in adipokines due to obesity have been established predominantly in adipocytes of white adipose tissue (WAT) and visceral adipose tissue (VAT); however, a growing field of research suggests that the inflammatory process may be similar in adipose depots within skeletal muscle (intermyocellular and perimuscular adipose tissue) (Khan et al., 2015) and the liver (Brenner et al., 2013).

**Figure 1**. Pro-inflammatory and anti-inflammatory processes in adipose tissue.



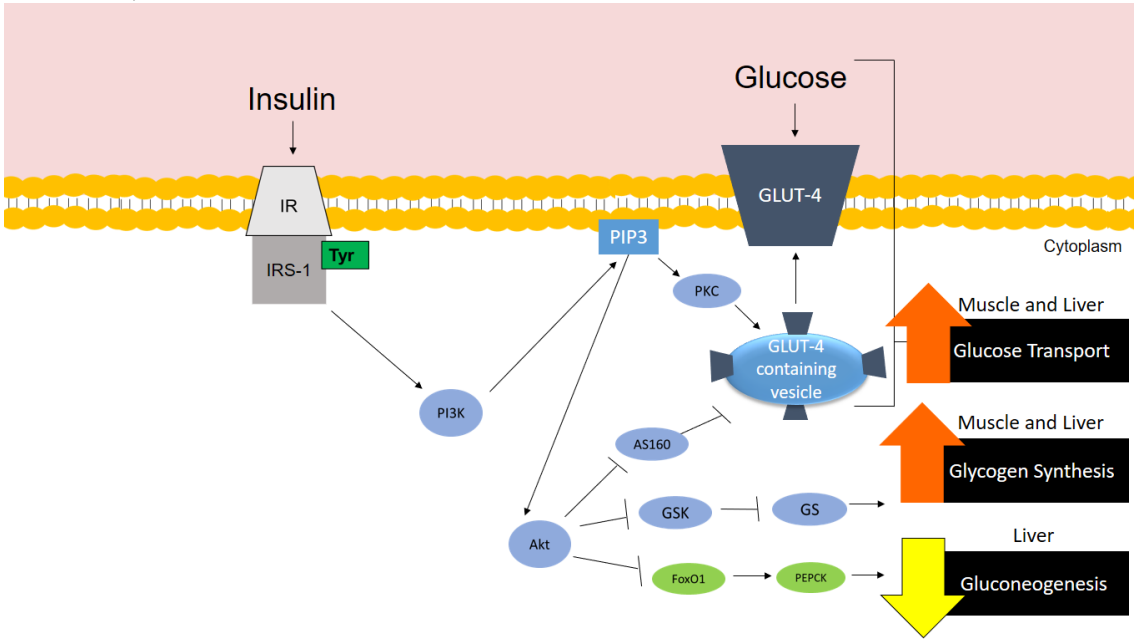

MCP-1: monocyte chemoattractant protein-1, ROS: reactive oxygen species, IFN-γ: interferon- γ, LPS: liposacharride, FFA: free fatty acids, TLR-4: toll-like receptor-4, TRAM, TRIF, TBK1, IKKE, AP-1: activator protein-1, IKB: NF-KB inhibitor, JNK: c-jun N-terminal kinase, TNF-α-R: TNF-α receptor, Ad-R: adiponectin receptor, IL-4R: interleukin-4 receptor, KLF4: Kruppel-like factor 4, STAT6: signal transducer and activator of transcription 6, SIRT1: sirtuin 1, FoxO1: Forkhead box protein O1, RXR: retinoid x receptor, C/EBP: Ccaat-enhancer binding proteins, IL-1ra: interleukin-1 receptor antagonist

*Obesity-induced Inflammation and T2D Risk Factors*

One of the earliest studies to support a mechanistic link between inflammation and insulin resistance was a time course study in mice where short-term declines in insulin sensitivity following a high-fat diet were explained by increases in FFA, whereas longer-term exposure to high-fat diet (3-7 days) was further explained by increases in TNF-α (Lee et al., 2011). Under normal physiological conditions, the insulin signaling pathway is activated by insulin and facilitates glucose transport (skeletal muscle and liver) (Leto & Saltiel, 2012), glycogen synthesis (skeletal muscle and liver) (Lin et al.,

2001) and reduces gluconeogenesis in the liver (Hatting et al., 2018). Insulin signaling is initiated by the phosphorylation of tyrosine residues on the insulin receptor substrate (IRS)-1 upon binding of insulin to its receptor. This activates protein kinase B (i.e., Akt) which leads to a series of molecular events that facilitates the aforementioned glucoregulatory functions in skeletal muscle and the liver as shown in Figure 2 (Lee & Pilch, 1994).

**Figure 2**. Insulin signaling pathway. Insulin signaling pathway figure adapted from Di Meo et al., 2017

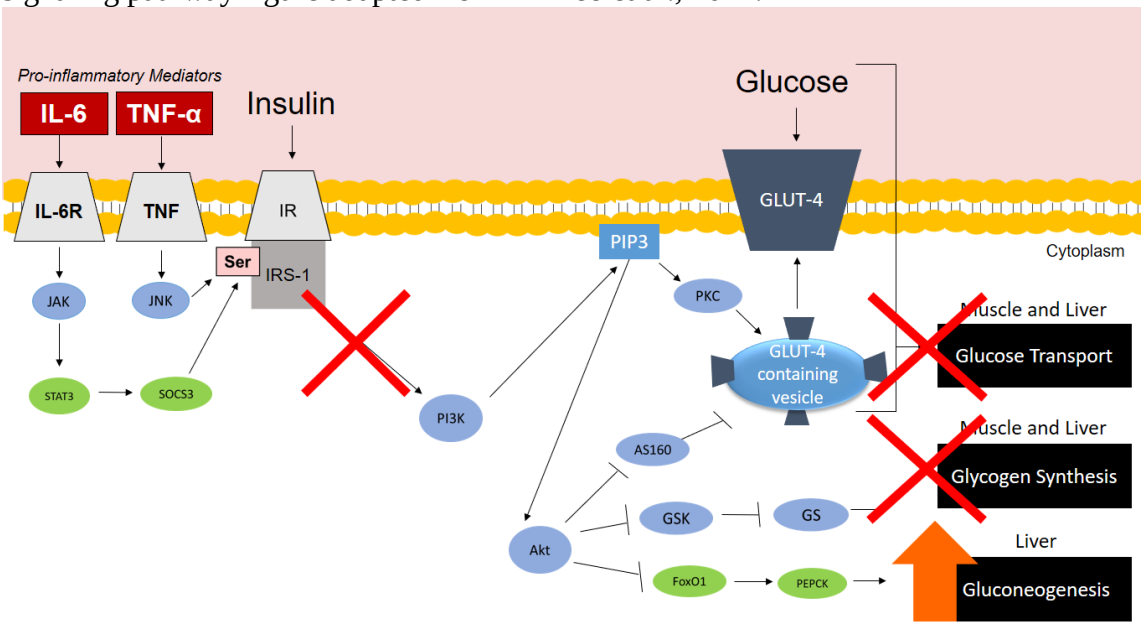



IRS-1: insulin receptor substrate-1, IR: insulin receptor, IL-10R: IL-10 receptor, APPL: adaptor proteins, Tyr: tyrosine, PI3K: phosphoinositide 3-kinase, phosphatidylinositol (3,4,5)-trisphosphate, Akt: protein kinase B, PKC: protein kinase C, AS160: Akt substrate of 160, GSK: glycogen synthase kinase, GS: glycogen synthase, PEPCK: phosphoenolpyruvate carboxykinase, GLUT-4: glucose transporter type 4

Interestingly, animal models have demonstrated that pro-inflammatory markers, IL-6 and TNF-α, inhibit the insulin signaling pathway through the phosphorylation of serine

residues, as opposed to tyrosine, on IRS-1 in adipocytes (Rui et al., 2001), hepatocytes (Senn et al., 2003), and myocytes (Hotamisligil et al., 1996) as depicted in Figure 3.

**Figure 3**. Insulin Signaling Pathway: Impact of Pro-inflammatory Markers. Insulin signaling pathway figure adapted from Di Meo et al., 2017.




JAK: Janus kinase, STAT3: signal transducers and activator of transcription factor 3, SOCS3: suppressor of cytokine signaling 3, Ser: serine residues, IRS-1: insulin receptor substrate-1, IR: insulin receptor, IL-10R: IL-10 receptor, APPL: adaptor proteins, Tyr: tyrosine, PI3K: phosphoinositide 3-kinase, phosphatidylinositol (3,4,5)-trisphosphate, Akt: protein kinase B, PKC: protein kinase C, AS160: Akt substrate of 160, GSK: glycogen synthase kinase, GS: glycogen synthase, PEPCK: phosphoenolpyruvate carboxykinase, GLUT-4: glucose transporter type 4

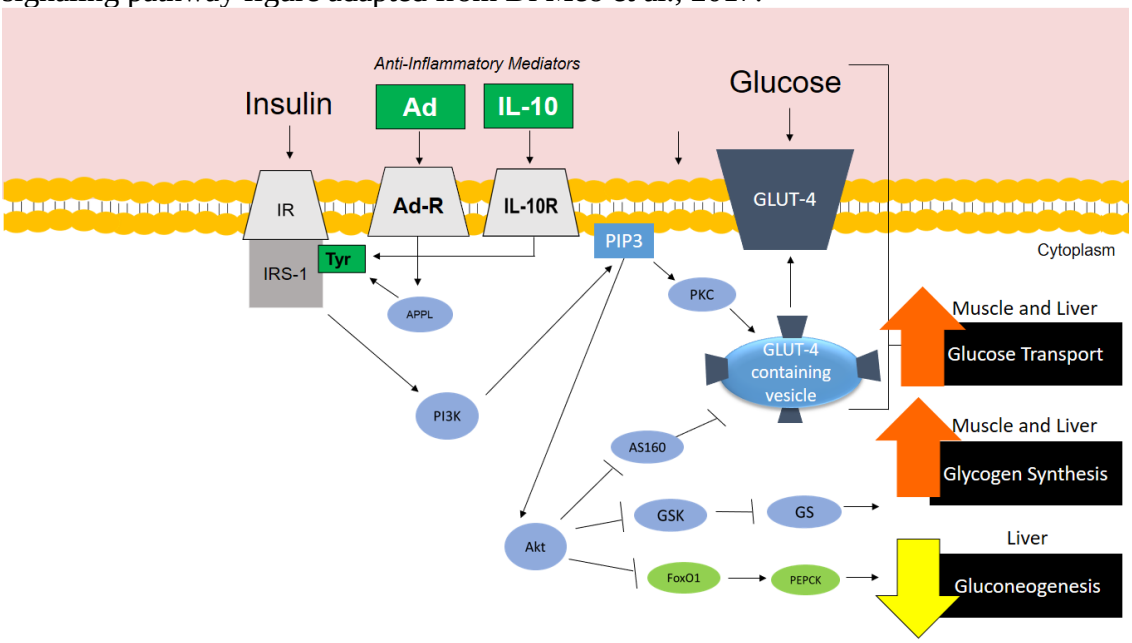
IL-1ra may be increased in pediatric obesity, and not decreased like adiponectin and IL-10, due to shared upstream pathways (i.e., NF-KB) that are also responsible for the production of pro-inflammatory markers (i.e., IL-6, TNF-α) (Darragh et al., 2010). It is plausible that IL-1ra serves as an anti-inflammatory compensatory response to attenuate

damage induced by pro-inflammation, and this notion has been supported by previous studies that have demonstrated the increased release of IL-1ra by fibroblasts, B-cell lymphoma cells, macrophage-like cancer cells, and prostate cancer cells in response to apoptosis (Chwee et al., 2016).

Furthermore, anti-inflammatory markers adiponectin and IL-10 have exhibited insulin sensitizing and β-cell protective properties. Adiponectin is typically measured as total adiponectin, but may be separated into high-, medium-, and low-molecular weight components, (Wang et al., 2008) This notion is important since high-molecular weight adiponectin (HMW Adpn) is considered the most biologically active for increasing insulin sensitivity (Liu & Liu, 2014). Adiponectin receptors, adiponectin-R1 and adiponectin-R2, are predominantly found in skeletal muscle and the liver, respectively (Wang et al., 2008) Upon activation of these receptors at hepatocytes and myocytes, APPL is an adaptor protein that is activated and stimulates AMPK-related pathways, but may also phosphorylate tyrosine residues, similar to insulin, on IRS-1 (Figure 4) (Lihn et al., 2005; Liu et al., 2017). Although IL-10 has been examined as an immunosuppressant, it has also recently gained attention as an insulin sensitizer (Dagdeviren et al., 2017; Dagdeviren et al., 2016; Hong et al., 2009). Transgenic mice with muscle-specific IL-10 overexpression that were fed a high-fat diet, compared to wild type mice on the same diet, led to increased insulin sensitivity (hyperinsulinemic euglycemic clamp), increased tyrosine phosphorylation of IRS-1 (Figure 4) and a reduced pro-inflammatory response (Hong et al., 2009). However, the molecular mechanisms by which IL-10 activates the

insulin signaling pathway are not as well understood as adiponectin and have yet to be elucidated.

**Figure 4**. Insulin Signaling Pathway: Impact of Anti-inflammatory Markers. Insulin signaling pathway figure adapted from Di Meo et al., 2017.




IRS-1: insulin receptor substrate-1, IR: insulin receptor, IL-10R: IL-10 receptor, APPL: adaptor proteins, Tyr: tyrosine, PI3K: phosphoinositide 3-kinase, phosphatidylinositol (3,4,5)-trisphosphate, Akt: protein kinase B, PKC: protein kinase C, AS160: Akt substrate of 160, GSK: glycogen synthase kinase, GS: glycogen synthase, PEPCK: phosphoenolpyruvate carboxykinase, GLUT-4: glucose transporter type 4

β-cell failure is the hallmark pathophysiological process that leads to clinical manifestations of T2D (i.e., increased blood glucose levels) and is partially caused by β-cell apoptosis (Weaver et al., 2012; Wijesekara et al., 2010). Pro-inflammatory cytokines, including TNF-α, have been shown to induce apoptosis of pancreatic β-cells, reduce glucose-stimulated insulin secretion, increase the genetic expression of MCP-1, and

pathophysiologic increases in oxidative stress in human pancreatic β-cells (Weaver et al., 2012). Additionally, adiponectin has demonstrated a more direct and protective role on β-cells through their proliferation (i.e., cell number) (Chetboun et al., 2012) and stimulation of gene expression and insulin secretion (Wijesekara et al., 2010). The literature on both pro- and anti-inflammatory adipokines and chemokines and β-cell function is scarce but preliminarily work supports this link. Whether favorable changes in relevant adipokines following interventions are associated with reductions in β-cell function has yet to be established.

Indeed, the aforementioned mechanistic studies have been translated to pediatric studies which have demonstrated significantly increased circulating levels of IL-6 (Huang et al., 2014; Kapiotis et al., 2006; Luciardi et al., 2018; Ottobelli Chielle et al., 2016; Paltoglou et al., 2017; Rainone et al., 2016), TNF-α (Agarwal et al., 2013; Moon et al., 2004), MCP-1 (Breslin et al., 2012; Luciardi et al., 2018), and IL-1ra (Seppä et al., 2018; Stoppa-Vaucher et al., 2012) with decreased levels of adiponectin (Coimbra et al., 2017; Lira et al., 2011; Park et al., 2007; Rambhojan et al., 2015) and IL-10 (Chang et al., 2013; Chang et al., 2014) among youth with obesity compared to their normal weight counterparts, as seen in adults (Ellulu et al., 2016; Hyun et al., 2008). Aside from their inflammatory roles, IL-6, TNF-α, MCP-1, and IL-1ra have been associated with an increased risk for T2D, while adiponectin and IL-10 have been associated a reduced risk of T2D. Due to the biologically active role that adipose tissue plays on inflammatory marker secretion (Ahima, 2006), it stands to reason that an obesogenic environment

increases the risk of T2D through increases in pro-inflammatory markers that pose a risk of damage or dysfunction at T2D-related tissues (i.e., adipose, hepatic, skeletal muscle, pancreatic).

*T2D Prevention among High-risk Populations*

Lifestyle intervention is the cornerstone approach for preventing T2D among adults with prediabetes as demonstrated by the hallmark United States (U.S.) Diabetes Prevention Program (DPP). The DPP demonstrated a 58% reduction in T2D incidence following a lifestyle intervention that targeted physical activity (180 min/wk moderate to vigorous exercise intensity) and individualized dietary education and support among adults with prediabetes compared to a placebo group (Knowler et al., 2002). A later study using DPP data attributed the reductions in T2D risk following lifestyle intervention partially to improvements in insulin sensitivity and β-cell function (Kitabchi et al., 2005). Since the publication of findings from the DPP, other studies have adapted its model and supported its efficacy among adults with prediabetes in clinical and community settings (Aziz et al., 2015). These optimistic findings from DPP models supported the National DPP (Albright, 2012), a program that was instated by the CDC in order to take diabetes prevention efforts to scale among high-risk adult populations and is covered by Medicare (Burd et al., 2020) in all states. Despite these efforts, only ~1% of adults with prediabetes in the U.S. have been reached by DPP programs (Ackermann & O'Brien, 2020). An

alarming issue that needs to be addressed is that similar large-scale programs are nonexistent for high-risk youth populations, likely due to the lack of an evidence base of effective, translatable frameworks. No studies, to our knowledge, have prioritized Latino youth with prediabetes to assess the efficacy of a diabetes prevention program on T2D risk factors (McCurley et al., 2017).

*Effects of Exercise Interventions on T2D Risk Factors and Inflammatory Markers*

Most physical activity interventions among high-risk youth have been tested in the form of physical exercise, which will be the focus of this review. Aerobic exercise interventions among youth with overweight or obesity have been the predominant focus of studies as compared to resistance training or other types of exercise (Stoner et al., 2019; Stoner et al., 2016). Aerobic exercise among youth with overweight or obesity has demonstrated increases in insulin sensitivity, and these effects are accentuated with longer program duration (≥12 weeks), higher frequency (≥3 days per week), higher session duration (≥60 minutes), and among adolescents (13-18 yr) compared to children (6-12 yr), regardless of the type of exercise (García-Hermoso et al., 2014). Resistance training has also demonstrated efficacy for increasing insulin sensitivity among Latino boys with overweight (Shaibi et al., 2006). A randomized control trial that compared aerobic exercise with resistance training demonstrated that both groups significantly reduced visceral adipose tissue, with only significant increases in insulin sensitivity following resistance training (Lee et al., 2012). In a follow-up study from the same lab,

adolescents with overweight and obesity demonstrated significant improvements in 2-hr glucose concentrations from OGTT following aerobic exercise, resistance training, and the combination of both (i.e., concurrent training) (Lee et al., 2019). However, only concurrent training and aerobic exercise only groups significantly increased insulin sensitivity levels (Lee et al., 2019).

As it relates to concurrent training, a meta-analysis supports the added benefit over aerobic exercise alone through greater reductions in total adiposity and visceral adipose tissue and increases in adiponectin (García-Hermoso et al., 2018). Whether concurrent training is superior for increasing insulin sensitivity among high-risk youth remains inconclusive, largely due to the heterogeneity in exercise protocols and measurements of insulin sensitivity across studies (Kim & Jeon, 2020). Both types of exercise, resistance training and aerobic exercise entail repetitive contractions of large skeletal muscles, tissue that is responsible for ~80% of insulin-mediated glucose uptake post-challenge (Ferrannini et al., 1988). These studies support the improvement of insulin sensitivity to aerobic and resistance training further supporting its promotion as a diabetes prevention behavioral target.

Exercise stimulates glucose uptake through skeletal muscle contractions via a non-insulin dependent pathway (i.e., AMP-activated protein kinase pathway) (Richter & Hargreaves, 2013), which may play a role in β-cell preservation through reductions in circulating glucose. However, less work has assessed the effects of exercise on β-cell function among youth (Kim & Jeon, 2020). Of these studies, aerobic exercise has

demonstrated significant improvements in estimates of β-cell function as supported by reductions in insulin area under the curve and increases in the insulinogenic index (insulin secretion estimate) and oral disposition index (oDI, β-cell function estimate) (C. L. Davis et al., 2012; Nassis et al., 2005; Shih & Kwok, 2018). Important to note was a dosage effect of longer duration aerobic exercise (40 minutes) on the oDI compared to control, which was not observed among the lower dosage group (20 minutes) of the same exercise (C. L. Davis et al., 2012). Resistance training, on the other hand, has yet to support the efficacy on β-cell function among high-risk youth (Davis, Kelly, et al., 2009; Davis, Tung, et al., 2009; Lee et al., 2012; Shaibi et al., 2006). However, it is important to mention that when β-cell function has been measured by the fasting intravenous glucose tolerance test in response to exercise, there were no significant effects, regardless of the type of exercise (aerobic vs resistance training vs concurrent training) (Davis, Kelly, et al., 2009; Davis, Tung, et al., 2009; Rosenbaum et al., 2007; Shaibi et al., 2006). Whether exercise improves β-cell function among high-risk youth warrants future investigation.

T2D is a chronic inflammatory disease whereby exercise may have therapeutic effects (Pedersen, 2017). Acute exercise has been associated with an increase in upstream anti-inflammatory markers. Among young and elderly adults, acute resistance training increased interleukin-4 and interleukin-33, activators of M2 macrophages (Della Gatta et al., 2014). Furthermore, acute exercise studies have demonstrated a robust IL-6 response to exercise from myocytes which upregulates IL-10 and IL-1ra (Dorneles et al., 2016;

Petersen & Pedersen, 2005). Thus, acute exercise may enhance anti-inflammatory capacity through repetitive bouts of exercise, such as in a training program, and reduce the risk of T2D by enhancing the defense against pro-inflammatory markers.

In obese mice, eight weeks of moderate to vigorous swimming reduced NF-KB activation in adipocytes and hepatocytes through improved endoplasmic reticulum stress, which was associated with increases in insulin sensitivity (da Luz et al., 2011). Other studies have demonstrated significant reductions in MCP-1 after continuous moderate intensity exercise (Annibalini et al., 2017) and MCP-1 receptors on monocytes and neutrophils after high-intensity interval training, which entails shorter acute bouts of high-intensity exercise (Barry et al., 2017). These findings suggest that exercise may reduce key upstream activators of the NF-KB pathway in M1 macrophages and, as a result, the downregulation of pro-inflammatory adipokines and chemokines.

Adiponectin, IL-6 and TNF-α are the most studied adipokines in response to exercise interventions among high-risk youth with predominant focus on adiponectin. Two meta-analyses have demonstrated favorable exercise effects on adiponectin. One of these studies showed that longer duration interventions (>12 weeks) were associated with increases in adiponectin among youth and adults with overweight or obesity (Yu et al., 2017). However, these effects were not sustained when two studies with high heterogeneity were omitted from the meta-analysis, and thus results should be interpreted carefully (Yu et al., 2017). A second meta-analysis among youth with overweight/obesity demonstrated significant increases in adiponectin from concurrent training (combination

of aerobic and resistance exercise) compared to aerobic exercise (mean difference=2.59 ug/mL) with greater effects among longer duration programs (García-Hermoso et al., 2018). This finding supports the use of various types of physical activities that include both aerobic and muscle strengthening components which align with the national guidelines for physical activity among youth (Piercy et al., 2018), and potentially the need for longer duration exercise sessions in order to increase adiponectin levels. These findings are supported by a separate meta-analysis among children and adolescents with overweight/obesity that demonstrated modest exercise-induced increases in adiponectin (mean difference=0.69 ug/mL), reductions in IL-6 (mean difference=-0.86 pg/mL) and inconsistent findings for TNF-α (Sirico et al., 2018). However, only two studies were included in analysis of IL-6 and TNF-α each (Sirico et al., 2018). Lastly, a meta-analysis that included nine physical activity intervention randomized control trials (five on IL-6 and four on TNF-α) showed no effects on TNF-α and a trending decrease in IL-6 (Han et al., 2019). Given the limited number of studies that were examined in these meta-analyses, it was difficult to differentiate whether certain types or dosages of exercise produced more pronounced results than others on these inflammatory markers. To this end, a randomized control trial among elderly and inactive adults with overweight exhibited a dose response of adiponectin to resistance training exercise (45% vs 60-65% vs 85% peak strength) where higher intensity interventions led to greater increases in adiponectin (Fatouros et al., 2005). The current evidence base suggests that longer duration interventions that include concurrent or resistance training may increase

adiponectin, whereas the data are inconsistent among other adipokines or chemokines due to the limited number of studies that have been conducted. Nonetheless, studies through animal models and clinical interventions underscore exercise as an effective strategy to reduce pro-inflammatory factors, potentially through increases in anti-inflammatory markers, that may lead to reduced risk for T2D.

*Effects of Dietary Interventions on T2D Risk Factors and Inflammatory Markers*

This next section will describe the effects of commonly tested dietary interventions and health promotion strategies (e.g., increased fiber, fruit, and vegetable intake) on T2D risk factors and pro- and anti-inflammatory factors.

Low glycemic index (GI)/glycemic load (GL) diets target the consumption of foods that minimize spikes in blood glucose and insulin and thus may be optimal for reducing T2D risk. One meta-analysis of low GI/GL diets, compared to high GI/GL diets, demonstrated reductions in fasting insulin concentrations as well as systemic inflammatory marker C-reactive protein (CRP) among adults with obesity (Schwingshackl & Hoffmann, 2013). Although there is no mechanistic link between insulin and CRP, insulin has been shown to upregulate chemokine MCP-1 (Westerbacka et al., 2008). Thus, it is possible that low GI/GL foods that reduce insulin levels may lead to less production of chemokines that facilitate macrophage infiltration. On the contrary, a systematic review and meta-analysis of 28 randomized control trials that compared low GI/GL compared to high GI/GL diets among adults exhibited no significant effects on IL-

6, TNF-α or adiponectin (Milajerdi et al., 2018). However, this analysis prioritized an adult population across a broad health spectrum (healthy to high-risk), and only five studies were included in the meta-analysis for each of IL-6 and TNF-α biomarkers. In a similarly motivated systematic review and meta-analysis on low GI/GL versus high GI/GL diets among adults with T2D and gestational diabetes, low GI/GL diets were associated with significant reductions in IL-6 and trending increases in adiponectin (Ojo et al., 2019). A limitation of this meta-analysis was that only two studies for each inflammatory adipokine (IL-6 and adiponectin) were included. The three aforementioned systematic reviews and meta-analyses on low GI/GL eating patterns, compared to high GI/GL ones, suggest that the former diet may be efficacious among individuals on the higher end of the T2D spectrum.

Few studies have tested low GI/GL interventions on insulin sensitivity among high-risk youth populations and have exhibited conflicting results (Ebbeling et al., 2003; Visuthranukul et al., 2015). One study demonstrated no differences in changes in insulin sensitivity or components of metabolic syndrome among a low GI/GL diet group compared to a low-fat diet group among Hispanic youth with obesity (Mirza et al., 2013), which is contrary to what has been found among adults. Liver fat is an ectopic adipose tissue depot that is linked to reduced insulin sensitivity, and a compelling study among youth with obesity and non-alcoholic fatty liver disease (NAFLD) demonstrated significant reductions in hepatic steatosis with trending improvements in insulin sensitivity ($p=0.07$) following an eight-week dietary intervention that focused on

reducing free sugar intake to less than 3% of daily calories compared to usual care (Schwimmer et al., 2019). This reduced free sugar intervention consisted of individualized meal planning as well as provisions of study meals for the entire household along with weekly phone calls to ensure diet adherence. Therefore, the intervention's scalability is questionable. Nonetheless, this study provides evidence to support a feasible health promotion focus point of reducing free added sugars from daily dietary intake, and whether this strategy improves proximal T2D risk factors warrants further investiagation.

Unsaturated fat, fruits, and vegetables are promoted for good health and have exhibited anti-inflammatory properties (2020 Dietary Guidelines Advisory Committee, 2020; Hosseini et al., 2018; Lenighan et al., 2019; Neumann & Egert, 2022). In high-fat diet induced obese mice, omega-3 polyunsaturated fatty acid (PUFA) supplementation led to reduced LPS-induced activation of TLR-4 receptors, one of the main triggers of the NF-KB pathway in macrophages (Martínez-Fernández et al., 2015). Additionally, PUFAs have been shown to activate PPAR-alpha and PPAR-γ which may reduce NF-KB activity (Martínez-Fernández et al., 2015). Interestingly, phytochemicals found in fruits, vegetables, and spices are known to induce shifts in macrophage activation from M1 to M2 phenotypes (Saqib et al., 2018) among possessing other anti-inflammatory effects (Hosseini et al., 2018). A systematic review and meta-analysis among adults of all ages (range 12-85 y inclusion) and health statuses (e.g., healthy, obese, HIV-infected) showed that consumption of fruits and vegetables, or their extracted phytochemicals (e.g.,

resveratrol from grapes, sulforaphane from broccoli) were associated with reductions in TNF-α (16 studies reviewed in meta-analysis), but inconsistent results were found for IL-6 (22 studies reviewed in meta-analysis) (Hosseini et al., 2018). However, the broad inclusion criteria of any age and health status, including athletes, limits the generalizability to high-risk populations. Aside from phytochemical effects, another benefit of increasing fruits and vegetable intake is the accompanying fiber component which has well-known cardiometabolic benefits (Grooms et al., 2013), including increased insulin sensitivity (Weickert & Pfeiffer, 2018) and glucose regulation (Garcia et al., 2007). To this end, the Insulin Resistance in Atherosclerosis Study demonstrated a positive association between fiber intake and insulin sensitivity and β-cell function among a multi-ethnic cohort with a mixture of healthy adults and adults with prediabetes (Liese et al., 2005). Further, in a meta-analysis of 16 studies on fiber intake interventions, a median of 10 grams per day of fiber (whether soluble fiber or through natural foods) was associated with reduced fasting insulin and glucose levels among adults with T2D (Mao, 2021). Taken together, these findings suggest that a well-balanced diet that includes fruits, vegetables, other foods with phytochemicals, and fiber intake may synergistically improve the pro- and anti-inflammatory milieus to reduce the risk of T2D.

The Mediterranean diet is a comprehensive dietary approach that targets the consumption of plant foods (i.e., fruits, vegetables, legumes), olive oil as a primary source of dietary fats, and low consumption of meats and dairy products (Willett, 2006). Studies have demonstrated efficacy of the Mediterranean diet on insulin sensitivity

among adults with NAFLD (Misciagna et al., 2017; Ryan et al., 2013). Although fewer studies have assessed β-cell function in response to dietary interventions, a meta-analysis that included three studies on low-fat, plant-based dietary interventions demonstrated significant improvements in β-cell function as measured by insulin secretion or C-peptide (Kahleova et al., 2011; Kahleova et al., 2018; Kahleova et al., 2019). Reducing consumption of glucose and lipids and eating plant-based foods that are low glycemic and fibrous may enhance glucose regulation by improving insulin sensitivity and β-cell function through favorable alterations in the pro- and anti-inflammatory milieus that are altered in obesity.

Studies of low-calorie diets among adults with overweight or obesity and NAFLD failed to exhibit significant effects on insulin sensitivity (Ghadimi et al., 2021). One meta-analysis found no significant effects of low calorie dietary interventions on insulin sensitivity, but sub-analyses demonstrated greater effect sizes among adults with obesity, compared to overweight, and in response to Mediterranean diets, compared to standard diets (Ghadimi et al., 2021). These results suggest that low-calorie diets may be more efficacious for increasing insulin sensitivity among individuals with more weight or adiposity to lose (obese compared to overweight) and through healthy balanced dietary patterns such as the Mediterranean diet.

One interesting study in 22 postmenopausal women with obesity tested a 6- to 7-month multiphasic (very low calorie, low calorie, weight maintenance) dietary weight loss intervention. In that study, two clusters of genes were identified: the first cluster

represented by adipocyte genes and metabolic pathways and the second cluster by macrophage genes and inflammatory pathways (Capel et al., 2009). During the dietary intervention including the weight maintenance phase, pro-inflammatory genes were downregulated and adipocyte genes upregulated. Further analyses indicated that the most robust responders of macrophage genes to the dietary intervention showed significant associations with decreases in insulin sensitivity (Capel et al., 2009). As for IL-10, the adipokine has only recently been identified as an insulin sensitizer (Dagdeviren et al., 2017; Dagdeviren et al., 2016; Hong et al., 2009), and thus dietary intervention effects on IL-10 are lacking. However, a randomized control trial published in 2020 found a significant increase in IL-10 concentrations (with reductions in NF-KB activation) following a Korean diet with a low dietary inflammatory index that targeted high amounts of vegetables, high vegetable protein and fat, low fat (animal fat), and a low glycemic index, compared to a Westernized isocaloric diet (Shin et al., 2020). Only 10 total participants were included (n=5 per group) in the study, which should be considered during interpretations.

*Exercise and Nutrition in Combination*

It has been shown that dietary interventions in combination with exercise is superior to diet alone on health outcomes (Elliot & Hamlin, 2018; Joseph et al., 2020; Stoner et al., 2016). These studies support the American Diabetes Association guidelines that recommend implementing intensive lifestyle intervention to prevent or delay the

onset of T2D among youth and adult populations with prediabetes (Draznin et al., 2022). Many lifestyle interventions that target increases in physical activity and healthy nutritional changes among high-risk youth have been tested in clinical settings; however, there are no studies that have tested an adapted DPP among Latino youth with prediabetes.

*Lifestyle Intervention Effects on Inflammatory Markers in Adults with Prediabetes*

The DPP demonstrated significant increases in adiponectin following lifestyle intervention among adults with prediabetes (Mather et al., 2008), which was accompanied by increases in insulin sensitivity and improvements in β-cell function (Kitabchi et al., 2005). Two other randomized control trials that tested adapted DPPs for high-risk adults exhibited significant reductions in IL-6 and TNF-α (one study trended for TNF-α at p=0.083) (Gokulakrishnan et al., 2017; Miller et al., 2014). Furthermore, data from the Finnish Diabetes Prevention Study (DPS) exhibited significant reductions in IL-6 following one year of intensive lifestyle intervention among adults with prediabetes (Herder et al., 2006). The DPP and Finnish DPS results indicate that obesity-related alterations in the pro- and ant-inflammatory milieus are reversible in the direction of homeostatic levels following lifestyle intervention. Two other lifestyle intervention studies among women (Villareal et al., 2006) and older adults with obesity (Esposito et al., 2003) demonstrated reductions in IL-6 with the former study also showing increases in adiponectin. The former study (Villareal et al., 2006) targeted unsupervised and

supervised exercise with a Mediterranean-style diet and the latter study (Esposito et al., 2003) targeted 270 minutes per week of moderate to vigorous physical activity with a low calorie diet. No studies have assessed the effects of lifestyle intervention on IL-10 among adults with prediabetes. These findings in adults suggest that diabetes prevention lifestyle interventions that target physical activity and dietary changes are capable of shifting the pro- and anti-inflammatory milieus toward homeostatic levels. Whether these findings translate to youth with prediabetes has yet to be established.

### *Lifestyle Intervention Effects on Pro- and Anti-inflammatory Markers among High-risk Youth*

The only study to adapt the DPP for youth with prediabetes that measured insulin sensitivity, β-cell function and glucose tolerance did not report on the response of inflammatory markers (Savoye et al., 2014). Other lifestyle interventions not specifically modeled after the DPP have demonstrated favorable changes in obesity-related pro- and anti-inflammatory markers, including adiponectin, IL-6 and TNF-α (Balagopal, George, Patton, et al., 2005; Balagopal, George, Yarandi, et al., 2005; Cambuli et al., 2008; Lee et al., 2010; Mager et al., 2015; Mayerhofer et al., 2020; Rambhojan et al., 2015; Roche et al., 2019; Rosenbaum et al., 2007; Roth et al., 2011). However, a majority of these are quasi-experimental and predominantly measure adiponectin in isolation (Blüher et al., 2014; Cambuli et al., 2008; Fu et al., 2007; Lee et al., 2010; Siegrist et al., 2013). Two randomized control trials that tested three-month lifestyle interventions that targeted

moderate to high intensity exercise and dietary education and support demonstrated no changes in adiponectin (Chae et al., 2010; Park et al., 2007). Given that several pro- and anti-inflammatory markers have been associated with obesity and T2D risk factors, it may be more informative to examine changes of an array of relevant markers following lifestyle intervention. Another randomized control trial examined the effects of nutrition education alone (n=39) or nutrition plus resistance training (n=31) on cardiometabolic and inflammatory markers compared to a control group (n=30), among Latino and African-American youth with obesity (Hasson et al., 2012). No significant effects were found on measures of insulin action nor adiponectin or TNF-α, which authors attributed to a potentially inadequate sample size. In another randomized control trial, a lifestyle intervention that targeted reductions in calorie intake (exchanging high-energy snacks to low-fat, low calorie snacks, decreasing meal portions, and reducing sugar-based carbonated drinks) (Balagopal, George, Patton, et al., 2005; Balagopal, George, Yarandi, et al., 2005) and increased physical activity (2 day/week of moderate to vigorous unsupervised walking, 1 day/week supervised family exercise) elicited significant decreases in IL-6 (Balagopal, George, Patton, et al., 2005) and increases in adiponectin and insulin sensitivity (Balagopal, George, Yarandi, et al., 2005). However, the study only included 15 participants (intervention n=8, control n=7), did not measure HMW Adpn, and was conducted in a pediatric obesity clinic, thereby limiting its ability to address T2D disparities on a population level. Nevertheless, this study (Balagopal, George, Yarandi, et al., 2005) supports the rationale that lifestyle intervention may

improve obesity-induced alterations in the pro- and anti-inflammatory milieus through increases in physical activity and healthy dietary behaviors among high-risk youth populations.

*Summary of Literature Review*

Latino youth are disproportionately impacted by obesity, prediabetes, and T2D. Obesity-related pro- and anti-inflammatory markers are associated with T2D risk factors, but Latino youth are underrepresented in these studies. Moreover, lifestyle intervention is the cornerstone approach to preventing T2D among adults with prediabetes, and no studies have assessed the efficacy of an adapted DPP among Latino youth with prediabetes. Furthermore, the mechanisms by which T2D is prevented has yet to be established.

# CHAPTER 3: STUDY I

# RELATIONSHIPS BETWEEN PRO- AND ANTI-INFLAMMATORY MARKERS AND T2D RISK FACTORS

## *INTRODUCTION*

Latino youth are disproportionately impacted by obesity (Hales et al., 2018), prediabetes (Andes et al., 2020), and type 2 diabetes (T2D) (Lawrence et al., 2021). Obesity is characterized by increases in pro-inflammatory markers and reductions in anti-inflammatory adipokines (increased anti-inflammatory markers in some cases) (Shapouri-Moghaddam et al., 2018), some of which have been mechanistically linked to T2D risk factors (Acosta et al., 2019; Chetboun et al., 2012; Dagdeviren et al., 2017; Hong et al., 2009; Hotamisligil et al., 1996; Morinaga et al., 2015; Pedersen, 2017; Rui et al., 2001; Westerbacka et al., 2008; Wijesekara et al., 2010). Moreover, among adolescents with obesity, pro- and anti-inflammatory markers have been differentiated by sex (Moon et al., 2004; Punthakee et al., 2006). Indeed among youth, obesity-induced alterations in pro- and anti-inflammatory markers have been associated with insulin resistance (i.e., decreased insulin sensitivity) and β-cell dysfunction (Breslin et al., 2012; Dorneles et al., 2016; Parish et al., 2016; Rambhojan et al., 2015; Roth et al., 2011; Seppä et al., 2018; Stoppa-Vaucher et al., 2012), two central pathophysiologic risk factors that contribute to impairments in glucose tolerance (Cerf, 2013). However, Latino youth are underrepresented in these studies and the inflammatory markers measured have been

limited. Given that the pathways by which T2D develops may differ across racial/ethnic groups (Abate & Chandalia, 2003; Golden et al., 2019; Wagenknecht et al., 2011), it is important to examine the associations between a comprehensive panel of pro- and anti-inflammatory markers and T2D risk factors among high-risk Latino youth and to examine differences by sex.

In obesity, immune cells infiltrate adipose tissue and serve as a major source of pro-inflammatory marker production, including adipokines and chemokines (Shapiro et al., 2011; Shapouri-Moghaddam et al., 2018). Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are pro-inflammatory cytokines secreted by adipose tissue (i.e., adipokines) that are increased in obesity (Breslin et al., 2012; Chang et al., 2015; Paltoglou et al., 2017) and have been associated with impairments in insulin sensitivity and β-cell function (Hotamisligil et al., 1996; Lee & Lee, 2014; Li et al., 2013; Rui et al., 2001; Senn et al., 2003). Monocyte chemoattractant protein-1 (MCP-1) is a chemokine activated by the same mechanism in macrophages as IL-6 and TNF-α that facilitates traffic of infiltrating pro-inflammatory immune cells and has also been associated with insulin resistance and β-cell dysfunction (Daniele et al., 2014; Kanda et al., 2006; Piemonti et al., 2002). Anti-inflammatory markers adiponectin and interleukin-10 (IL-10) are secreted by adipose tissue and exert insulin sensitizing and β-cell enhancing effects (Acosta et al., 2019; Chetboun et al., 2012; Dagdeviren et al., 2017; Liu & Liu, 2014; Liu et al., 2017; Wijesekara et al., 2010). However, in obesity, adiponectin and IL-10 are significantly reduced, potentially hampering defense mechanisms that aid in combating

pro-inflammation (Balagopal, George, Yarandi, et al., 2005; Dorneles et al., 2016). IL-1ra is secreted by adipose tissue and exerts its anti-inflammatory effects by competing for the IL-1R1 receptors (Böni-Schnetzler et al., 2018; Sha & Markovic-Plese, 2011). Interestingly, unlike adiponectin and IL-10, IL-1ra is significantly increased in obesity (Seppä et al., 2018; Stoppa-Vaucher et al., 2012), which may be due to its upregulation by adipose-derived macrophages that are similar to those that produce pro-inflammatory markers (i.e., NF-KB signaling) (Darragh et al., 2010).

Previous studies among youth have predominantly examined the associations between pro- and anti-inflammatory markers and insulin sensitivity (Alikaşifoğlu et al., 2009; Cambuli et al., 2008; Chae et al., 2010; Chang et al., 2015; Ho et al., 2005; Luciardi et al., 2018; Mayerhofer et al., 2020; Ottobelli Chielle et al., 2016; Roth et al., 2011; Santiprabhob et al., 2018; Seppä et al., 2018; Stoppa-Vaucher et al., 2012; Vos et al., 2011), with fewer studies having examined these relationships with β-cell function (Reinehr, 2019; Reinehr et al., 2016). Identifying important inflammatory markers that are associated with T2D risk factors and understanding whether sex is a moderator will inform future diabetes prevention interventions with physiologic targets that may enhance their effectiveness among high-risk youth. Therefore, the purposes of this study were to examine the associations between pro- and anti-inflammatory markers and insulin sensitivity, β-cell function, and glucose tolerance among high-risk Latino youth and to examine sex differences.

*METHODS*

*Research Design.* This study is a secondary analysis that leverages data from a larger NIH-funded trial (NCT02615353) that enrolled 117 Latino youth with prediabetes and obesity into a randomized control trial (Soltero et al., 2017).

*Participants.* Latino youth with prediabetes and obesity were recruited and enrolled into this study. Specific inclusion criteria were as follows: 1) self-reported Latino descent, 2) ages 12-16 years, 3) BMI%$\geq 95^{th}$ for age and sex, and 4) prediabetes as defined by HbA1c 5.7-6.4%, fasting glucose 100-125 mg/dL, or 2-hr glucose 120-199 mg/dL following a 75-g oral glucose tolerance test (OGTT). Youth were excluded if they were 1) taking medication(s) or diagnosed with a condition that influences carbohydrate metabolism, physical activity, and/or cognition, 2) met criteria for T2D (fasting glucose≥126 mg/dL, HbA1c≥6.5%, or 2-hr glucose≥200 mg/dL), 3) recently hospitalized (within previous two months), 4) currently enrolled in (or within 6 months) a formal weight loss program, or 5) an uncontrolled mental health condition. Given the cross-sectional design of the present study, only youth with complete data at baseline on all biomarkers of interest (described below) were included (n=65). Recruitment methods for this study have been previously published and included referral sources from clinics, the community, local media outlets, and word-of-mouth (Vander Wyst et al., 2020). Youth provided written assent and parents provided written consent prior to participation in the study. This study was conducted according to the Declaration of Helsinki and approved by the Arizona State University (ASU) Institutional Review Board.

*Procedures.* Participants arrived at the ASU clinical research unit after an overnight fast. Height was measured to the nearest 0.1 cm using a portable stadiometer (SECA 213; SECA North America, Chino, California) and weight was measured to the nearest 0.1 kg using an electronic scale (TBF300A; Tanita Corporation of America, Arlington Heights, Illinois). Body mass index (BMI) and BMI percentiles were calculated for age and sex using the CDC growth charts. To screen for eligibility, blood samples were collected and analyzed by a CLIA-certified laboratory to assess HbA1c and fasting glucose followed by a 75-g oral glucose tolerance test (OGTT) to assess 2-hr glucose concentrations. These clinical lab results were reviewed by the study physician and returned to study participants. Participants meeting eligibility criteria were scheduled for their T1 visit within 4 weeks of their screening.

*Biomarker Assessment*. Inflammatory markers IL-6, MCP-1, IL-10, and IL-1ra were measured in fasting serum using mesoscale V-PLEX technologies (Meso Scale Discovery, Rockville, MD). A 96-well assay plate is coated with linkers that are assigned to each biomarker, or analyte (IL-6, MCP-1, IL-10, IL-1ra). An antibody bound to the respective linkers captures the target analyte before a detection antibody is bound to each analyte. The mesoscale device uses electrochemiluminescence to measure the concentrations of each analyte in pg/mL. When interpreting the results, its should be noted that IL-10 was detected at very low concentrations of its standard curve with 95% being detected under the lower detection limit of assay standard curves. TNF-α was analyzed through mesoscale U-PLEX technologies which did not require the step to coat

the plate with linkers given its specificity to TNF-α. HMW Adpn was measured in serum using an enzyme-linked immunosorbent assay (Salem, NH) which similarly uses antibodies to capture HMW Adpn and the other antibody as a detector during analysis. HMW Adpn was measured in µg/mL by spectrophotometry at 450nm.

*T2D Risk Factors.* T2D risk factors included insulin sensitivity, β-cell function, and glucose tolerance using insulin and glucose concentrations from an OGTT. Glucose was measured in plasma by the cobas c111 analyser (Roche Diagnostics, Indianapolis, IN) and insulin in serum by ALPCO ELISA kits (Salem, NH). Insulin sensitivity was estimated by the whole-body insulin sensitivity index (WBISI). The WBISI was generated from insulin and glucose concentrations during the OGTT and has been validated among youth with obesity (Yeckel et al., 2004). Fasting, 30', 60', 90', and 120' insulin and glucose concentrations are inserted into a formula,

$$\frac{10{,}000}{\sqrt{I_0 \times G_0 \times Mean(I_0, I_{30}, I_{60}, I_{90}, I_{120}) \times Mean(G_0, G_{30}, G_{60}, G_{90}, G_{120})}}$$

, to generate a WBISI score where higher scores correspond to increased insulin sensitivity levels. Insulin secretion was estimated by the insulinogenic index (IGI = $\Delta G_{30}$-$G_0$ / $\Delta I_{30}$-$I_0$), and β-cell function was estimated by the oral disposition index (oDI = insulin sensitivity x insulin secretion) (Caprio, 2012; Sjaarda et al., 2012). Glucose tolerance was measured by 2-hr post-challenge glucose concentrations during the OGTT. Body composition assessment included total fat mass, total lean mass, and body fat percent by dual-energy X-ray absorptiometry (DEXA).

*Statistical Analysis.* Baseline sex comparisons were assessed by an independent t-test, and correlations were analyzed by two-tailed Pearson correlation coefficient. In order to assess the associations between pro- and anti-inflammatory markers and insulin sensitivity, β-cell function, and glucose tolerance, multiple linear regressions that use robust maximum likelihood estimation methods were conducted with the T2D risk factor as the dependent variable and all inflammatory markers included in each model as predictors. Age, sex, and fat mass were included as covariates in multiple linear regression models. The alpha level for all analyses was set at 0.05. Baseline comparisons and correlations were assessed using IBM SPSS 28.0.1 (Chicago, IL), and multiple linear regressions were assessed with Mplus 8.7 (Los Angeles, CA).

## *RESULTS*

Characteristics and sex comparisons at baseline are described in Table 1. Pro-inflammatory markers TNF-α and MCP-1 were significantly greater among boys compared to girls ($p<0.05$) with no other differences by sex in any baseline markers.

**Table 1**. Baseline characteristics across all youth (n=65) and by sex.

| Parameter | All (n=65) | Girls (n=26) | Boys (n=39) | p-value |
|---|---|---|---|---|
| Age, y | 13.3±1.4 | 13.2±1.0 | 13.4±1.5 | 0.658 |
| BMI, kg/m$^2$ | 32.7±4.8 | 33.2±5.2 | 32.3±4.6 | 0.464 |
| BMI-z | 2.2±0.3 | 2.2±0.3 | 2.3±0.3 | 0.255 |
| WC, cm | 105±11 | 102±10 | 106±11 | 0.119 |
| Fat mass, kg | 47.5±9.4 | 37.7±8.3 | 37.3±10.2 | 0.863 |
| A1C, % | 5.6±0.3 | 5.6±0.3 | 5.6±0.3 | 0.942 |
| Fasting Glucose, mg/dL | 102±7 | 101±8 | 102±6 | 0.526 |
| 2-hr Glucose, mg/dL | 146±28 | 149±26 | 144±30 | 0.461 |
| WBISI | 1.7±1.2 | 1.5±0.9 | 1.9±1.3 | 0.25 |
| oDI | 4.6±2.6 | 4.3±2.7 | 4.9±2.5 | 0.35 |
| IL-6, pg/mL | 2.3±1.9 | 2.7±2.5 | 2.0±1.4 | 0.114 |
| TNF-α, pg/mL | 1.7±0.5 | 1.5±0.4 | 1.8±0.5 | **0.008** |
| MCP-1, pg/mL | 642±269 | 521±203 | 723±279 | **0.002** |
| HMW Adpn, ug/mL | 1.7±1.7 | 2.1±2.5 | 1.5±0.8 | 0.169 |
| IL-10, pg/mL | 0.6±1.0 | 0.6±1.4 | 0.6±0.6 | 0.784 |
| IL-1ra, pg/mL | 1140±916 | 1072±667 | 1186±106 | 0.627 |

BMI: body mass index; BMI-z: BMI z-score; WC: waist circumference, A1C: hemoglobin A1C; WBISI: whole-body insulin sensitivity index; oDI: oral disposition index; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; MCP-1: monocyte chemoattractant protein-1; HMW Adpn: high molecular weight adiponectin; IL-10: interleukin-10; IL-1ra: interleukin-1 receptor antagonist

Table 2 displays correlation coefficients that describe the bivariate associations between pro- and anti-inflammatory markers and measures of adiposity, insulin sensitivity, β-cell function, and glucose tolerance. IL-6 and IL-1ra were positively associated with BMI ($p<0.05$). IL-6, TNF-α, MCP-1, and IL-1ra were positively associated with BMI-z (all $p<0.05$). HMW Adpn and IL-1ra were negatively and

positively associated with waist circumference, respectively (both $p<0.05$). Only IL-1ra was positively associated with fat mass ($p<0.05$). In regards to T2D risk factors, only IL-1ra was significantly and negatively associated with insulin sensitivity ($p<0.05$), while HMW Adpn (positively) and MCP-1 (negatively) trended towards significance ($p<0.10$). HMW Adpn and IL-1ra were positively and negatively associated with oDI ($p<0.05$), respectively. Lastly, MCP-1 and IL-1ra were positively associated with glucose tolerance measured by 2-hr glucose concentrations ($p<0.05$). IL-10 was not associated with any of the risk factors.

**Table 2**. Baseline correlations: inflammatory markers, adiposity and T2D risk factors (n=65)

| | | Age | BMI | BMI-z | WC | Fat Mass | WBISI | oDI | 2-hr Glucose |
|---|---|---|---|---|---|---|---|---|---|
| IL-6 | *r* | -0.225 | **0.291** | **0.325** | 0.158 | 0.217 | -0.150 | -0.181 | 0.142 |
| | *p* | 0.072 | **0.019** | **0.008** | 0.209 | 0.083 | 0.232 | 0.150 | 0.261 |
| TNF-α | *r* | -0.205 | 0.128 | **0.296** | 0.194 | 0.176 | -0.133 | 0.084 | -0.070 |
| | *p* | 0.102 | 0.308 | **0.017** | 0.121 | 0.160 | 0.292 | 0.507 | 0.579 |
| MCP-1 | *r* | -0.061 | 0.092 | **0.28** | 0.213 | 0.089 | -0.224 | -0.165 | **0.252** |
| | *p* | 0.627 | 0.465 | **0.024** | 0.088 | 0.483 | 0.073 | 0.190 | **0.043** |
| HMW Adpn | *r* | -0.034 | -0.077 | -0.079 | **-0.27** | -0.149 | 0.218 | **0.389** | -0.132 |
| | *p* | 0.789 | 0.542 | 0.533 | **0.030** | 0.236 | 0.081 | **0.001** | 0.296 |
| IL-10 | *r* | -0.092 | -0.024 | 0.030 | -0.112 | -0.112 | 0.056 | -0.152 | 0.070 |
| | *p* | 0.464 | 0.848 | 0.815 | 0.373 | 0.373 | 0.655 | 0.225 | 0.578 |
| IL-1ra | *r* | 0.199 | **0.303** | **0.341** | **0.305** | **0.268** | **-0.318** | **-0.249** | **0.26** |
| | *p* | 0.113 | **0.014** | **0.005** | **0.013** | **0.031** | **0.010** | **0.045** | **0.036** |

**Bolded** font indicates significance at 0.05 alpha level

Multiple linear regression models for insulin sensitivity, β-cell function, and glucose tolerance can be found in Tables 3, 4 and 5, respectively. MCP-1, HMW Adpn, and IL-1ra were significant predictors of WBISI (all $p<0.05$). For every one pg/mL decrease in MCP-1 and IL-1ra, there was a 0.001 and 0.03 unit increase in WBISI (both $p<0.05$), respectively. For every one µg/mL increase in HMW Adpn, there was a 0.2 unit increase in WBISI ($p<0.05$). HMW Adpn was the only significant predictor of oDI so that for every one µg/mL increase in HMW Adpn, there was a 0.6 unit increase in oDI ($p<0.05$). Lastly, MCP-1, HMW Adpn, and IL-1ra significantly predicted 2-hr glucose levels (all $p<0.05$). For every one pg/mL increase in MCP-1 and IL-1ra, there was a 0.03, and 0.09 mg/dL increase in 2-hr glucose concentrations, respectively. Furthermore, for every one µg/mL increase in HMW Adpn, there was a 2.2 mg/dL reduction in 2-hr glucose levels.

**Table 3**. Multiple linear regression model: Insulin Sensitivity

| Dependent Variable: *WBISI* | | | |
|---|---|---|---|
| Predictors | β | SE | p-value |
| *IL-6* | -0.06 | 0.15 | 0.69 |
| *TNF-α* | -0.6 | 0.5 | 0.299 |
| *MCP-1* | -0.001 | 0.001 | **0.027** |
| *HMW Adpn* | 0.16 | 0.03 | **<0.001** |
| *IL-10* | 0.3 | 0.4 | 0.437 |
| *IL-1ra* | -0.03 | 0.01 | **0.006** |
| *Age* | 0.00 | 0.10 | 0.994 |
| *Sex* | 0.9 | 0.4 | **0.021** |
| *Fat Mass* | -0.01 | 0.02 | 0.715 |

**Bolded** p-values indicate significance at 0.05 alpha level

**Table 4**. Multiple linear regression model: β-cell function

| Dependent Variable: *oDI* | | | |
|---|---|---|---|
| Predictors | β | SE | p-value |
| *IL-6* | 0.1 | 0.2 | 0.473 |
| *TNF-α* | 1.1 | 0.7 | 0.129 |
| *MCP-1* | -0.001 | 0.001 | 0.159 |
| *HMW Adpn* | 0.6 | 0.1 | **<0.001** |
| *IL-10* | -0.5 | 0.4 | 0.196 |
| *IL-1ra* | -0.007 | 0.004 | 0.078 |
| *Age* | 0.4 | 0.2 | 0.057 |
| *Sex* | 0.9 | 0.7 | 0.176 |
| *Fat Mass* | -0.05 | 0.03 | 0.14 |

**Bolded** p-values indicate significance at 0.05 alpha level

**Table 5**. Multiple linear regression model: Glucose Tolerance

| Dependent Variable: *2-hr Glucose* | | | |
|---|---|---|---|
| Predictors | β | SE | p-value |
| *IL-6* | 1.0 | 2.4 | 0.738 |
| *TNF-α* | -5.6 | 11.0 | 0.609 |
| *MCP-1* | 0.03 | 0.01 | **0.033** |
| *HMW Adpn* | -2.2 | 0.9 | **0.018** |
| *IL-10* | -1.3 | 3.6 | 0.723 |
| *IL-1ra* | 0.09 | 0.03 | **0.009** |
| *Age* | -1.7 | 2.3 | 0.454 |
| *Sex* | -10.9 | 10.1 | 0.282 |
| *Fat Mass* | -0.4 | 0.3 | 0.249 |

**Bolded** p-values indicate significance at 0.05 alpha level

*DISCUSSION*

The assessment of pro- and anti-inflammatory markers and their relationships with T2D risk factors among Latino youth is limited (Arslanian et al., 2017; Cruz et al., 2004; Nemet et al., 2003; Ohman-Hanson et al., 2016; Rosenbaum et al., 2007). These findings suggest that higher levels of MCP-1 and IL-1ra and lower levels of HMW Adpn are associated with lower insulin sensitivity and β-cell function among Latino youth with prediabetes and obesity. Additionally, TNF-α and MCP-1 concentrations were higher among boys compared to girls. These findings expand upon the relationships between pro- and anti-inflammatory markers and insulin sensitivity, β-cell function, and glucose tolerance among a high-risk Latino youth population.

Adiponectin may be the most studied adipokine among youth and is reduced in obesity (Orlando et al., 2019). Adiponectin is almost exclusively produced by adipocytes and well-known for its association with reduced T2D risk (Choi et al., 2020). A prior study among Mexican-American children and adolescents (8-16 y) demonstrated that higher adiponectin levels predicted a lower prevalence of T2D (Cruz et al., 2004). Furthermore, the landmark TODAY trial (Treatment Options for T2D in Adolescents and Youth) demonstrated that low baseline HMW Adpn levels predicted glycemic failure, suggesting lower β-cell responsiveness among youth with hypoadiponectinemia (Arslanian et al., 2017). Given these prior studies on adiponectin among youth, it is not surprising that our results indicated HMW Adpn as a predictor of insulin sensitivity, β-cell function, and glucose tolerance. Of interest to note was the prediction strength of

insulin sensitivity (0.6 unit increase) and 2-hr glucose concentrations (2.2 mg/dL decrease) for every one unit increase in HMW Adpn. These findings support adiponectin as a potential target for diabetes prevention interventions among Latino youth.

The chemokine, MCP-1, is significantly increased in pediatric obesity (Breslin et al., 2012; Luciardi et al., 2018; Parish et al., 2016) and plays a role in facilitating traffic of macrophages into adipose tissue. One study among adolescents with obesity supported an inverse association between MCP-1 and insulin sensitivity (Parish et al., 2016) while two other studies in youth with obesity failed to support an association between MCP-1 and insulin sensitivity or fasting glucose (Akcan et al., 2020; Morishita et al., 2016). In the present cohort of Latino youth, MCP-1 predicted lower insulin sensitivity and higher 2-hour glucose concentrations among high-risk Latino youth, independent of age, sex, and adiposity. Although the clinical relevance of the β coefficient for MCP-1 is questionable at -0.001, the range of MCP-1 levels in the current cohort was 641.7 mg/dL. Using this range and our prediction equation, a 0.6 unit difference in WBISI exists between the individual with the highest MCP-1 level and the lowest MCP-1 level in our dataset, which may be clinically relevant. Whether MCP-1 directly impacts mechanisms involved in insulin action and glucose regulation has not been established; however, a study in obese mice demonstrated the development of insulin resistance following intravenous infusion of MCP-1 without changes in macrophage infiltration of adipose tissue (Tateya et al., 2010), supporting a potential mechanistic link between MCP-1 and pathophysiologic risk.

The most robust finding in the present study was that IL-1ra was significantly associated with all measures of adiposity, insulin sensitivity, β-cell function, and glucose tolerance. We are aware of at least two other studies that examined the relationship between IL-1ra and T2D risk factors in youth populations. In one study among 12-year old children, IL-1ra was significantly increased among youth with obesity compared to normal weight, and IL-1ra was negatively associated with insulin sensitivity (Seppä et al., 2018). These results were replicated among White youth in the second study (Stoppa-Vaucher et al., 2012). It is known that IL-1ra is secreted by adipose tissue (Juge-Aubry et al., 2003) and is upregulated by the NF-KB pathway which also produces pro-inflammatory markers IL-6, TNF-α, and IL-1β (Lawrence, 2009). In pancreatic β-cells, IL-1ra neutralizes the IL-1R1 receptor thereby preventing IL-1β and IL-1α from activating pathways that lead to reduced β-cell proliferation and insulin production (Böni-Schnetzler et al., 2018). Due to its origin from the NF-KB pathway, it stands to reason that IL-1ra, unlike adiponectin and IL-10, is increased in obesity, potentially as a compensatory mechanism to combat the pro-inflammatory risk to diabetes-relevant tissues (i.e., pancreas, liver, muscle). Like MCP-1, it is unknown whether IL-1ra has direct mechanistic effects on insulin action and glucose regulation, but our findings among others support this direct link. It should not go without mention that IL-1ra is part of the anti-inflammatory response of skeletal muscle tissue to acute exercise (Petersen & Pedersen, 2005). In the context of obesity, however, reductions in basal IL-1ra

concentrations among youth with obesity is considered a healthy response to intervention (Frühbeck et al., 2022).

In recent years, the understanding of traditional and novel chemokines and cytokines has grown considerably (Kany et al., 2019). Based on our findings, it is evident that aside from IL-10, all other pro- and anti-inflammatory markers were associated with T2D risk factors. It was not surprising that IL-10 was not associated with any of the risk factors given the lack of variability within this specific cohort with 88% exhibiting IL-10 concentrations <1.0 pg/mL. Given that each of these inflammatory markers exerts distinct metabolic and immunologic functions that modulate risk for T2D, it is important to understand how changes following diabetes prevention interventions impact pathophysiologic processes.

Lastly, TNF-α was significantly elevated among Latino boys compared to Latina girls in the present study, supporting previous work among other adolescent populations (Moon et al., 2004; Punthakee et al., 2006). It appears that the differences in pro-inflammatory and anti-inflammatory markers by sex do not emerge until adolescence as several studies have demonstrated no sex differences in TNF-α or adiponectin among younger pediatric populations (Dixon et al., 2004; Gil-Campos et al., 2011; Moon et al., 2004; Punthakee et al., 2006; Reinehr et al., 2005). To our knowledge, MCP-1 has not been analyzed by sex in pediatric obesity studies, and thus our findings that boys have elevated MCP-1 levels compared to girls are novel to the field. Latino boys exhibit significantly higher levels of visceral adipose tissue and liver fat compared to Latina girls

(Vander Wyst et al., 2021). Given that TNF-α and MCP-1 are implicated in non-alcoholic fatty liver disease (NAFLD) (Brenner et al., 2013; Haukeland et al., 2006; Kirovski et al., 2011), it stands to reason that elevated TNF-α and MCP-1 among Latino boys may be associated with the increased risk of T2D through the development and progression of NAFLD. Understanding the pathophysiologic mechanisms that may differentiate T2D risk by sex among high-risk Latino youth will inform future precision approaches to prevention among this specific ethnic youth population.

A strength of this study is the prioritization of an underrepresented Latino youth population in a study that examines the relationships of an array of obesity-related pro- and anti-inflammatory markers. Furthermore, this study included in its analysis understudied, yet relevant, chemokines and cytokines (i.e., MCP-1, IL-10, IL-1ra) and therefore adds novel information to the body of knowledge in pediatric obesity. We appreciate that this study is not without limitations. This study was a cross-sectional study and thus causal inferences cannot be made. Prioritizing Latino youth limits the generalizability of these findings to other youth populations. Furthermore, the WBISI and oDI are not the gold standard approaches for measuring insulin sensitivity and β-cell function; however, they have been validated or compared against their respective gold standard methods in youth with obesity (Caprio, 2012; Sjaarda et al., 2012; Yeckel et al., 2004) are widely used in the pediatric obesity literature (Chen et al., 2018; Hannon et al., 2018).

In summary, increased HMW Adpn and reduced MCP-1 and IL-1ra are independent predictors of insulin sensitivity and glucose intolerance, whereas only HMW Adpn predicted β-cell function independent of age, sex, and adiposity. Whether changes in these inflammatory markers track with improvements in T2D risk factors following diabetes prevention interventions among high-risk pediatric populations warrants future investigation.

# CHAPTER 4: STUDY II

# EFFECTS OF A DIABETES PREVENTION PROGRAM ON INSULIN SENSITIVITY, β-CELL FUNCTION, AND GLUCOSE TOLERANCE AMONG LATINO YOUTH WITH PREDIABETES

## *INTRODUCTION*

Latinos are disproportionately impacted by type 2 diabetes (T2D) (Lawrence et al., 2021), and these disparities emerge early in life (Dabelea et al., 2014). The Centers for Disease Control and Prevention (CDC) estimated that Latino youth have a 50% lifetime risk of developing T2D (Narayan et al., 2003). Based upon compelling findings from the United States Diabetes Prevention Program (U.S. DPP) (Knowler et al., 2002), lifestyle intervention is considered the first-line approach for preventing T2D among adults with prediabetes (Association, 2019). The DPP has been adapted for many high-risk adult populations (Aziz et al., 2015), yet very few studies describe adaptations for high-risk pediatric populations (Brown et al., 2013; Hingle et al., 2019; Savoye et al., 2014).

Given that Latino youth exhibit disproportionately higher rates of prediabetes compared to non-Hispanic White youth (Andes et al., 2020), there is a need for DPP adaptations that are culturally tailored to the specific needs of this underrepresented ethnic subgroup (Cruz & Granados, 2019). To this end, our team previously demonstrated that a culturally-grounded, community-based DPP adaptation for Latino

youth with obesity increased insulin sensitivity (Soltero et al., 2018). As part of this trial, youth with prediabetes (n=24) who were automatically assigned to the lifestyle intervention arm (i.e., not randomized) demonstrated significant improvements in glucose tolerance. In that study, there was no control group of Latino youth with prediabetes. Accordingly, a rigorous trial was warranted in this vulnerable and underrepresented population sub-group.

The purpose of this study was to examine the efficacy of a diabetes prevention program on insulin sensitivity, β-cell function, and glucose tolerance among Latino youth with prediabetes and obesity.

## *METHODS*

*Participants.* Latino youth with prediabetes and obesity were recruited and enrolled into this study. Specific inclusion criteria were as follows: 1) self-reported Latino descent, 2) ages 12-16 years, 3) BMI%$\geq 95^{th}$ for age and sex, and 4) prediabetes as defined by HbA1c 5.7-6.4%, fasting glucose 100-125 mg/dL, or 2-hr glucose 120-199 mg/dL following a 75-g oral glucose tolerance test (OGTT). Youth were excluded if they were 1) taking medication(s) or diagnosed with a condition that influences carbohydrate metabolism, physical activity, and/or cognition, 2) met criteria for T2D (fasting glucose≥126 mg/dL, HbA1c≥6.5%, or 2-hr glucose≥200 mg/dL), 3) recently hospitalized (within previous two months), 4) currently enrolled in (or within 6 months) a formal weight loss program, or 5) an uncontrolled mental health condition. This study was

approved by the Arizona State University (ASU) Institutional Review Board and is in accordance with the Declaration of Helsinki. Youth provided written assent and parents provided written consent prior to study participation. Recruitment commenced in May 2016 and continued through March 2020.

*Research Design.* This study was a two-arm parallel randomized controlled trial comparing a six-month lifestyle intervention (INT) to a usual care control (UCC) condition (Soltero et al., 2017). Data were collected at baseline (T1) and at six months (T2). After the T1 visit, youth were randomized to either lifestyle intervention or usual care in a 2:1 ratio (INT:UCC). Youth provided written assent and parents provided written consent prior to participation in the study. This study was conducted according to the Declaration of Helsinki and approved by the Arizona State University (ASU) Institutional Review Board.

*Recruitment.* Participants were recruited through local schools, community organizations, churches, and media outlets tailored to the local Latino community (Vander Wyst et al., 2020). Research personnel conducted an initial phone screen with interested individuals to confirm age, Latino descent, an estimate of BMI and to provide a thorough description of study participation. Thereafter, interested individuals scheduled a health screening visit to determine study eligibility.

*Health Screening.* Participants arrived at the ASU clinical research unit after an overnight fast. Height was measured to the nearest 0.1 cm using a portable stadiometer (SECA 213; SECA North America, Chino, California) and weight was measured to the

nearest 0.1 kg using an electronic scale (TBF300A; Tanita Corporation of America, Arlington Heights, Illinois). Body mass index (BMI) and BMI percentiles were calculated for age and sex using the CDC growth charts. To screen for eligibility, blood samples were collected and analyzed by a CLIA-certified laboratory to assess HbA1c and fasting glucose followed by a 75-g oral glucose tolerance test (OGTT) to assess 2-hr glucose concentrations. These clinical lab results were reviewed by the study physician, returned to study participants, and used to anchor conversations about diabetes risk in lifestyle intervention or usual care sessions. Participants meeting eligibility criteria were scheduled for their T1 visit within 4 weeks of their screening.

*T1-T2 Study Visits:* Participants returned to the ASU clinical research unit following an overnight fast for assessment of height, weight, and waist circumference, resting heart rate, seated blood pressure, and total body composition by dual x-ray absorptiometry (DEXA, Lunar iDXA, GE Healthcare). Insulin sensitivity and glucose tolerance were measured via a multiple sample 2-hr OGTT with glucose and insulin concentrations measured at fasting and every 30 minutes. Samples collected for measurement of glucose and insulin at T1 through T3 were stored at -80°C and analyzed in batches by research laboratories at the end of the study. Clinical lab results at T1 (screening labs) and T2 were used to identify youth that may develop diabetes. If youth met criteria for T2D using clinical lab results, he or she was to be referred for follow-up care. Ethnicity, country of origin, and preferred language were reported by youth, and

monthly income and participation in government assistance programs were reported by parent(s) using staff-generated questionnaires.

*T2D Risk Factors.* Insulin sensitivity was estimated by the whole-body insulin sensitivity index (WBISI). The WBISI was generated from insulin and glucose concentrations during the OGTT and has been validated among youth with obesity (Yeckel et al., 2004). Glucose was measured in plasma by the cobas c111 analyser (Roche Diagnostics, Indianapolis, IN) and insulin in serum by ALPCO ELISA kits (Salem, NH), both in duplicate. Fasting, 30', 60', 90', and 120' insulin and glucose concentrations are inserted into a formula (10,000/√Fasting Glucose x Fasting Insulin x Mean OGTT Glucose x Mean OGTT Insulin) to generate a WBISI score where higher scores correspond to increased insulin sensitivity levels. Insulin secretion was estimated by the insulinogenic index (IGI = $\Delta G_{30}$-$G_0$ / $\Delta I_{30}$-$I_0$), and β-cell function was estimated by the oral disposition index (oDI = insulin sensitivity x insulin secretion) (Caprio, 2012; Sjaarda et al., 2012). Glucose tolerance was measured by 2-hr post-challenge glucose concentrations during the OGTT. Body composition assessment included total fat mass, total lean mass, and body fat percent by dual-energy X-ray absorptiometry (DEXA).

*Intervention Group - Lifestyle*. The lifestyle intervention included 1 day/week of nutrition and health education with behavior change skills training and 3 days/week of physical activity. The development of the intervention curriculum was led by our community partners and has been refined through rigorous trials over the last 10 years (Shaibi et al., 2012; Soltero et al., 2018; Soltero et al., 2019). The curriculum is informed

by Social Cognitive Theory by applying behavioral strategies utilized in the U.S. DPP, including goal setting, fostering social support, and enhancing self-efficacy to facilitate health behavior change. Nutrition and health education sessions were delivered by bilingual, bicultural *Promotoras* (community health educators), all of whom underwent manualized training in curriculum content and delivery by the director of the family wellness program of our community partners who is also a registered dietitian. Curriculum content focuses on the reduction of saturated fat intake, added sugars, and sugar-sweetened beverages, managing portion sizes, and increasing intake of fiber, fruit, and vegetables.

Unlike the weight loss goal of >7% in the U.S. DPP, the intervention focuses on diabetes risk reduction as the primary goal. Critical intervention inputs of the intervention to enhance the enactment of health behaviors included fostering social support from family and peers and enhancing self-efficacy for making healthy behavior changes. Social support was fostered through a) Appraisal: providing OGTT results from screening and basing health goals aimed at reducing T2D risk, b) Informational: Promotoras delivered diabetes-related health and nutrition education, c) Instrumental: Families exchanged contact information and children exchanged school information to facilitate interaction outside of the program, and d) Emotional: emotional well-being was woven throughout the curriculum with an emphasis placed on building self-esteem, positive self-affirmation, and reducing negative influences from family and peers. Self-efficacy was enhanced through a) Goal-setting: setting, monitoring, and achieving health

behavior goals, b) Vicarious Experience and Role Modeling: Promotoras and peers role play situations and exercise staff modeled activities, and c) Verbal Encouragement: Promotoras, family, and peers encouraged youth to make healthy behavior changes.

Children were presented with the results of their OGTT early on in the intervention as a way to frame the discussion around diabetes and health. Each session began with a low fat, high fiber snack and recipe (role modeling), acknowledgment and reinforcement of healthy behavior changes and progress towards individual goals (emotional and instrumental support), problem-solving challenges, and an outline of the session's goals. Children were incentivized through a point system for attendance, completing out of class 'assignments' such as helping to prepare a healthy meal for the family (enacting behaviors), participating in group discussions, and making progress towards their individual health goals. Parents and children worked with other families during classes and were encouraged to do so outside of class in order to build a support network that extended beyond the program. Classes were delivered using a tiered approach where the first 16 sessions were delivered weekly while the last 4 sessions are spread over 8 weeks (total intervention period is six months).

Physical activity was delivered by YMCA instructors twice per week for 60 minutes/session and included structured and unstructured components. The structured component included two days per week of supervised physical activity sessions led by the YMCA instructors and delivered to groups of 8-10 youth for 60 minutes per session. Sessions included aerobic and resistance exercise delivered in a progressive manner with

the first 2-4 weeks focusing on motor skill acquisition, exercise confidence, developing a fitness base, and building camaraderie among participants. Aerobic exercises included group activity classes (e.g., spinning and cardio kick-boxing) with the goal of maintain heart rates > 150 beats per minute. Real-time heart-rate monitoring was used to monitor and document exercise intensity throughout the program. This intensity was based on previous literature that has demonstrated significant improvements in metabolic risk factors among youth with obesity (Gutin et al., 2002). Resistance exercise includes circuit training using age and size appropriate equipment and is incorporated because our previous studies suggest this form of exercise is both enjoyable and metabolically beneficial for youth with obesity (Benson et al., 2008). In addition to structured physical activity classes, youth are 'prescribed' an additional day of unstructured physical activity of at least 60 minutes with a family member or peer in the program. This allowed for flexibility in pursuing preferred activities that can be done at the YMCA or elsewhere in the community in order to promote social support, role modeling, bonding among youth and families, and facilitate sustainability.

*Usual Care Control (UCC) Group*. Participants randomized to UCC met with a pediatric endocrinologist and a bilingual, bicultural registered dietitian to discuss laboratory results and develop SMART goals for making healthy lifestyle changes. These visits followed T1 and T2 visits. The UCC group was offered an abridged lifestyle intervention after study completion.

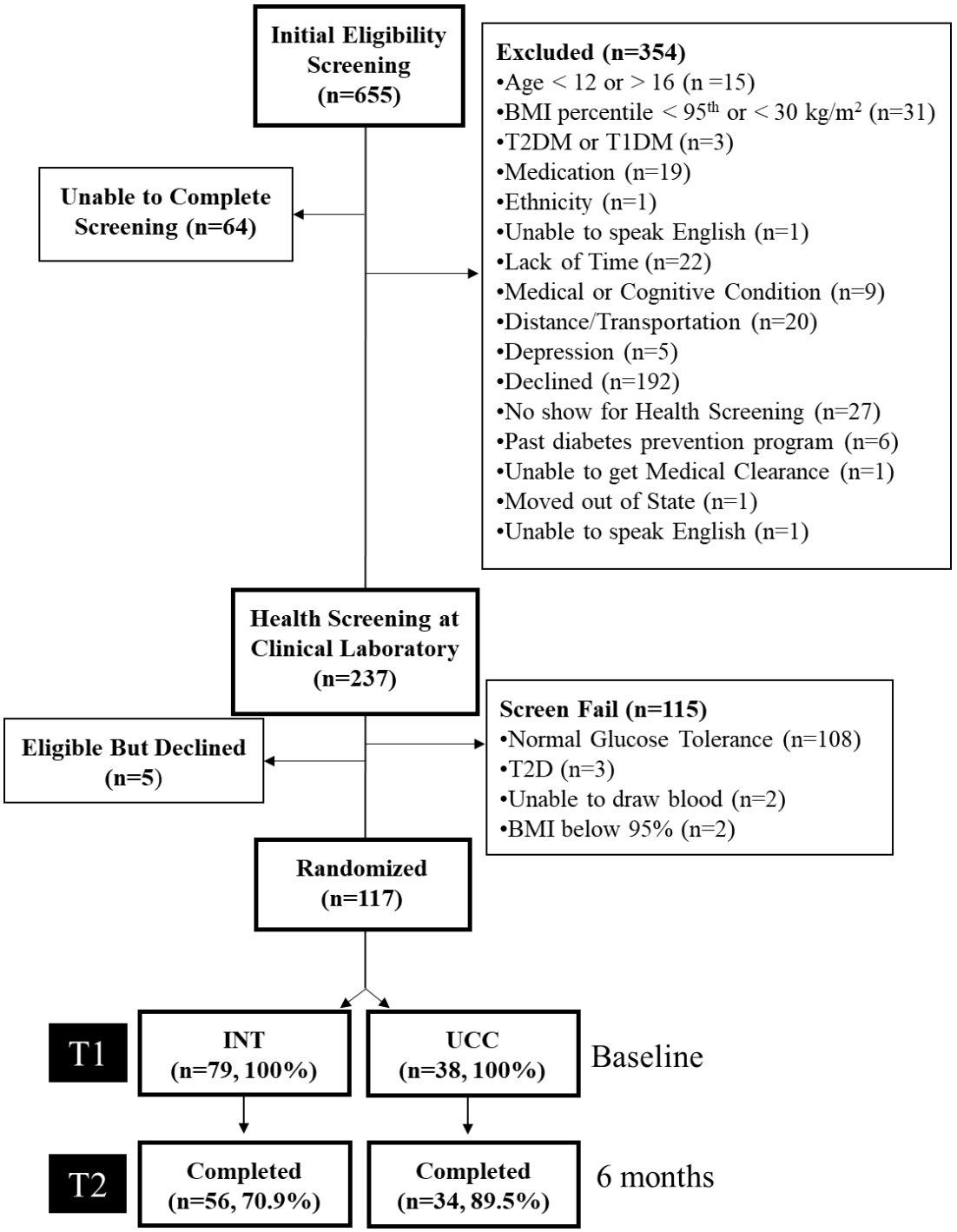
*Analytical Approach.* Sample size was determined using data from a previous lifestyle intervention among Latino youth with prediabetes and obesity where we observed an effect size of 1.25 for reductions in 2-hr glucose concentrations (Soltero et al., 2018). Assuming $\alpha$=0.05 and power=85% to detect intervention effects of 1.25 on changes in glucose tolerance, a sample size of 100 was required. To account for attrition, we set a goal of recruiting 120 youth in the study.

Baseline characteristics between groups were compared using independent t-tests (continuous variables) and chi-square tests (categorical variables) using IBM SPSS 28.0.1 (Chicago, IL). Changes in outcomes were compared between groups using covariance pattern models which assess the difference in changes in outcomes from T1 to T2 using Mplus 8.7 (Los Angeles, CA). Full information maximum likelihood (FIML) was used to account for missing data. Auxiliary variables were not included given their lack of efficiency in models with small sample sizes (Savalei, 2009). Data are presented as mean±SD, FIML-adjusted mean±SE, or FIML-adjusted ΔMean±95%CI when appropriate.

*RESULTS*

One hundred seventeen youth (mean±SD, age 13.5±1.4 y, 40.2% girls, BMI-z 2.3±0.3) were enrolled (Figure 5) into the study.

**Figure 5**. CONSORT Flow Diagram



Their sociodemographic characteristics are described in Tables 6 and 7. Over 95% of youth were of Mexican ancestry with most born in the United States. Most (82.1%) reported English as their preferred language. Seven families reported a monthly household income between $0-$500, and the majority of families (74.6%) reported a monthly household income from $501-$3,000. Three-fourths (75.2%) of families reported having Medicaid health insurance, and just over one-third (37.6%) reported being on the supplemental nutritional assistance program.

**Table 6**. Baseline sociodemographic data in all youth (n=117)

| **Parameter** | | **n (%)** |
|---|---|---|
| Ethnicity | | |
| | *Mexican* | 112 (95.7%) |
| | *Central American* | 4 (3.4%) |
| | *South American* | 1 (0.9%) |
| Country of Origin | | |
| | *United States* | 82 (70.0%) |
| | *Mexico* | 11 (9.4%) |
| | *Central America* | 1 (0.9%) |
| | *Did not respond* | 23 (19.7%) |
| Preferred Language | | |
| | *English* | 96 (82.1%) |
| | *Spanish* | 13 (11.1%) |
| | *Did not respond* | 8 (6.8%) |

**Table 7**. Baseline sociodemographic data as reported by parents (n=117)

| Parameter | | n (%) |
|---|---|---|
| Monthly Income | | |
| | *$0 - 500* | 7 (6.0%) |
| | *$501 - 1,000* | 29 (24.8%) |
| | *$1,001 - 2,000* | 32 (27.4%) |
| | *$2,001 - 3,000* | 24 (20.5%) |
| | *$3,001 - 4,000* | 10 (8.5%) |
| | *$4,001 - 5,000* | 4 (3.4%) |
| | *Other amount* | 2 (1.7%) |
| | *Do not know* | 4 (3.4%) |
| | *Refused to respond* | 2 (1.7%) |
| | *Did not respond* | 3 (2.6%) |
| Government Assistance Programs | | |
| | *WIC Services* | 25 (21.4%) |
| | *Medicaid* | 88 (75.2%) |
| | *Food Stamps* | 44 (37.6%) |

Baseline characteristics and group comparisons are displayed in Table 3.

**Table 8**. Baseline Characteristics

| Parameter | **ALL (n=117)** | **UCC (n=38)** | **INT (n=79)** |
|---|---|---|---|
| Age, y | 13.5±1.4 | 13.6±1.5 | 13.5±1.3 |
| Female, n (%) | 47 (40.1%) | 14 (36.8%) | 33 (41.8%) |
| Height, cm | 164±9 | 164±8 | 164±9 |
| Weight, kg | 91.3±20.3 | 94.5±23.9 | 89.8±18.3 |
| Pubertal Development Scale | | | |
| *Pre-pubertal* | 17 (16.8%) | 7 (20.6%) | 10 (14.9%) |
| *Mid-pubertal* | 51 (50.5%) | 18 (52.9%) | 33 (49.3%) |
| *Post-pubertal* | 33 (32.7%) | 9 (26.5%) | 24 (35.8%) |
| Gestational Diabetes Mellitus* | 13 (12.4%) | 6 (16.2%) | 7 (10.3%) |
| Family History of T2D, n (%) | | | |
| *Parents, Siblings only* | 25 (21.4%) | 7 (18.4%) | 18 (22.8%) |
| *Parents, Siblings, Grandparents* | 98 (83.8%) | 30 (78.9%) | 68 (86.1%) |
| BMI, $kg/m^2$ | 33.8±5.4 | 34.9±6.7 | 33.3±4.6 |
| BMI percentile | 98.4±1.2 | 98.3±1.4 | 98.3±1.1 |
| BMI z-score | 2.28±0.32 | 2.33±0.37 | 2.25±0.30 |
| Waist Circumference, cm | 107±14 | 110±16 | 106±13 |
| Fat mass, kg | 40.0±12.4 | 42.7±15.1 | 38.8±10.9 |
| Lean mass, kg | 43.8±9.1 | 43.7±10.1 | 43.8±8.7 |
| HbA1c, % | 5.63±0.28 | 5.64±0.27 | 5.63±0.29 |
| Fasting Glucose, mg/dL | 102±8 | 103±7 | 101±8 |
| 2-h Glucose, mg/dL | 144±30 | 144±29 | 144±30 |
| Fasting Insulin, uIU/mL | 23.8±13.5 | 23.1±11.0 | 24.1±14.6 |
| 2-h Insulin, uIU/mL | 216±176 | 210±166 | 219±181 |
| WBISI | 1.88±1.61 | 1.92±1.94 | 1.87±1.44 |
| Weight-specific Quality of Life | 74.8±18.9 | 73.8±18.0 | 75.3±19.4 |

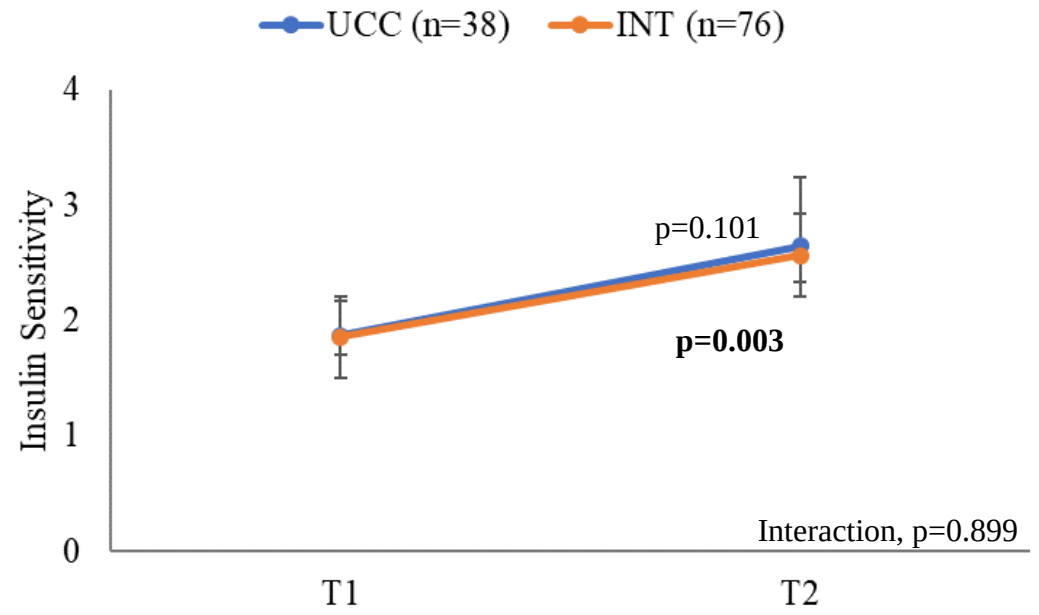
Data are presented as Mean±SD for continuous variables

Laboratory measurements are from the T1 visit, not the screening visit determining eligibility

*History of gestational diabetes in the participant's mother

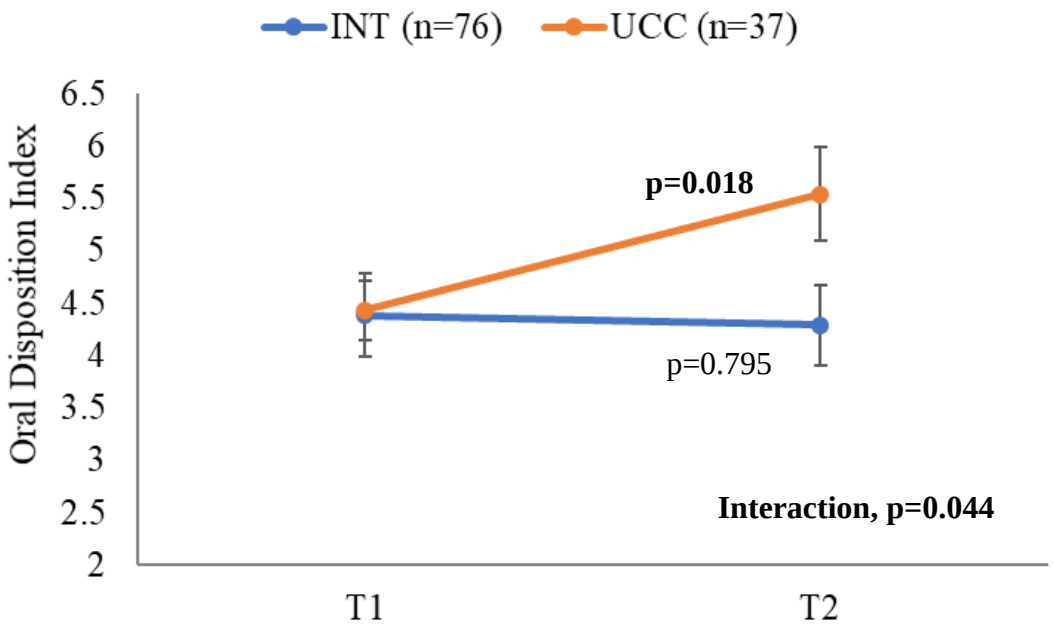
Changes in insulin sensitivity, β-cell function, and glucose tolerance are illustrated in Figures 6-8, respectively, and secondary outcomes presented in Table 9. At six months, insulin sensitivity increased by 37% ($p=0.001$) following lifestyle intervention and usual care (37%, $p=0.101$) and these changes were not significantly different between groups ($p=0.899$). β-cell function, measured by oDI, was significantly increased following INT at T2 (25%, $p=0.018$), and these changes were significantly greater (interaction, $p<0.05$) than that observed among UCC (-2%, $p=0.795$). Two-hour glucose concentrations were significantly reduced in the INT group (-13 mg/dL, $p=0.001$) but not in the UCC group (-5 mg/dL, $p=0.316$). However, the difference in changes in 2-hr glucose between groups was not statistically significant (Δ-8 mg/dL, $p=0.232$). According to the clinical lab results, no youth developed diabetes over the course of the study, despite eight individuals meeting criteria for T2D at various times during the trial using 2-hr glucose concentrations generated from non-actionable research laboratory results.

**Figure 6**. Changes in insulin sensitivity (WBISI) within and between INT and UCC.



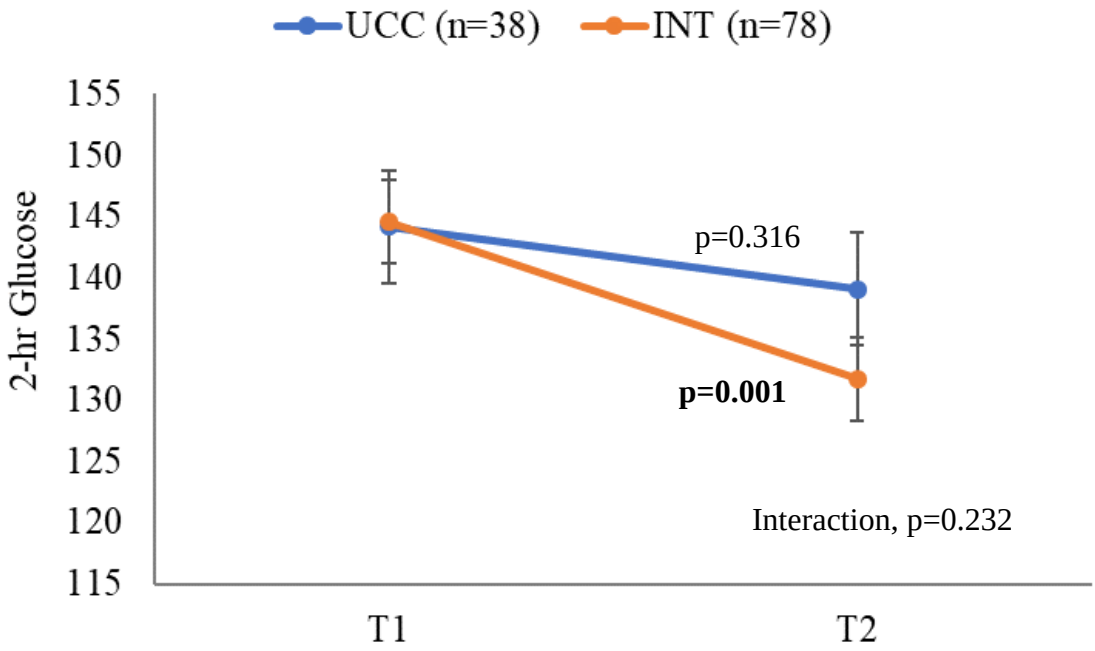

Data are presented as Mean±SE

**Figure 7**. Changes in oDI within and between INT and UCC.




Data are presented as Mean±SE

**Figure 8**. Changes in 2-hr glucose levels from OGTT within and between INT and UCC.




Data are presented as Mean±SE

**Table 9**. Changes in primary and secondary outcomes among INT and UCC groups from T1-T2.

| | Usual Care Control | | | Intervention | | | Treatment Effect |
|---|---|---|---|---|---|---|---|
| **Parameter** | ***n*** | **T1** | **T2** | ***n*** | **T1** | **T2** | **ΔT2-T1 (95%CI) p-value** |
| WBISI | 38 | 1.9±0.3 | 2.6±0.6 p=0.101 | 76 | 1.9±0.2 | 2.6±0.3 **p=0.003** | -0.1 (-1.1, 0.9) p=0.899 |
| oDI | 37 | 4.4±0.4 | 4.3±0.4 p=0.795 | 76 | 4.4±0.3 | 5.5±0.4 **p=0.018** | 1.2 (0.03, 2.37) p=0.044 |
| 2-h Glucose | 38 | 144±5 | 139±5 p=0.316 | 78 | 145±3 | 132±3 **p=0.001** | -8 (-20, 5) p=0.232 |
| Fasting Glucose | 38 | 103±1 | 105±4 p=0.507 | 79 | 101±1 | 99±1 **p=0.021** | -5 (-12, 2) p=0.222 |
| HbA1c | 38 | 5.6±0.04 | 5.7±0.06 p=0.387 | 79 | 5.6±0.03 | 5.6±0.03 p=0.268 | -0.07 (-0.17, 0.03) p=0.177 |
| Weight | 38 | 94.5±3.3 | 97.4±3.4 **p<0.001** | 79 | 89.8±1.7 | 92.0±1.8 **p<0.001** | -0.8 (-2.3, 0.8) p=0.349 |
| BMI | 38 | 34.9±1.1 | 35.3±1.1 **p=0.045** | 79 | 33.3±0.5 | 33.5±0.6 p=0.111 | -0.2 (-0.7, 0.3) p=0.449 |
| BMI-z | 38 | 2.3±0.1 | 2.3±0.1 p=0.775 | 79 | 2.3±0.03 | 2.2±0.04 p=0.105 | -0.02 (-0.07, 0.03) p=0.429 |
| Fat Mass | 38 | 42.9±2.4 | 43.6±2.3 p=0.262 | 79 | 38.8±1.2 | 38.4±1.3 p=0.368 | -1 (-2, 2) p=0.151 |
| Lean Mass | 38 | 44.0±1.6 | 45.9±1.5 **p<0.001** | 79 | 43.8±1.0 | 46.2±1.1 **p<0.001** | 0.5 (-0.4, 1.4) p=0.307 |
| Body Fat % | 38 | 47.4±0.8 | 46.9±0.9 p=0.205 | 79 | 45.4±0.6 | 43.9±0.6 **p<0.001** | **-1.0 (-2.0, 0.9) p=0.042** |
| Fasting Insulin | 38 | 23±2 | 21±2 p=0.318 | 78 | 24±2 | 19±1 **p=0.003** | -3 (-8, 2) p=0.192 |
| IGI | 38 | 3.3±0.3 | 3.3±0.4 p=0.962 | 77 | 3.3±0.2 | 3.2±0.3 p=0.597 | -0.1 (-0.9, 0.7) p=0.803 |

Data under T1, T2, and T3 columns are presented as FIML-adjusted Mean±SE. Bolded data are significant at $p<0.05$.

WSQOL: weight-specific quality of life; IGI: insulinogenic index; oDI: oral disposition index; HbA1c: hemoglobin A1C

Treatment Effect column displays FIML-adjusted differences in changes (mean$\Delta$±95%CI) in outcomes between INT and UCC from T1-T2.

*DISCUSSION*

Despite the increasing prevalence of T2D among children and adolescents (Lawrence et al., 2021), the evidence for diabetes prevention among youth with prediabetes remains limited (Magge et al., 2020). Therefore, we developed and tested a culturally-grounded diabetes prevention intervention for Latino youth with prediabetes. Our findings demonstrated that lifestyle intervention was efficacious for improving β-cell function compared to usual care. Furthermore, both groups significantly increased insulin sensitivity, and there were no differences in 2-hr glucose between groups. These findings add to the current literature focused on diabetes prevention in a vulnerable and underrepresented population sub-group.

The only other randomized control trial to our knowledge that tested an adapted DPP among youth with prediabetes is the Yale Bright Bodies study (Savoye et al., 2014). Despite significant increases in insulin sensitivity (measured by WBISI) following the Yale Bright Bodies lifestyle intervention, β-cell function (measured by oDI) was not significantly improved as compared to standard clinical care (Savoye et al., 2014). Our study demonstrated significant improvements in oDI following lifestyle intervention compared to usual care with increases in insulin sensitivity among both groups at similar magnitudes (0.7 unit increase in both groups). Similar to Yale Bright Bodies, we did not observe significant changes in insulin secretion, as measured by the IGI, within or between either of the groups. Glucose and insulin concentrations during an OGTT are influenced by factors beyond insulin sensitivity, including β-cell hyperresponsiveness,

glucose absorption rates, and the incretin effect (Hücking et al., 2008; Kim, Tfayli, Bacha, Lee, Michaliszyn, et al., 2020). Given that the response of β-cell function, but not insulin sensitivity, differentiated INT and UCC groups, it stands to reason that lifestyle-induced improvements in β-cell function resulted from other factors that influence the OGTT beyond insulin sensitivity.

Other lifestyle interventions that were not specifically modeled after the DPP have demonstrated improvements in insulin sensitivity among youth with overweight or obesity (Balagopal, George, Patton, et al., 2005; Huang et al., 2014; Lira et al., 2012; Miranda et al., 2014; Peña et al., 2020; Roberts et al., 2013; Roth et al., 2011; Shaibi et al., 2012; Soltero et al., 2018). In regard to lifestyle intervention effects on β-cell function among high-risk youth, the evidence is limited (Savoye et al., 2014). The Yale Bright Bodies lifestyle intervention demonstrated non-significant but greater average increases in oDI (4.7 unit increase) compared to the 1.1 unit increase following lifestyle intervention in the present study. Some distinctions of Yale Bright Bodies were the broader standard errors compared to our oDI analysis, differences in insulin measurement methods, and a slightly younger population at higher risk for T2D based on baseline characteristics. The DPP in adults demonstrated improvements in oDI and reductions in T2D risk (Kitabchi et al., 2005; Knowler et al., 2002); however, these findings should be interpreted with caution given the hyperresponsiveness of β-cell insulin secretion among youth compared to adults (Arslanian et al., 2021). Interestingly, two landmark trials that tested medication regimens, including insulin therapy, have failed to support the efficacy

on β-cell preservation among youth with prediabetes or T2D (Consortium, 2018; Zeitler et al., 2012), illuminating the severity of this disease among high-risk pediatric populations. Hence, our findings that lifestyle intervention induced improvements in β-cell function compared to usual care are optimistic.

Interestingly, usual care led to similar increases in insulin sensitivity that were not different compared to lifestyle intervention. The overarching framework for this work was informed by an expanded Ecodevelopmental Model that considers multiple levels (i.e., individual, family, community, and culture) of influence on T2D risk reduction among Latino youth (Castro et al., 2009). To this end, our long-standing collaboration with community stakeholders informed the design of the trial that included a usual care control group rather than a true control condition. The "usual care" was intended to mirror care provided to adolescents with obesity by our collaborating children's hospital, following standard guidelines for treating pediatric obesity (Cardel et al., 2020) and prediabetes (Magge et al., 2020). The rationale for this approach was to consider the ethics of randomizing youth with prediabetes to a true control condition given the potential for conversion to frank T2D (Weiss et al., 2005), and to address the limited access to diabetes prevention services for low-income Latino youth in the local community and other barriers to health care (Flores & Vega, 1998). These findings of increases in insulin sensitivity among both groups may support the notion that providing access to diabetes prevention services, including usual care, may be perceived as added benefit and motivation to adopt healthy behaviors that reduce risk of T2D.

Compared to the present study, Yale Bright Bodies demonstrated a larger magnitude of reductions in 2-hr glucose levels following six months of lifestyle intervention (-27 mg/dL) as compared to standard clinical care (-10 mg/dL) (Savoye et al., 2014). A key distinction between the Yale Bright Bodies intervention and ours was their focus on weight management and incentivizing weight loss after weekly weigh-ins of youth participants. In contrast, our curriculum considers both culture and biology, rather than weight loss per se, and emphasizes specific changes in behaviors and proximal T2D risk factors where participants are provided the results of their OGTT during intervention sessions to anchor the conversation around diabetes and health (Shaibi et al., 2012). This approach acknowledges that reductions in T2D risk factors among youth may occur in the absence of weight loss (Shaibi et al., 2015), which may be a particularly relevant strategy when tailoring diabetes prevention efforts for minority populations (Mezuk & Allen, 2021). Further, although we found no differences in 2-hr glucose changes between groups, it is important to note the greater lowering effect of lifestyle intervention on 2-hr glucose as demonstrated by the more negative 95% confidence intervals of the differences in changes between INT and UCC (-20 mg/dL to 5 mg/dL). This effect between INT and UCC may have been masked by larger standard errors in the UCC group due to a smaller sample size. It is possible that improvements in β-cell function following lifestyle intervention led to this greater lowering effect on 2-hr glucose. A previous study suggested that ~35-50% recovery is needed in oDI in order to observe clinically meaningful improvements in glucose tolerance (Kim, Tfayli, Bacha,

Lee, Gebara, et al., 2020). However, that study was cross-sectional and glucose tolerance was measured by glucose AUC whereas the present study assessed 2-hr glucose, thus making it challenging to make comparisons.

The targeted health behaviors through lifestyle intervention included increased physical activity and adopting healthy dietary changes. Physical activity interventions, particularly in the form of exercise, have demonstrated increases in insulin sensitivity and improvements in β-cell function (C. L. Davis et al., 2012; J. N. Davis et al., 2012; Lee et al., 2012; Lee et al., 2019; Shaibi et al., 2006). Furthermore, increases in fiber intake (Garcia et al., 2007; Mao, 2021; Weickert & Pfeiffer, 2018) and a healthy balanced diet that includes plant-based foods, fruits and healthy fats (i.e., Mediterranean diet) (Misciagna et al., 2017; Ryan et al., 2013) have demonstrated improvements in insulin sensitivity with few studies having demonstrated improvements in β-cell function following plant-based diets (Kahleova et al., 2011; Kahleova et al., 2018; Kahleova et al., 2019). It is possible that the greater improvements in β-cell function following lifestyle intervention are explained by greater increases in physical activity and/or improvements in dietary changes compared to usual care. However, biologically implausible physical activity data and incomplete dietary data in our dataset prevented their inclusion in the analysis.

The present study is the first, to our knowledge, to rigorously evaluate the efficacy of a culturally-grounded lifestyle intervention aimed at preventing diabetes in Latino youth with prediabetes, but the focus on Latino youth as an underrepresented sub-

group limits the generalizability to other high-risk pediatric populations. Estimates of insulin sensitivity and β-cell function are not the gold-standard approaches but have been validated against gold standard methods among youth with obesity (Sjaarda et al., 2012; Yeckel et al., 2004). Furthermore, regression to the mean may have influenced improvements in outcomes, including insulin sensitivity and 2-hr glucose thus limiting conclusions on a true treatment effect. However, this argument is unlikely given the differentiations in β-cell function response which uses the same glucose and insulin values from OGTT as the measures for insulin sensitivity and glucose tolerance. Lastly, physical activity and dietary changes were not analyzed due to either implausible data or an incomplete dataset.

In summary, lifestyle intervention led to significant improvements in β-cell function as compared to usual care, while both INT and UCC led to improvements in insulin sensitivity among Latino youth with prediabetes and obesity. However, change in 2-hr glucose levels were not significantly different between groups. How to expand T2D prevention efforts for high-risk youth with prediabetes to meet the growing demands among underserved communities warrants additional consideration.

# CHAPTER 5: STUDY III

# EFFECTS OF A DIABETES PREVENTION PROGRAM ON PRO- AND ANTI-INFLAMMATORY FACTORS AMONG LATINO YOUTH WITH PREDIABETES

## *INTRODUCTION*

T2D is a chronic inflammatory disease that can be prevented or delayed among adults with prediabetes following intensive lifestyle intervention as demonstrated by the United States (U.S.) Diabetes Prevention Program (DPP) (Knowler et al., 2002). In addition to reducing the risk of T2D, the U.S. DPP and adapted models have supported significant increases in anti-inflammatory marker adiponectin and reductions in pro-inflammatory markers, IL-6 and TNF-α (Gokulakrishnan et al., 2017; Mather et al., 2008; Miller et al., 2014). However, no studies to our knowledge have examined the response of pro- and anti-inflammatory markers to an adapted DPP among youth with prediabetes.

Other lifestyle intervention studies not specifically modeled after the U.S. DPP have assessed changes in inflammatory markers. However, these studies have focused predominantly on CRP and adiponectin (Balagopal, George, Patton, et al., 2005; Balagopal, George, Yarandi, et al., 2005; Blüher et al., 2014; Cambuli et al., 2008; Chae et al., 2010; Fu et al., 2007; Gokulakrishnan et al., 2017; Huang et al., 2014; Izadpanah et al., 2012; Kelishadi et al., 2008; Lira et al., 2012; Marti et al., 2018; Park et al., 2007; Pejsova et al., 2019; Rambhojan et al., 2015; Roberts et al., 2013; Roth et al., 2011; Rynders et al., 2012; Siegrist et al., 2013; Vos et al., 2011) with less attention to other

relevant adipokines and chemokines that are linked to obesity T2D risk factors, including monocyte chemoattractant protein-1 (MCP-1), interleukin-10 (IL-10), and interleukin-1 receptor antagonist (IL-1ra) (Dorneles et al., 2016; Parish et al., 2016; Shapouri-Moghaddam et al., 2018). It is critical to understand the response of key pro- and anti-inflammatory markers to lifestyle intervention and how these markers are associated with T2D risk factors following lifestyle intervention.

Therefore, the purpose of this study was two-fold: 1) to examine the effects of a diabetes prevention lifestyle intervention on pro- and anti-inflammatory markers among Latino youth with prediabetes and obesity compared to usual care, and 2) to explore whether pro- and anti-inflammatory markers are associated with insulin sensitivity, β-cell function, and glucose tolerance following lifestyle intervention or usual care.

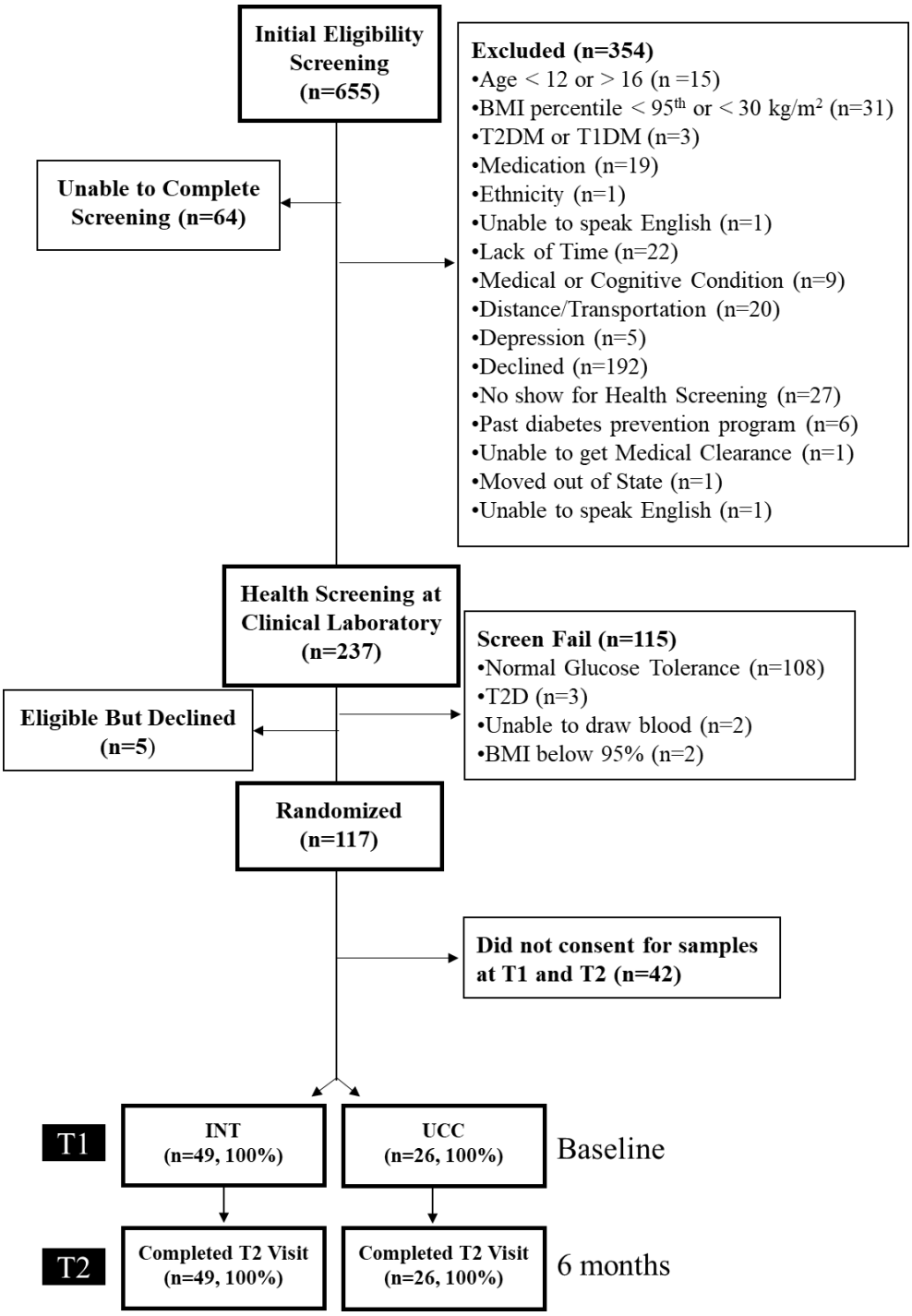
*METHODS*

*Participants.* Latino youth with prediabetes and obesity were recruited and enrolled into a larger NIH-funded randomized control trial (NCT02615353) that enrolled 117 youth. Specific inclusion criteria were as follows: 1) self-reported Latino descent, 2) ages 12-16 years, 3) BMI%$\geq 95^{th}$ for age and sex, and 4) prediabetes as defined by HbA1c 5.7-6.4%, fasting glucose 100-125 mg/dL, or 2-hr glucose 120-199 mg/dL following a 75-g oral glucose tolerance test (OGTT). Youth were excluded if they were 1) taking medication(s) or diagnosed with a condition that influences carbohydrate metabolism, physical activity, and/or cognition, 2) met criteria for T2D (fasting glucose≥126 mg/dL,

HbA1c≥6.5%, or 2-hr glucose≥200 mg/dL), 3) recently hospitalized (within previous two months), 4) currently enrolled in (or within 6 months) a formal weight loss program, or 5) an uncontrolled mental health condition.

Given that the present study was a sub-analysis under a parent study, only youth of parent(s) / guardian(s) who provided consent for additionally stored serum samples and had data at T1 and T2 were included in the present analysis (Figure 9). This study was approved by the Arizona State University (ASU) Institutional Review Board and is in accordance with the Declaration of Helsinki. Youth provided written assent, and parents provided written consent prior to study participation.

**Figure 9**. CONSORT Flow Diagram



*Study Design.* This study was a secondary analysis as part of a two-arm parallel randomized control trial testing the efficacy of a six-month diabetes prevention lifestyle intervention (INT) against a usual care control (UCC) condition (Soltero et al., 2017) Data were collected at baseline (T1) and at six months (T2).

*Recruitment.* Participants were recruited through local schools, community organizations, churches, and media outlets tailored to the local Latino community (Vander Wyst et al., 2020). Research personnel conducted an initial phone screen with interested individuals to confirm age, Latino descent, an estimate of BMI and to provide a thorough description of study participation. Thereafter, interested individuals scheduled a health screening visit to determine study eligibility.

*Health Screening.* Participants arrived at the ASU clinical research unit after an overnight fast. Height was measured to the nearest 0.1 cm using a portable stadiometer (SECA 213; SECA North America, Chino, California) and weight was measured to the nearest 0.1 kg using an electronic scale (TBF300A; Tanita Corporation of America, Arlington Heights, Illinois). Body mass index (BMI) and BMI percentiles were calculated for age and sex using the CDC growth charts. To screen for eligibility, blood samples were collected and analyzed by a CLIA-certified laboratory to assess HbA1c and fasting glucose followed by a 75-g oral glucose tolerance test (OGTT) to assess 2-hr glucose concentrations. These clinical lab results were reviewed by the study physician, returned to study participants, and used to anchor conversations about diabetes risk in

lifestyle intervention or usual care sessions. Participants meeting eligibility criteria were scheduled for their T1 visit within 4 weeks of their screening.

*T1-T2 Study Visits:* Participants returned to the ASU clinical research unit following an overnight fast for assessment of height, weight, and waist circumference, resting heart rate, seated blood pressure, and total body composition by dual x-ray absorptiometry (DEXA, Lunar iDXA, GE Healthcare). Insulin sensitivity and glucose tolerance were measured via a multiple sample 2-hr OGTT with glucose and insulin concentrations measured at fasting and every 30 minutes. Samples collected for measurement of glucose and insulin at T1 through T3 were stored at -80°C and analyzed in batches by research laboratories at the end of the study. Additional serum samples were collected and stored at -80°C for further analysis of inflammatory biomarkers.

*Biomarker Assessment*. Inflammatory markers IL-6, MCP-1, IL-10, and IL-1ra were measured in serum using mesoscale V-PLEX technologies (Meso Scale Discovery, Rockville, MD). A 96-well assay plate is coated with linkers that are assigned to each biomarker, or analyte (IL-6, MCP-1, IL-10, IL-1ra). An antibody bound to the respective linkers captures the target analyte before a detection antibody is bound to each analyte. The mesoscale device uses electrochemiluminescence to measure the concentrations of each analyte in pg/mL. When interpreting the results, its should be noted that IL-10 was detected at very low concentrations of its standard curve with 95% being detected under the lower detection limit of assay standard curves. TNF-α was analyzed through mesoscale U-PLEX technologies which did not require the step to coat the plate with

linkers given its specificity to TNF-α. HMW Adpn was measured in serum using an enzyme-linked immunosorbent assay (Salem, NH) which similarly uses antibodies to capture HMW Adpn and the other antibody as a detector during analysis. HMW Adpn was measured by spectrophotometry at 450nm.

*T2D risk factors*. Insulin sensitivity was estimated by the whole-body insulin sensitivity index (WBISI). The WBISI was generated from insulin (plasma, ALPCO, Salem, NH) and glucose (plasma, cobas c111 analyser, Roche Diagnostics, Indianapolis, IN) concentrations during the OGTT and has been validated among youth with obesity (Yeckel et al., 2004). Fasting, 30', 60', 90', and 120' insulin and glucose concentrations are inserted into a formula, $\frac{10{,}000}{\sqrt{I_0 \times G_0 \times Mean(I_0, I_{30}, I_{60}, I_{90}, I_{120}) \times Mean(G_0, G_{30}, G_{60}, G_{90}, G_{120})}}$, to generate a WBISI score where higher scores correspond to increased insulin sensitivity levels. Insulin secretion was estimated by the insulinogenic index (IGI = $\Delta G_{30}$-$G_0$ / $\Delta I_{30}$-$I_0$), and β-cell function was estimated by the oral disposition index (oDI = insulin sensitivity x insulin secretion) (Sjaarda et al., 2012). Glucose tolerance was measured by 2-hr post-challenge glucose concentrations during the OGTT. Body composition assessment included total fat mass, total lean mass, and body fat percent.

*Intervention Group - Lifestyle*. The lifestyle intervention included 1 day/week of nutrition and health education with behavior change skills training and 3 days/week of physical activity. Health education sessions were delivered by bilingual, bicultural community health educators from a local community clinic to groups of 8-10 families

and promoted the adoption of a healthy balanced diet, including reducing saturated fat intake, added sugars, and sugar-sweetened beverages, managing portion sizes, and increasing intake of fiber, fruit, and vegetables. Participants set weekly individual health behavior goals using the Specific, Measurable, Attainable, Relevant, and Timely (SMART) goal framework. Family discussions included identifying roles for eating and meal preparation at home, discussing family meals, and practicing mindfulness and respect of one another. Physical activity was delivered by YMCA instructors twice per week for 60 minutes/session. Physical activity curriculum included circuit training, sports activities (e.g., basketball, soccer), agility and cardiovascular exercises so that average target heart rates per session were ≥150 beats per minute. A third day of physical activity was promoted and monitored by instructors on a weekly basis to complete a minimum of 180 minutes of moderate-to-vigorous physical activity per week.

*Usual Care Control (UCC) Group*. Participants randomized to UCC met with a pediatric endocrinologist and a bilingual, bicultural registered dietitian to discuss laboratory results and develop SMART goals for making healthy lifestyle changes. These visits followed T1 and T2 visits. The UCC group was offered an abridged version of the lifestyle intervention after completion of the study.

*Analytical Approach.* Baseline characteristics between groups were compared using independent t-tests (continuous variables) and chi-square tests (categorical variables) with IBM SPSS 28.0.1 (Chicago, IL). Changes in outcomes were compared between groups using covariance pattern models in Mplus 8.7 (Los Angeles, CA) which

assess the difference in changes in outcomes from T1 to T2. Full information maximum likelihood (FIML) was used to account for missing data. Auxiliary variables were not included given their lack of efficiency in models with small sample sizes (Savalei, 2009). Data are presented as mean±SD, FIML-adjusted mean±SE, or FIML-adjusted ΔMean±95%CI when appropriate.

*RESULTS*

Seventy-five Latino youth who were enrolled into the larger trial (Soltero et al., 2017) were included in the present analysis. Baseline characteristics are described in Table 10 with randomization group comparisons. There were no significant differences in diabetes risk factors or inflammatory markers between INT and UCC (all $p>0.05$).

**Table 10**. Baseline Characteristics

| Parameter | All (n=75) | INT (n=46) | UCC (n=29) | p-value |
|---|---|---|---|---|
| Age, y | 13.4±1.4 | 13.5±1.4 | 13.4±1.5 | 0.898 |
| BMI, kg/m$^2$ | 33.2±5.6 | 32.6±4.5 | 34.1±6.9 | 0.242 |
| BMI-z | 2.2±0.3 | 2.2±0.3 | 2.3±0.4 | 0.424 |
| WC, cm | 106±14 | 104±11 | 108±17 | 0.135 |
| Fat mass, kg | 38.8±12.4 | 41.1±15.7 | 37.5±9.9 | 0.231 |
| A1C, % | 5.6±0.3 | 5.6±0.3 | 5.6±0.3 | 0.862 |
| Fasting Glucose, mg/dL | 102±7 | 101±7 | 102±7 | 0.369 |
| 2-hr Glucose, mg/dL | 143±29 | 143±27 | 144±31 | 0.853 |
| WBISI | 1.8±1.2 | 1.8±1.2 | 1.7±1.2 | 0.746 |
| oDI | 5.0±4.1 | 5.0±2.6 | 5.1±5.7 | 0.888 |
| IL-6, pg/mL | 2.3±1.8 | 2.0±1.6 | 2.8±2.1 | 0.087 |
| TNF-α, pg/mL | 1.7±0.5 | 1.7±0.5 | 1.6±0.4 | 0.704 |
| MCP-1, pg/mL | 648±272 | 655±249 | 637±308 | 0.783 |
| HMW Adpn, ug/mL | 1.7±1.6 | 1.9±1.9 | 1.4±0.6 | 0.161 |
| IL-10, pg/mL | 0.6±1.0 | 0.7±1.3 | 0.5±0.5 | 0.58 |
| IL-1ra, pg/mL | 120±98 | 107±79 | 140±120 | 0.159 |

INT = Intervention group; UCC: Usual Care Control group
BMI: body mass index; BMI-z: BMI z-score; WC: waist circumference, A1C: hemoglobin A1C; WBISI: whole-body insulin sensitivity index; oDI: oral disposition index; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; MCP-1: monocyte chemoattractant protein-1; HMW Adpn: high molecular weight adiponectin; IL-10: interleukin-10; IL-1ra: interleukin-1 receptor antagonist

Given that this was an analysis of the sub-sample analysis from a larger study, the primary and secondary outcomes are presented in Table 11 among this specific cohort of 75 youth. Insulin sensitivity (WBISI) was significantly increased within both INT (39%, $p=0.009$) and UCC (47%, $p=0.027$) with no differences between groups (interaction, $p>0.05$). There were no significant differences (interaction, $p>0.05$) in oDI following INT (12%, $p=0.347$) or UCC (0%, $p=0.909$). Similarly, no significant reductions in 2-hr glucose concentrations were observed (interaction, $p>0.05$) between INT (-7 mg/dL, $p=0.075$) and UCC (-6 mg/dL, $p=0.307$). Weight and lean mass significantly increased following both INT and UCC with no differences between groups (interactions, $p>0.05$), and no other differences in changes of additional outcomes were observed between INT and UCC.

**Table 11**. Changes in primary and secondary outcomes within and between INT and UCC groups from T1-T2 in this cohort (n=75)

| | Usual Care Control | | | Intervention | | | Treatment Effect |
|---|---|---|---|---|---|---|---|
| **Parameter** | ***n*** | **T1** | **T2** | ***n*** | **T1** | **T2** | **ΔT2-T1 (95%CI) p-value** |
| WBISI | 29 | 1.7±0.2 | 2.5±0.5 **p=0.027** | 45 | 1.8±0.2 | 2.5±0.4 **p=0.009** | -0.2 (-1.1, 0.7) p=0.899 |
| oDI | 28 | 4.1±0.4 | 4.1±0.4 0.909 | 45 | 4.9±0.4 | 5.5±0.5 p=0.347 | 0.5 (-0.9, 1.8) p=0.501 |
| 2-h Glucose | 29 | 144±6 | 138±5 p=0.307 | 46 | 143±3 | 136±4 p=0.075 | -1 (-16, 13) p=0.848 |
| Fasting Glucose | 29 | 102±1 | 101±1 p=0.268 | 46 | 101±1 | 99±1 p=0.098 | -0.4 (-4, 3) p=0.218 |
| HbA1c | 29 | 5.6±0.05 | 5.7±0.10 p=0.152 | 46 | 5.6±0.04 | 5.6±0.03 p=0.263 | -0.1 (-0.2, 0.008) p=0.070 |
| Weight | 29 | 91.5±4.3 | 97.5±3.8 **p=0.010** | 46 | 88.0±2.8 | 92.1±2.1 **p=0.003** | -1.2 (-3.0, 0.6) p=0.195 |
| BMI | 29 | 34.1±1.3 | 34.5±1.3 p=0.075 | 46 | 32.6±0.7 | 32.7±0.7 p=0.666 | -0.3 (-0.9, 0.3) p=0.462 |
| BMI-z | 29 | 2.3±0.07 | 2.3±0.08 p=0.505 | 46 | 2.2±0.04 | 2.2±0.05 **p=0.039** | -0.02 (-0.09, 0.04) p=0.409 |
| Fat Mass | 29 | 41.2±2.8 | 41.8±2.7 p=0.342 | 46 | 37.5±1.5 | 36.8±1.7 p=0.135 | -1.3 (-2.9, 0.2) p=0.099 |
| Lean Mass | 29 | 42.9±1.7 | 44.9±1.6 **p<0.001** | 46 | 43.4±1.4 | 45.6±1.5 **p<0.001** | 0.2 (-0.7, 1.1) p=0.621 |
| Body Fat % | 29 | 46.9±1.0 | 46.3±1.1 p=0.180 | 46 | 45.0±0.6 | 43.3±0.7 **p<0.001** | -1.06 (-2.13, -0.01) p=0.052 |
| Fasting Insulin | 29 | 23.6±2.0 | 21.5±2.3 p=0.254 | 46 | 22.0±1.7 | 18.8±1.5 **p=0.039** | -1.0 (-5.8, 3.8) p=0.688 |
| IGI | 29 | 3.1±0.3 | 3.1±0.4 p=0.890 | 45 | 3.4±0.3 | 3.1±0.4 p=0.263 | -0.2 (-1.1, 0.6) p=0.612 |

**Bolded** font indicates statistical significance at 0.05 alpha level

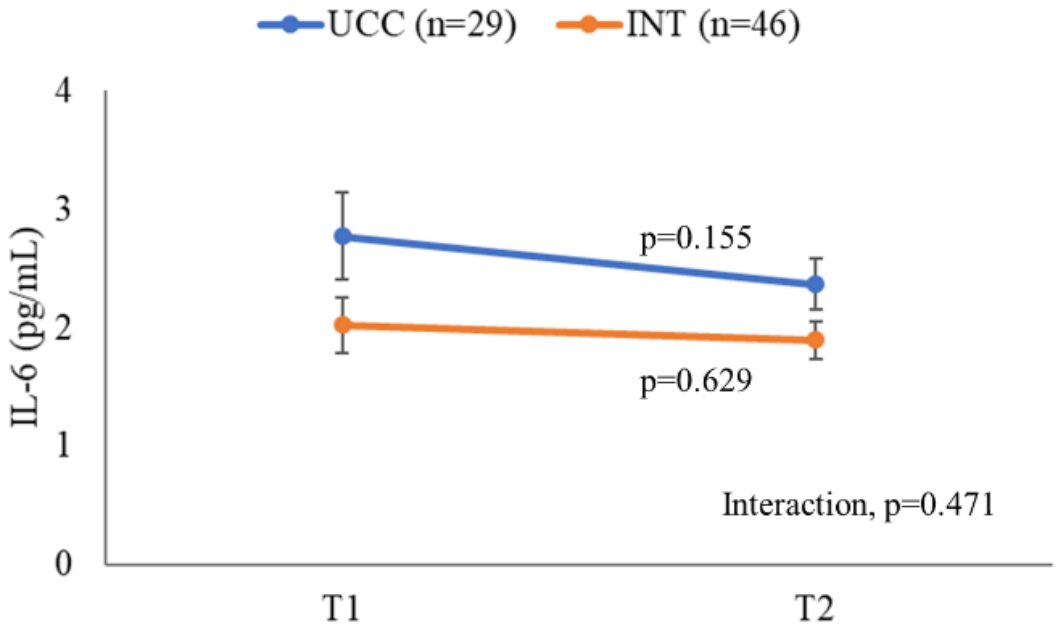
Data under T1 and T2 columns are presented as FIML-adjusted Mean±SE.

IGI: insulinogenic index; oDI: oral disposition index; HbA1c: hemoglobin A1C

Treatment Effect column displays FIML-adjusted differences in changes (meanΔ±95%CI) in outcomes between INT and UCC from T1-T2.

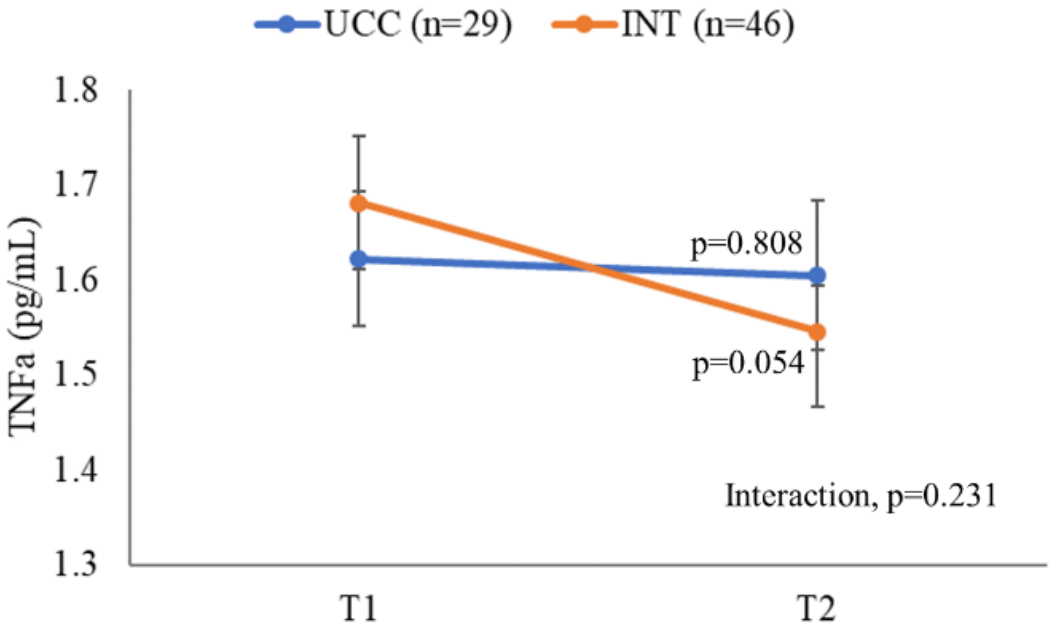
Changes in pro- and anti-inflammatory markers are illustrated in Figures 10-15 with raw data presented in Table 12. Changes in IL-6 (-9%), TNF-α (-12%), or MCP-1 (5%) following INT were not significantly different (interactions, $p>0.05$) than changes seen in UCC (-14%, 0%, 5%, respectively). All three anti-inflammatory markers were significantly reduced within the INT group, including HMW Adpn (-11%), IL-10 (-57%), and IL-1ra (-17%); however, these changes were not significantly different (interactions, $p>0.05$) than the changes observed among UCC (-7%, 0%, and -8%).

**Figure 10**. Changes in IL-6 within and between INT and UCC.



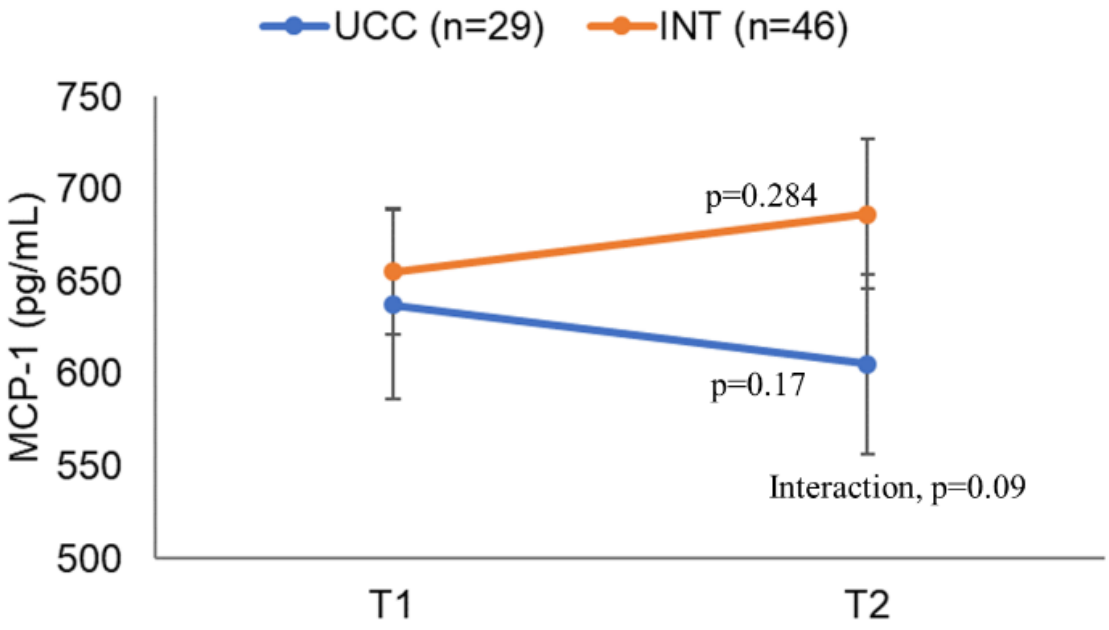

Data are presented as Mean±SE

**Figure 11**. Changes in TNF-α within and between INT and UCC.



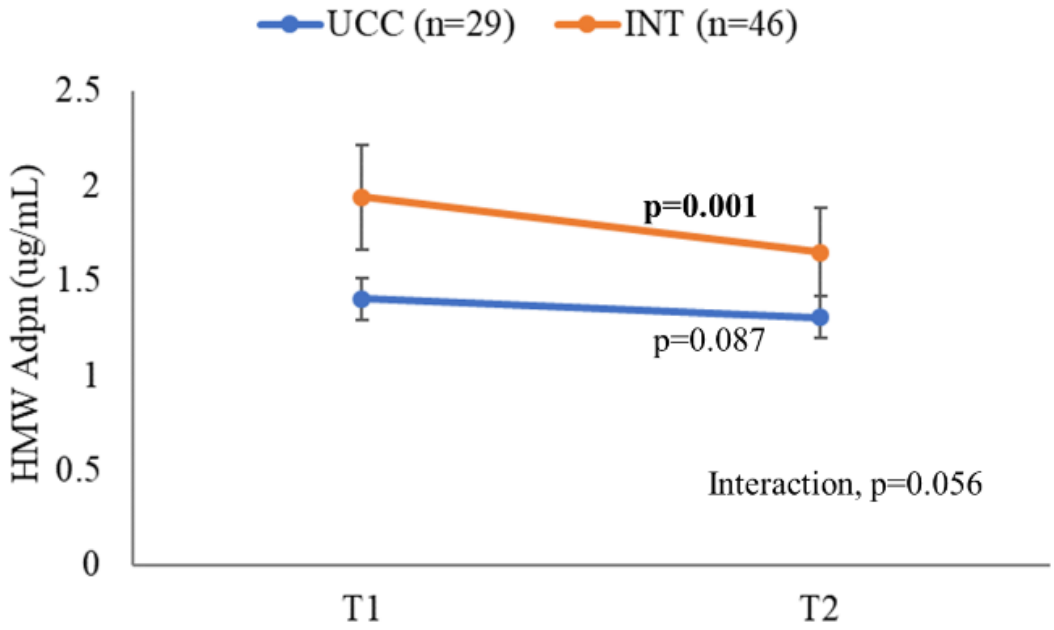

Data are presented as Mean±SE

**Figure 12**. Differences in changes in MCP-1 within and between INT and UCC.



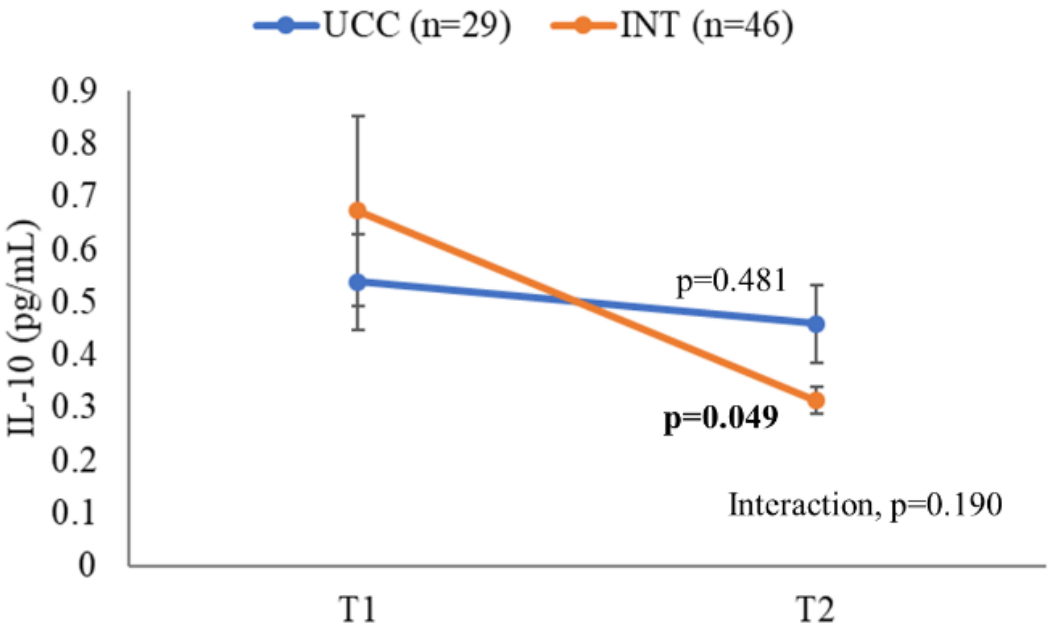

Data are presented as Mean±SE

**Figure 13**. Differences in changes in HMW Adpn within and between INT and UCC.



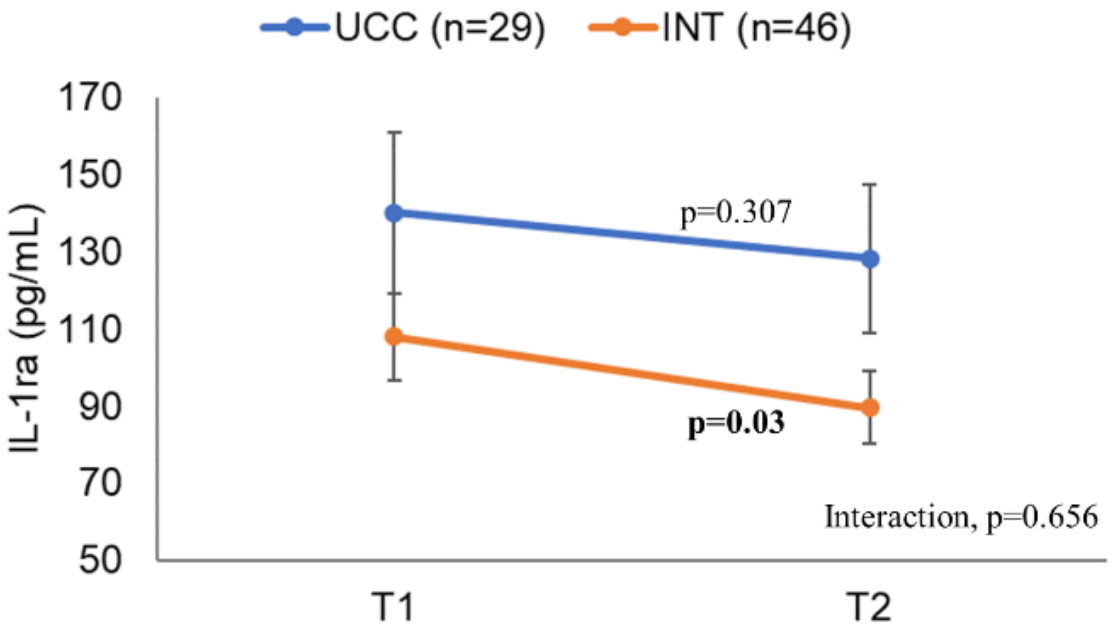

Data are presented as Mean±SE

**Figure 14**. Differences in changes in IL-10 within and between INT and UCC.




Data are presented as Mean±SE

**Figure 15**. Differences in changes in IL-1ra within and between INT and UCC.




Data are presented as Mean±SE

**Table 12**. Changes in inflammatory outcomes within and between INT and UCC groups from T1-T2.

| | Usual Care Control | | | Intervention | | | Treatment Effect |
|---|---|---|---|---|---|---|---|
| **Parameter** | ***n*** | **T1** | **T2** | ***n*** | **T1** | **T2** | **ΔT2-T1 (95%CI) p-value** |
| IL-6 | 26 | 2.8±0.4 | 2.4±0.2 p=0.155 | 49 | 2.0±0.2 | 1.9±0.2 p=0.629 | 0.3 (-0.5, 1.0) p=0.471 |
| TNF-α | 26 | 1.6±0.07 | 1.6±0.08 p=0.795 | 49 | 1.7±0.07 | 1.5±0.05 p=0.054 | -0.1 (-0.3, 0.1) p=0.231 |
| MCP-1 | 26 | 637±51 | 605±48 p=0.170 | 49 | 655±34 | 686±41 p=0.284 | 63 (-10, 136) p=0.090 |
| HMW Adpn | 26 | 1.4±0.1 | 1.3±0.1 p=0.087 | 49 | 1.9±0.3 | 1.7±0.2 **p=0.001** | -0.2 (-2.2, 1.8) p=0.056 |
| IL-10 | 26 | 0.5±0.09 | 0.5±0.07 p=0.481 | 49 | 0.7±0.02 | 0.3±0.03 **p=0.049** | -0.3 (-0.7, 0.1) p=0.190 |
| IL-1ra | 26 | 1,401±209 | 1,282±194 p=0.307 | 49 | 1,080±113 | 896±93 **p=0.030** | -64 (-346, 218) p=0.656 |

**Bolded** font indicates significance at 0.05 alpha level

Data under T1 and T2 columns are presented as FIML-adjusted Mean±SE. Bolded data are significant at p<0.05. Treatment Effect column displays FIML-adjusted differences in changes (meanΔ±95%CI) in outcomes between INT and UCC from T1-T2.

*DISCUSSION*

Despite numerous studies that support reductions of T2D risk factors following lifestyle intervention among high-risk youth (Balagopal, George, Patton, et al., 2005; Huang et al., 2014; Miranda et al., 2014; Peña et al., 2020; Roberts et al., 2013; Shaibi et al., 2012; Soltero et al., 2018), the mechanisms have yet to be established. Our findings demonstrated no significant differences in changes of pro- (IL-6, TNF-α, MCP-1) or anti-inflammatory (HMW Adpn, IL-10, IL-1ra) markers following lifestyle intervention as compared to usual care among Latino youth with prediabetes and obesity. Although not significant, these findings add to the body of knowledge by assessing an array of relevant

pro- and anti-inflammatory markers in response to a culturally-grounded and adapted DPP for high-risk Latino youth and may inform the refinement of future interventions.

The Yale Bright Bodies study was the only other randomized control trial, to our knowledge, that tested an adapted DPP among youth with prediabetes but did not report on inflammatory outcomes (Savoye et al., 2014). Other lifestyle intervention studies among youth with overweight or obesity not specifically modeled after the DPP have demonstrated increases in adiponectin (Balagopal, George, Yarandi, et al., 2005; Cambuli et al., 2008; Lee et al., 2010; Mayerhofer et al., 2020; Rambhojan et al., 2015; Roche et al., 2019; Roth et al., 2011), no changes in IL-10 (Lira et al., 2011; Mager et al., 2015; Roberts et al., 2013), reductions in IL-6 (Balagopal, George, Patton, et al., 2005; Mager et al., 2015; Rosenbaum et al., 2007), and conflicting results on TNF-α (Hasson et al., 2012; Lira et al., 2011; Roberts et al., 2013; Rosenbaum et al., 2007; Roth et al., 2011). It is clear that more focus is needed on non-traditional chemokines and cytokines that have emerged as biomarkers relevant to T2D, including MCP-1 (Parish et al., 2016) and IL-1ra (Seppä et al., 2018; Stoppa-Vaucher et al., 2012). A further limitation of these studies is the predominance of quasi-experimental designs with no control groups. Of the randomized control trials that have been conducted, two studies failed to demonstrate significant changes in total adiponectin following lifestyle intervention compared to control groups, despite significant reductions in weight, adiposity, and C-reactive protein (established marker of systemic inflammation) and improvements in insulin sensitivity (Chae et al., 2010; Park et al., 2007). Another randomized control trial demonstrated

increases in total adiponectin with reductions in IL-6 following a lifestyle intervention that did not induce weight loss but significantly reduced fat mass and improved insulin sensitivity (Balagopal, George, Patton, et al., 2005; Balagopal, George, Yarandi, et al., 2005). Our results exhibited no significant differences in either of the inflammatory markers between INT and UCC groups. In the present study, both INT and UCC significantly increased insulin sensitivity levels, and our data suggest that these improvements are likely due to changes in factors beyond the inflammatory markers measured in the present study.

It has been established that 5-7% weight loss is a critical mediator of T2D prevention among adults with prediabetes (Hamman et al., 2006) which was accompanied by increases in adiponectin (Mather et al., 2008). However, such targets have not been established among youth, since unlike in adults, children and adolescents are still growing. In the present study, there were no significant differences between groups in changes in weight or other measures of adiposity. Given that unhealthy adipose tissue in obesity is the proposed source of increases in pro-inflammatory markers and reductions of anti-inflammatory markers, it is possible that targeting reductions in total, regional, or ectopic adiposity depots, and not necessarily weight, may yield significant changes in the inflammatory milieus.

Using surgical weight loss as a model, reductions in adiposity have been associated with improvements in pro- and anti-inflammatory markers in the pediatric population. Among adolescents with non-alcoholic steatohepatitis, laparoscopic sleeve

gastrectomy led to significant reductions in serum pro-inflammatory markers, IL-6, IL-1β, and TNF-α with significant increases in adiponectin at one-year follow-up (Black, 2020). These changes were accompanied by decreases in visceral adipose tissue adipocyte size, reductions in visceral adipose tissue inflammation, and improvements in liver histology. Furthermore, reductions in IL-6 and IL-1β were associated with reductions in adipocyte size at one year (Black, 2020). These findings were corroborated by data analyzed from the Teen-LABS (Longitudinal Assessment of Bariatric Surgery) study and the Adolescent Gastric Bypass and Diabetes Precursors Study which demonstrated reductions in IL-6 and increases in adiponectin following either Roux-en-Y or vertical sleeve gastrectomy (Kelly et al., 2016). The physiologic changes due to the expansion of adipocytes in obesity are associated with increases in infiltrating immune cells that secrete pro-inflammatory factors (Lee et al., 2014), decreases in anti-inflammatory macrophage phenotypes (Lumeng et al., 2007), and increased endoplasmic reticulum stress which is associated with the disruption of adiponectin secretion through the misfolding of its proteins (Hosogai et al., 2007; Liu & Liu, 2014). Therefore, the reductions in adipocyte size following weight loss surgery may be associated with physiological changes within adipose tissue that shifts the pro- and anti-inflammatory milieus towards homeostatic levels. The current lifestyle intervention targeted proximal T2D risk factors (i.e, insulin sensitivity glucose tolerance) and whether targeting reductions of adiposity in ectopic depots (i.e., liver, visceral fat) is needed to modify the pro- and anti-inflammatory milieus warrants further investigation.

This is the first study, to our knowledge, that has assessed the response of an array of obesity-related pro- and anti-inflammatory markers following a diabetes prevention program adapted for Latino youth with prediabetes. We appreciate that this study is not without limitations. Our study was underpowered given that this study leveraged stored biospecimens from a larger grant, and these data will support future work to appropriately power trials. Furthermore, WBISI and oDI are estimates of insulin sensitivity and β-cell function, respectively, and are not the gold standard; however, they have been validated against gold-standard methods in youth with obesity (Sjaarda et al., 2012; Yeckel et al., 2004). Lastly, the generalizability of results is limited to Latino youth.

In summary, lifestyle intervention had no effects on obesity-related pro- or anti-inflammatory markers among Latino youth with prediabetes and obesity as compared to usual care. Diabetes prevention lifestyle interventions that target the inflammatory milieus that are shifted by obesity may need further refinement.

# CHAPTER 6:

# SUMMARY AND CONCLUSIONS

Latino youth are disproportionately impacted by obesity and type 2 diabetes (T2D), compared to White youth. Lifestyle intervention is the first-line approach to diabetes prevention among adults with prediabetes. Only one other study to our knowledge has tested an adapted DPP among a youth cohort with prediabetes. Given that Latino youth have a 50% lifetime risk of developing T2D, there is an urgent need to develop and test pragmatic diabetes prevention lifestyle interventions among high-risk Latino youth that are scalable at large. Furthermore, the mechanisms by which lifestyle intervention reduces T2D risk factors has yet to be elucidated, and obesity-related pro- and anti-inflammatory factors stand as prime candidates.

The goals of this dissertation were two-fold: (1) to examine the associations of pro- and anti-inflammatory markers with insulin sensitivity, β-cell function, and glucose tolerance and (2) to examine the efficacy of a diabetes prevention program on T2D risk factors and pro- and anti-inflammatory markers among Latino youth with prediabetes and obesity as compared to usual care. A series of three studies (Studies I, II, and III) were conducted to fulfill the two aforementioned goals of this dissertation.

In Study I, we found that reduced high-molecular weight (HMW Adpn), increased monocyte chemoattractant protein (MCP-1), and increased interleukin-1 receptor antagonist (IL-1ra) predicted decreased insulin sensitivity and glucose tolerance, whereas only decreased HMW Adpn was associated with lower β-cell function among Latino

youth with prediabetes and obesity. These observed associations were independent of age, sex, and adiposity. These findings support previous work to suggest that adiponectin, MCP-1, and IL-1ra are associated with T2D risk; however, our hypothesis that IL-6, TNF-α, and IL-10 would predict insulin sensitivity, β-cell function, or glucose tolerance was not supported.

In Study II, we demonstrated that a culturally-grounded, community-based lifestyle intervention was efficacious in improving β-cell function compared to usual care. Interestingly, both lifestyle intervention and usual care groups increased insulin sensitivity levels with no differences between groups. Despite reductions in 2-hr glucose concentrations following lifestyle intervention, these changes were not significantly different than usual care. These findings of improvements in β-cell function are promising given the severity of T2D in youth, and especially since previous medication trials have failed to preserve β-cell function among high-risk youth and youth with T2D. The findings that both groups improved insulin sensitivity levels may support the notion that providing diabetes prevention services to high-risk Latino youth, including usual care, may lead to reductions in T2D risk.

In Study III, we found no significant differences in the changes of pro- or anti-inflammatory factors following lifestyle intervention compared to usual care. Analyses among the cohort of this study demonstrated increases in insulin sensitivity among both lifestyle intervention and usual care groups, suggesting these effects were not mediated by changes in the pro- and anti-inflammatory factors assessed. Furthermore, no

significant differences in weight or adiposity were observed between groups. It is possible that either reductions in levels of adiposity may be needed in order to observe significant changes in pro- and anti-inflammatory factors.

We appreciate that this dissertation is not without limitations. In Studies I, II, and III, the prioritization of Latino youth with prediabetes and obesity limits generalizability to other youth populations. The measures used for insulin sensitivity (whole body insulin sensitivity index) and β-cell function (oral disposition index) are not the gold standard but have been validated against gold standard measures. In Studies II and III, the lack of a "true" control group limits our conclusions. Lastly, Study III was a secondary analysis and thus was not powered to detect significant effects on the pro- and anti-inflammatory outcomes of interest.

Despite these limitations, this dissertation adds to the body of knowledge in the field of pediatric obesity and diabetes prevention. First, the prioritization of Latino youth, although limited in generalizability, increases the representation of this sub-group in clinical research and enhances our understanding of potential inflammatory markers to be targeted in future interventions. Furthermore, this study rigorously assessed the efficacy of a culturally-grounded, community-based lifestyle intervention that was pragmatically designed for expediting its translation into the real world. Studies I and III are novel to the field by including the assessment of intervention effects of traditionally studied as well as understudied pro- and anti-inflammatory markers in relation to T2D risk factors, including β-cell function among a high-risk Latino youth population.

REFERENCES

2020 Dietary Guidelines Advisory Committee, D. e. P. S. (2020). Dietary Patterns and Risk of Cardiovascular Disease: A Systematic Review. In. https://doi.org/NBK578519

Abate, N., & Chandalia, M. (2003). The impact of ethnicity on type 2 diabetes. *J Diabetes Complications*, *17*(1), 39-58. https://doi.org/10.1016/s1056-8727(02)00190-3

Ackermann, R. T., & O'Brien, M. J. (2020). Evidence and Challenges for Translation and Population Impact of the Diabetes Prevention Program. *Curr Diab Rep*, *20*(3), 9. https://doi.org/10.1007/s11892-020-1293-4

Acosta, J. R., Tavira, B., Douagi, I., Kulyté, A., Arner, P., Rydén, M., & Laurencikiene, J. (2019). Human-Specific Function of IL-10 in Adipose Tissue Linked to Insulin Resistance. *J Clin Endocrinol Metab*, *104*(10), 4552-4562. https://doi.org/10.1210/jc.2019-00341

Agarwal, C., Cohen, H. W., Muzumdar, R. H., Heptulla, R. A., Renukuntla, V. S., & Crandall, J. (2013). Obesity, hyperglycemia and endothelial function in inner city Bronx adolescents: a cross-sectional study. *Int J Pediatr Endocrinol*, *2013*(1), 18. https://doi.org/10.1186/1687-9856-2013-18

Aggarwal, B. B. (2000). Tumour necrosis factors receptor associated signalling molecules and their role in activation of apoptosis, JNK and NF-kappaB. *Ann Rheum Dis*, *59 Suppl 1*, i6-16. https://doi.org/10.1136/ard.59.suppl_1.i6

Ahima, R. S. (2006). Adipose tissue as an endocrine organ. *Obesity (Silver Spring)*, *14 Suppl 5*, 242S-249S. https://doi.org/10.1038/oby.2006.317

Akcan, N., Obaid, M., Salem, J., & Bundak, R. (2020). Evidence in obese children: contribution of tri-ponderal mass index or body mass index to dyslipidemia, obesity-inflammation, and insulin sensitivity. *J Pediatr Endocrinol Metab*, *33*(2), 223-231. https://doi.org/10.1515/jpem-2019-0106

Akdis, C. A., & Blaser, K. (2001). Mechanisms of interleukin-10-mediated immune suppression. *Immunology*, *103*(2), 131-136. https://doi.org/10.1046/j.1365-2567.2001.01235.x

Albright, A. (2012). The National Diabetes Prevention Program: From Research to Reality. *Diabetes Care Educ Newsl*, *33*(4), 4-7.

Alikaşifoğlu, A., Gönç, N., Özön, Z. A., Sen, Y., & Kandemir, N. (2009). The relationship between serum adiponectin, tumor necrosis factor-alpha, leptin levels

and insulin sensitivity in childhood and adolescent obesity: adiponectin is a marker of metabolic syndrome. *J Clin Res Pediatr Endocrinol*, *1*(5), 233-239. https://doi.org/10.4274/jcrpe.v1i5.233

Andes, L. J., Cheng, Y. J., Rolka, D. B., Gregg, E. W., & Imperatore, G. (2020). Prevalence of Prediabetes Among Adolescents and Young Adults in the United States, 2005-2016. *JAMA Pediatr*, *174*(2), e194498. https://doi.org/10.1001/jamapediatrics.2019.4498

Annibalini, G., Lucertini, F., Agostini, D., Vallorani, L., Gioacchini, A., Barbieri, E., . . . Stocchi, V. (2017). Concurrent Aerobic and Resistance Training Has Anti-Inflammatory Effects and Increases Both Plasma and Leukocyte Levels of IGF-1 in Late Middle-Aged Type 2 Diabetic Patients. *Oxid Med Cell Longev*, *2017*, 3937842. https://doi.org/10.1155/2017/3937842

Arslanian, S., El Ghormli, L., Bacha, F., Caprio, S., Goland, R., Haymond, M. W., . . . Group, T. S. (2017). Adiponectin, Insulin Sensitivity, β-Cell Function, and Racial/Ethnic Disparity in Treatment Failure Rates in TODAY. *Diabetes Care*, *40*(1), 85-93. https://doi.org/10.2337/dc16-0455

Arslanian, S. A., El Ghormli, L., Young Kim, J., Tjaden, A. H., Barengolts, E., Caprio, S., . . . Consortium, R. (2021). OGTT Glucose Response Curves, Insulin Sensitivity, and β-Cell Function in RISE: Comparison Between Youth and Adults at Randomization and in Response to Interventions to Preserve β-Cell Function. *Diabetes Care*. https://doi.org/10.2337/dc20-2134

American Diabetes Association (2019). 13. Children and Adolescents: . *Diabetes Care*, *42*(Suppl 1), S148-S164. https://doi.org/10.2337/dc19-S013

Aziz, Z., Absetz, P., Oldroyd, J., Pronk, N. P., & Oldenburg, B. (2015). A systematic review of real-world diabetes prevention programs: learnings from the last 15 years. *Implement Sci*, *10*, 172. https://doi.org/10.1186/s13012-015-0354-6

Azzu, V., Vacca, M., Virtue, S., Allison, M., & Vidal-Puig, A. (2020). Adipose Tissue-Liver Cross Talk in the Control of Whole-Body Metabolism: Implications in Nonalcoholic Fatty Liver Disease. *Gastroenterology*, *158*(7), 1899-1912. https://doi.org/10.1053/j.gastro.2019.12.054

Balagopal, P., George, D., Patton, N., Yarandi, H., Roberts, W. L., Bayne, E., & Gidding, S. (2005). Lifestyle-only intervention attenuates the inflammatory state associated with obesity: a randomized controlled study in adolescents. *J Pediatr*, *146*(3), 342-348. https://doi.org/10.1016/j.jpeds.2004.11.033

Balagopal, P., George, D., Yarandi, H., Funanage, V., & Bayne, E. (2005). Reversal of obesity-related hypoadiponectinemia by lifestyle intervention: a controlled,

randomized study in obese adolescents. *J Clin Endocrinol Metab*, *90*(11), 6192-6197. https://doi.org/10.1210/jc.2004-2427

Barrett, T., Jalaludin, M. Y., Turan, S., Hafez, M., Shehadeh, N., & Panel, N. N. P. T. D. G. E. (2020). Rapid progression of type 2 diabetes and related complications in children and young people-A literature review. *Pediatr Diabetes*, *21*(2), 158-172. https://doi.org/10.1111/pedi.12953

Barry, J. C., Simtchouk, S., Durrer, C., Jung, M. E., & Little, J. P. (2017). Short-Term Exercise Training Alters Leukocyte Chemokine Receptors in Obese Adults. *Med Sci Sports Exerc*, *49*(8), 1631-1640. https://doi.org/10.1249/MSS.0000000000001261

Benson, A. C., Torode, M. E., & Fiatarone Singh, M. A. (2008). Effects of resistance training on metabolic fitness in children and adolescents: a systematic review. *Obes Rev*, *9*(1), 43-66. https://doi.org/10.1111/j.1467-789X.2007.00388.x

Biscetti, F., Nardella, E., Cecchini, A. L., Flex, A., & Landolfi, R. (2020). Biomarkers of vascular disease in diabetes: the adipose-immune system cross talk. *Intern Emerg Med*, *15*(3), 381-393. https://doi.org/10.1007/s11739-019-02270-6

Bjornstad, P., Drews, K. L., Caprio, S., Gubitosi-Klug, R., Nathan, D. M., Tesfaldet, B., . . . Group, T. S. (2021). Long-Term Complications in Youth-Onset Type 2 Diabetes. *N Engl J Med*, *385*(5), 416-426. https://doi.org/10.1056/NEJMoa2100165

Black, D. D. (2020). Impact of Bariatric Surgery on Adipose Tissue and Liver Inflammation in Adolescents with Nonalcoholic Steatohepatitis. *J Pediatr*, *216*, 7-9. https://doi.org/10.1016/j.jpeds.2019.08.063

Blüher, S., Panagiotou, G., Petroff, D., Markert, J., Wagner, A., Klemm, T., . . . Mantzoros, C. S. (2014). Effects of a 1-year exercise and lifestyle intervention on irisin, adipokines, and inflammatory markers in obese children. *Obesity (Silver Spring)*, *22*(7), 1701-1708. https://doi.org/10.1002/oby.20739

Boutagy, N. E., McMillan, R. P., Frisard, M. I., & Hulver, M. W. (2016). Metabolic endotoxemia with obesity: Is it real and is it relevant? *Biochimie*, *124*, 11-20. https://doi.org/10.1016/j.biochi.2015.06.020

Brenner, C., Galluzzi, L., Kepp, O., & Kroemer, G. (2013). Decoding cell death signals in liver inflammation. *J Hepatol*, *59*(3), 583-594. https://doi.org/10.1016/j.jhep.2013.03.033

Breslin, W. L., Johnston, C. A., Strohacker, K., Carpenter, K. C., Davidson, T. R., Moreno, J. P., . . . McFarlin, B. K. (2012). Obese Mexican American children

have elevated MCP-1, TNF-α, monocyte concentration, and dyslipidemia. *Pediatrics*, *129*(5), e1180-1186. https://doi.org/10.1542/peds.2011-2477

Brown, B., Noonan, C., Harris, K. J., Parker, M., Gaskill, S., Ricci, C., . . . Gress, S. (2013). Developing and piloting the Journey to Native Youth Health program in Northern Plains Indian communities. *Diabetes Educ*, *39*(1), 109-118. https://doi.org/10.1177/0145721712465343

Burd, C., Gruss, S., Albright, A., Zina, A., Schumacher, P., & Alley, D. (2020). Translating Knowledge into Action to Prevent Type 2 Diabetes: Medicare Expansion of the National Diabetes Prevention Program Lifestyle Intervention. *Milbank Q*, *98*(1), 172-196. https://doi.org/10.1111/1468-0009.12443

Butler, A. M. (2017). Social Determinants of Health and Racial/Ethnic Disparities in Type 2 Diabetes in Youth. *Curr Diab Rep*, *17*(8), 60. https://doi.org/10.1007/s11892-017-0885-0

Böni-Schnetzler, M., Häuselmann, S. P., Dalmas, E., Meier, D. T., Thienel, C., Traub, S., . . . Donath, M. Y. (2018). β Cell-Specific Deletion of the IL-1 Receptor Antagonist Impairs β Cell Proliferation and Insulin Secretion. *Cell Rep*, *22*(7), 1774-1786. https://doi.org/10.1016/j.celrep.2018.01.063

Cambuli, V. M., Musiu, M. C., Incani, M., Paderi, M., Serpe, R., Marras, V., . . . Baroni, M. G. (2008). Assessment of adiponectin and leptin as biomarkers of positive metabolic outcomes after lifestyle intervention in overweight and obese children. *J Clin Endocrinol Metab*, *93*(8), 3051-3057. https://doi.org/10.1210/jc.2008-0476

Capel, F., Klimcáková, E., Viguerie, N., Roussel, B., Vítková, M., Kováciková, M., . . . Langin, D. (2009). Macrophages and adipocytes in human obesity: adipose tissue gene expression and insulin sensitivity during calorie restriction and weight stabilization. *Diabetes*, *58*(7), 1558-1567. https://doi.org/10.2337/db09-0033

Caprio, S. (2012). The oral disposition index: a valuable estimate of β-cell function in obese youth. *J Pediatr*, *161*(1), 3-4. https://doi.org/10.1016/j.jpeds.2012.02.013

Cardel, M. I., Atkinson, M. A., Taveras, E. M., Holm, J. C., & Kelly, A. S. (2020). Obesity Treatment Among Adolescents: A Review of Current Evidence and Future Directions. *JAMA Pediatr*, *174*(6), 609-617. https://doi.org/10.1001/jamapediatrics.2020.0085

Cartwright, K. (2021). Social determinants of the Latinx diabetes health disparity: A Oaxaca-Blinder decomposition analysis. *SSM Popul Health*, *15*, 100869. https://doi.org/10.1016/j.ssmph.2021.100869

Castro, F. G., Shaibi, G. Q., & Boehm-Smith, E. (2009). Ecodevelopmental contexts for preventing type 2 diabetes in Latino and other racial/ethnic minority populations. *J Behav Med*, *32*(1), 89-105. https://doi.org/10.1007/s10865-008-9194-z

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

Chae, H. W., Kwon, Y. N., Rhie, Y. J., Kim, H. S., Kim, Y. S., Paik, I. Y., . . . Kim, D. H. (2010). Effects of a structured exercise program on insulin resistance, inflammatory markers and physical fitness in obese Korean children. *J Pediatr Endocrinol Metab*, *23*(10), 1065-1072. https://doi.org/10.1515/jpem.2010.168

Chang, C. J., Jian, D. Y., Lin, M. W., Zhao, J. Z., Ho, L. T., & Juan, C. C. (2015). Evidence in obese children: contribution of hyperlipidemia, obesity-inflammation, and insulin sensitivity. *PLoS One*, *10*(5), e0125935. https://doi.org/10.1371/journal.pone.0125935

Chang, J. S., Chang, C. C., Chien, E., Lin, S. S., Cheng-Shiuan, T., Bai, C. H., & Chao, K. C. (2013). Association between interleukin 1β and interleukin 10 concentrations: a cross-sectional study in young adolescents in Taiwan. *BMC Pediatr*, *13*, 123. https://doi.org/10.1186/1471-2431-13-123

Chang, J. S., Li, Y. L., Lu, C. H., Owaga, E., Chen, W. Y., & Chiou, H. Y. (2014). Interleukin-10 as a potential regulator of hepcidin homeostasis in overweight and obese children: a cross-sectional study in Taiwan. *Nutrition*, *30*(10), 1165-1170. https://doi.org/10.1016/j.nut.2014.02.021

Chen, M. E., Aguirre, R. S., & Hannon, T. S. (2018). Methods for Measuring Risk for Type 2 Diabetes in Youth: the Oral Glucose Tolerance Test (OGTT). *Curr Diab Rep*, *18*(8), 51. https://doi.org/10.1007/s11892-018-1023-3

Chetboun, M., Abitbol, G., Rozenberg, K., Rozenfeld, H., Deutsch, A., Sampson, S. R., & Rosenzweig, T. (2012). Maintenance of redox state and pancreatic beta-cell function: role of leptin and adiponectin. *J Cell Biochem*, *113*(6), 1966-1976. https://doi.org/10.1002/jcb.24065

Choi, H. M., Doss, H. M., & Kim, K. S. (2020). Multifaceted Physiological Roles of Adiponectin in Inflammation and Diseases. *Int J Mol Sci*, *21*(4). https://doi.org/10.3390/ijms21041219

Chwee, J. Y., Khatoo, M., Tan, N. Y., & Gasser, S. (2016). Apoptotic Cells Release IL1 Receptor Antagonist in Response to Genotoxic Stress. *Cancer Immunol Res*, *4*(4), 294-302. https://doi.org/10.1158/2326-6066.CIR-15-0083

Clark, M. L., & Utz, S. W. (2014). Social determinants of type 2 diabetes and health in the United States. *World J Diabetes*, *5*(3), 296-304. https://doi.org/10.4239/wjd.v5.i3.296

Coimbra, S., Catarino, C., Nascimento, H., Inês Alves, A., Filipa Medeiros, A., Bronze-da-Rocha, E., . . . Belo, L. (2017). Physical exercise intervention at school improved hepcidin, inflammation, and iron metabolism in overweight and obese children and adolescents. *Pediatr Res*, *82*(5), 781-788. https://doi.org/10.1038/pr.2017.139

Consortium, R. (2018). Impact of Insulin and Metformin Versus Metformin Alone on β-Cell Function in Youth With Impaired Glucose Tolerance or Recently Diagnosed Type 2 Diabetes. *Diabetes Care*, *41*(8), 1717-1725. https://doi.org/10.2337/dc18-0787

Cruz, M., García-Macedo, R., García-Valerio, Y., Gutiérrez, M., Medina-Navarro, R., Duran, G., . . . Kumate, J. (2004). Low adiponectin levels predict type 2 diabetes in Mexican children. *Diabetes Care*, *27*(6), 1451-1453. https://doi.org/10.2337/diacare.27.6.1451

Cruz, P., & Granados, A. (2019). Type 2 Diabetes in Latino Youth: A Clinical Update and Current Challenges. *Curr Probl Pediatr Adolesc Health Care*, *49*(1), 16-22. https://doi.org/10.1016/j.cppeds.2018.11.008

da Luz, G., Frederico, M. J., da Silva, S., Vitto, M. F., Cesconetto, P. A., de Pinho, R. A., . . . De Souza, C. T. (2011). Endurance exercise training ameliorates insulin resistance and reticulum stress in adipose and hepatic tissue in obese rats. *Eur J Appl Physiol*, *111*(9), 2015-2023. https://doi.org/10.1007/s00421-010-1802-2

Dabelea, D., Mayer-Davis, E. J., Saydah, S., Imperatore, G., Linder, B., Divers, J., . . . Study, S. f. D. i. Y. (2014). Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA*, *311*(17), 1778-1786. https://doi.org/10.1001/jama.2014.3201

Dagdeviren, S., Jung, D. Y., Friedline, R. H., Noh, H. L., Kim, J. H., Patel, P. R., . . . Kim, J. K. (2017). IL-10 prevents aging-associated inflammation and insulin resistance in skeletal muscle. *FASEB J*, *31*(2), 701-710. https://doi.org/10.1096/fj.201600832R

Dagdeviren, S., Jung, D. Y., Lee, E., Friedline, R. H., Noh, H. L., Kim, J. H., . . . Kim, J. K. (2016). Altered Interleukin-10 Signaling in Skeletal Muscle Regulates Obesity-Mediated Inflammation and Insulin Resistance. *Mol Cell Biol*, *36*(23), 2956-2966. https://doi.org/10.1128/MCB.00181-16

Daniele, G., Guardado Mendoza, R., Winnier, D., Fiorentino, T. V., Pengou, Z., Cornell, J., . . . Folli, F. (2014). The inflammatory status score including IL-6, TNF-α, osteopontin, fractalkine, MCP-1 and adiponectin underlies whole-body insulin resistance and hyperglycemia in type 2 diabetes mellitus. *Acta Diabetol*, *51*(1), 123-131. https://doi.org/10.1007/s00592-013-0543-1

Darragh, J., Ananieva, O., Courtney, A., Elcombe, S., & Arthur, J. S. (2010). MSK1 regulates the transcription of IL-1ra in response to TLR activation in macrophages. *Biochem J*, *425*(3), 595-602. https://doi.org/10.1042/BJ20091062

Davis, C. L., Pollock, N. K., Waller, J. L., Allison, J. D., Dennis, B. A., Bassali, R., . . . Gower, B. A. (2012). Exercise dose and diabetes risk in overweight and obese children: a randomized controlled trial. *JAMA*, *308*(11), 1103-1112. https://doi.org/10.1001/2012.jama.10762

Davis, J. N., Kelly, L. A., Lane, C. J., Ventura, E. E., Byrd-Williams, C. E., Alexandar, K. A., . . . Goran, M. I. (2009). Randomized control trial to improve adiposity and insulin resistance in overweight Latino adolescents. *Obesity (Silver Spring)*, *17*(8), 1542-1548. https://doi.org/10.1038/oby.2009.19

Davis, J. N., Tung, A., Chak, S. S., Ventura, E. E., Byrd-Williams, C. E., Alexander, K. E., . . . Goran, M. I. (2009). Aerobic and strength training reduces adiposity in overweight Latina adolescents. *Med Sci Sports Exerc*, *41*(7), 1494-1503. https://doi.org/10.1249/MSS.0b013e31819b6aea

Davis, J. N., Ventura, E. E., Tung, A., Munevar, M. A., Hasson, R. E., Byrd-Williams, C., . . . Goran, M. I. (2012). Effects of a randomized maintenance intervention on adiposity and metabolic risk factors in overweight minority adolescents. *Pediatr Obes*, *7*(1), 16-27. https://doi.org/10.1111/j.2047-6310.2011.00002.x

Dayer, J. M., Chicheportiche, R., Juge-Aubry, C., & Meier, C. (2006). Adipose tissue has anti-inflammatory properties: focus on IL-1 receptor antagonist (IL-1Ra). *Ann N Y Acad Sci*, *1069*, 444-453. https://doi.org/10.1196/annals.1351.043

Della Gatta, P. A., Garnham, A. P., Peake, J. M., & Cameron-Smith, D. (2014). Effect of exercise training on skeletal muscle cytokine expression in the elderly. *Brain Behav Immun*, *39*, 80-86. https://doi.org/10.1016/j.bbi.2014.01.006

Dixon, D., Goldberg, R., Schneiderman, N., & Delamater, A. (2004). Gender differences in TNF-alpha levels among obese vs nonobese Latino children. *Eur J Clin Nutr*, *58*(4), 696-699. https://doi.org/10.1038/sj.ejcn.1601852

Dorneles, G. P., Haddad, D. O., Fagundes, V. O., Vargas, B. K., Kloecker, A., Romão, P. R., & Peres, A. (2016). High intensity interval exercise decreases IL-8 and

enhances the immunomodulatory cytokine interleukin-10 in lean and overweight-obese individuals. *Cytokine*, *77*, 1-9. https://doi.org/10.1016/j.cyto.2015.10.003

Draznin, B., Aroda, V. R., Bakris, G., Benson, G., Brown, F. M., Freeman, R., . . . Committee:, A. D. A. P. P. (2022). 14. Children and Adolescents: Standards of Medical Care in Diabetes-2022. *Diabetes Care*, *45*(Suppl 1), S208-S231. https://doi.org/10.2337/dc22-S014

Ebbeling, C. B., Leidig, M. M., Sinclair, K. B., Hangen, J. P., & Ludwig, D. S. (2003). A reduced-glycemic load diet in the treatment of adolescent obesity. *Arch Pediatr Adolesc Med*, *157*(8), 773-779. https://doi.org/10.1001/archpedi.157.8.773

Elliot, C. A., & Hamlin, M. J. (2018). Combined diet and physical activity is better than diet or physical activity alone at improving health outcomes for patients in New Zealand's primary care intervention. *BMC Public Health*, *18*(1), 230. https://doi.org/10.1186/s12889-018-5152-z

Ellulu, M. S., Khaza'ai, H., Rahmat, A., Patimah, I., & Abed, Y. (2016). Obesity can predict and promote systemic inflammation in healthy adults. *Int J Cardiol*, *215*, 318-324. https://doi.org/10.1016/j.ijcard.2016.04.089

Engin, A. B. (2017). Adipocyte-Macrophage Cross-Talk in Obesity. *Adv Exp Med Biol*, *960*, 327-343. https://doi.org/10.1007/978-3-319-48382-5_14

Esposito, K., Pontillo, A., Di Palo, C., Giugliano, G., Masella, M., Marfella, R., & Giugliano, D. (2003). Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA*, *289*(14), 1799-1804. https://doi.org/10.1001/jama.289.14.1799

Fatouros, I. G., Tournis, S., Leontsini, D., Jamurtas, A. Z., Sxina, M., Thomakos, P., . . . Mitrakou, A. (2005). Leptin and adiponectin responses in overweight inactive elderly following resistance training and detraining are intensity related. *J Clin Endocrinol Metab*, *90*(11), 5970-5977. https://doi.org/10.1210/jc.2005-0261

Ferrannini, E., Simonson, D. C., Katz, L. D., Reichard, G., Bevilacqua, S., Barrett, E. J., . . . DeFronzo, R. A. (1988). The disposal of an oral glucose load in patients with non-insulin-dependent diabetes. *Metabolism*, *37*(1), 79-85. https://doi.org/10.1016/0026-0495(88)90033-9

Flores, G., & Vega, L. R. (1998). Barriers to health care access for Latino children: a review. *Fam Med*, *30*(3), 196-205.

Frühbeck, G., Catalán, V., Ramírez, B., Valentí, V., Becerril, S., Rodríguez, A., . . . Gómez-Ambrosi, J. (2022). Serum Levels of IL-1 RA Increase with Obesity and Type 2 Diabetes in Relation to Adipose Tissue Dysfunction and are Reduced

After Bariatric Surgery in Parallel to Adiposity. *J Inflamm Res*, *15*, 1331-1345. https://doi.org/10.2147/JIR.S354095

Fu, J. F., Liang, L., Zou, C. C., Hong, F., Wang, C. L., Wang, X. M., & Zhao, Z. Y. (2007). Prevalence of the metabolic syndrome in Zhejiang Chinese obese children and adolescents and the effect of metformin combined with lifestyle intervention. *Int J Obes (Lond)*, *31*(1), 15-22. https://doi.org/10.1038/sj.ijo.0803453

Garcia, A. L., Otto, B., Reich, S. C., Weickert, M. O., Steiniger, J., Machowetz, A., . . . Koebnick, C. (2007). Arabinoxylan consumption decreases postprandial serum glucose, serum insulin and plasma total ghrelin response in subjects with impaired glucose tolerance. *Eur J Clin Nutr*, *61*(3), 334-341. https://doi.org/10.1038/sj.ejcn.1602525

García-Hermoso, A., Ramírez-Vélez, R., Ramírez-Campillo, R., Peterson, M. D., & Martínez-Vizcaíno, V. (2018). Concurrent aerobic plus resistance exercise versus aerobic exercise alone to improve health outcomes in paediatric obesity: a systematic review and meta-analysis. *Br J Sports Med*, *52*(3), 161-166. https://doi.org/10.1136/bjsports-2016-096605

García-Hermoso, A., Saavedra, J. M., Escalante, Y., Sánchez-López, M., & Martínez-Vizcaíno, V. (2014). Endocrinology and Adolescence: aerobic exercise reduces insulin resistance markers in obese youth: a meta-analysis of randomized controlled trials. *Eur J Endocrinol*, *171*(4), R163-171. https://doi.org/10.1530/EJE-14-0291

Gepstein, V., & Weiss, R. (2019). Obesity as the Main Risk Factor for Metabolic Syndrome in Children. *Front Endocrinol (Lausanne)*, *10*, 568. https://doi.org/10.3389/fendo.2019.00568

Ghadimi, M., Mohammadi, R., Daneshzad, E., Moazzami, B., & Mohammadpour, Z. (2021). Effectiveness of dietary interventions on cardio-metabolic risk factors in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. *Ann Gastroenterol*, *34*(3), 415-423. https://doi.org/10.20524/aog.2021.0601

Giannini, C., Weiss, R., Cali, A., Bonadonna, R., Santoro, N., Pierpont, B., . . . Caprio, S. (2012). Evidence for early defects in insulin sensitivity and secretion before the onset of glucose dysregulation in obese youths: a longitudinal study. *Diabetes*, *61*(3), 606-614. https://doi.org/10.2337/db11-1111

Gil-Campos, M., Ramírez Tortosa, M. C., Aguilera, C. M., Cañete, R., & Gil, A. (2011). Fasting and postprandial adiponectin alterations anticipate NEFA and TNF-α

changes in prepubertal obese children. *Nutr Metab Cardiovasc Dis*, *21*(1), 62-68. https://doi.org/10.1016/j.numecd.2009.07.003

Gokulakrishnan, K., Ranjani, H., Weber, M. B., Pandey, G. K., Anjana, R. M., Balasubramanyam, M., . . . Mohan, V. (2017). Effect of lifestyle improvement program on the biomarkers of adiposity, inflammation and gut hormones in overweight/obese Asian Indians with prediabetes. *Acta Diabetol*, *54*(9), 843-852. https://doi.org/10.1007/s00592-017-1015-9

Golden, S. H., Yajnik, C., Phatak, S., Hanson, R. L., & Knowler, W. C. (2019). Racial/ethnic differences in the burden of type 2 diabetes over the life course: a focus on the USA and India. *Diabetologia*, *62*(10), 1751-1760. https://doi.org/10.1007/s00125-019-4968-0

Grooms, K. N., Ommerborn, M. J., Pham, D. Q., Djoussé, L., & Clark, C. R. (2013). Dietary fiber intake and cardiometabolic risks among US adults, NHANES 1999-2010. *Am J Med*, *126*(12), 1059-1067.e1051-1054. https://doi.org/10.1016/j.amjmed.2013.07.023

Gutin, B., Barbeau, P., Owens, S., Lemmon, C. R., Bauman, M., Allison, J., . . . Litaker, M. S. (2002). Effects of exercise intensity on cardiovascular fitness, total body composition, and visceral adiposity of obese adolescents. *Am J Clin Nutr*, *75*(5), 818-826. https://doi.org/10.1093/ajcn/75.5.818

Hales, C. M., Carroll, M. D., Fryar, C. D., & Ogden, C. L. (2017). Prevalence of Obesity Among Adults and Youth: United States, 2015-2016. *NCHS Data Brief*(288), 1-8.

Hales, C. M., Fryar, C. D., Carroll, M. D., Freedman, D. S., & Ogden, C. L. (2018). Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016. *JAMA*, *319*(16), 1723-1725. https://doi.org/10.1001/jama.2018.3060

Hamman, R. F., Wing, R. R., Edelstein, S. L., Lachin, J. M., Bray, G. A., Delahanty, L., . . . Wylie-Rosett, J. (2006). Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care*, *29*(9), 2102-2107. https://doi.org/10.2337/dc06-0560

Han, Y., Liu, Y., Zhao, Z., Zhen, S., Chen, J., Ding, N., . . . Wen, D. (2019). Does Physical Activity-Based Intervention Improve Systemic Proinflammatory Cytokine Levels in Overweight or Obese Children and Adolescents? Insights from a Meta-Analysis of Randomized Control Trials. *Obes Facts*, *12*(6), 653-668. https://doi.org/10.1159/000501970

Hannon, T. S., & Arslanian, S. A. (2015). The changing face of diabetes in youth: lessons learned from studies of type 2 diabetes. *Ann N Y Acad Sci*, *1353*, 113-137. https://doi.org/10.1111/nyas.12939

Hannon, T. S., Kahn, S. E., Utzschneider, K. M., Buchanan, T. A., Nadeau, K. J., Zeitler, P. S., . . . Consortium, R. (2018). Review of methods for measuring β-cell function: Design considerations from the Restoring Insulin Secretion (RISE) Consortium. *Diabetes Obes Metab*, *20*(1), 14-24. https://doi.org/10.1111/dom.13005

Hasson, R. E., Adam, T. C., Davis, J. N., Kelly, L. A., Ventura, E. E., Byrd-Williams, C. E., . . . Goran, M. I. (2012). Randomized controlled trial to improve adiposity, inflammation, and insulin resistance in obese African-American and Latino youth. *Obesity (Silver Spring)*, *20*(4), 811-818. https://doi.org/10.1038/oby.2010.343

Hatting, M., Tavares, C. D. J., Sharabi, K., Rines, A. K., & Puigserver, P. (2018). Insulin regulation of gluconeogenesis. *Ann N Y Acad Sci*, *1411*(1), 21-35. https://doi.org/10.1111/nyas.13435

Haukeland, J. W., Damås, J. K., Konopski, Z., Løberg, E. M., Haaland, T., Goverud, I., . . . Aukrust, P. (2006). Systemic inflammation in nonalcoholic fatty liver disease is characterized by elevated levels of CCL2. *J Hepatol*, *44*(6), 1167-1174. https://doi.org/10.1016/j.jhep.2006.02.011

Herder, C., Peltonen, M., Koenig, W., Kräft, I., Müller-Scholze, S., Martin, S., . . . Tuomilehto, J. (2006). Systemic immune mediators and lifestyle changes in the prevention of type 2 diabetes: results from the Finnish Diabetes Prevention Study. *Diabetes*, *55*(8), 2340-2346. https://doi.org/10.2337/db05-1320

Hill-Briggs, F., Adler, N. E., Berkowitz, S. A., Chin, M. H., Gary-Webb, T. L., Navas-Acien, A., . . . Haire-Joshu, D. (2020). Social Determinants of Health and Diabetes: A Scientific Review. *Diabetes Care*. https://doi.org/10.2337/dci20-0053

Hingle, M. D., Turner, T., Going, S., Ussery, C., Roe, D. J., Saboda, K., . . . Stump, C. (2019). Feasibility of a family-focused YMCA-based diabetes prevention program in youth: The E.P.I.C. Kids (Encourage, Practice, and Inspire Change) Study. *Prev Med Rep*, *14*, 100840. https://doi.org/10.1016/j.pmedr.2019.100840

Ho, R. C., Davy, K. P., Hickey, M. S., & Melby, C. L. (2005). Circulating tumor necrosis factor alpha is higher in non-obese, non-diabetic Mexican Americans compared to non-Hispanic white adults. *Cytokine*, *30*(1), 14-21. https://doi.org/10.1016/j.cyto.2004.10.015

Hong, E. G., Ko, H. J., Cho, Y. R., Kim, H. J., Ma, Z., Yu, T. Y., . . . Kim, J. K. (2009). Interleukin-10 prevents diet-induced insulin resistance by attenuating macrophage and cytokine response in skeletal muscle. *Diabetes*, *58*(11), 2525-2535. https://doi.org/10.2337/db08-1261

Hosogai, N., Fukuhara, A., Oshima, K., Miyata, Y., Tanaka, S., Segawa, K., . . . Shimomura, I. (2007). Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. *Diabetes*, *56*(4), 901-911. https://doi.org/10.2337/db06-0911

Hosseini, B., Berthon, B. S., Saedisomeolia, A., Starkey, M. R., Collison, A., Wark, P. A. B., & Wood, L. G. (2018). Effects of fruit and vegetable consumption on inflammatory biomarkers and immune cell populations: a systematic literature review and meta-analysis. *Am J Clin Nutr*, *108*(1), 136-155. https://doi.org/10.1093/ajcn/nqy082

Hotamisligil, G. S., Peraldi, P., Budavari, A., Ellis, R., White, M. F., & Spiegelman, B. M. (1996). IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. *Science*, *271*(5249), 665-668. https://doi.org/10.1126/science.271.5249.665

Huang, F., Del-Río-Navarro, B. E., Pérez-Ontiveros, J. A., Ruiz-Bedolla, E., Saucedo-Ramírez, O. J., Villafaña, S., . . . Hong, E. (2014). Effect of six-month lifestyle intervention on adiponectin, resistin and soluble tumor necrosis factor-α receptors in obese adolescents. *Endocr J*, *61*(9), 921-931. https://doi.org/10.1507/endocrj.ej14-0157

Hyun, Y. J., Koh, S. J., Chae, J. S., Kim, J. Y., Kim, O. Y., Lim, H. H., . . . Lee, J. H. (2008). Atherogenecity of LDL and unfavorable adipokine profile in metabolically obese, normal-weight woman. *Obesity (Silver Spring)*, *16*(4), 784-789. https://doi.org/10.1038/oby.2007.127

Hücking, K., Watanabe, R. M., Stefanovski, D., & Bergman, R. N. (2008). OGTT-derived measures of insulin sensitivity are confounded by factors other than insulin sensitivity itself. *Obesity (Silver Spring)*, *16*(8), 1938-1945. https://doi.org/10.1038/oby.2008.336

Izadpanah, A., Barnard, R. J., Almeda, A. J., Baldwin, G. C., Bridges, S. A., Shellman, E. R., . . . Roberts, C. K. (2012). A short-term diet and exercise intervention ameliorates inflammation and markers of metabolic health in overweight/obese children. *Am J Physiol Endocrinol Metab*, *303*(4), E542-550. https://doi.org/10.1152/ajpendo.00190.2012

Jensen, E. (2021). *The Chance That Two People Chosen at Random Are of Different Race or Ethnicity Groups Has Increased Since 2010*. Retrieved March 31, 2022 from

Jortay, J., Senou, M., Delaigle, A., Noel, L., Funahashi, T., Maeda, N., . . . Brichard, S. M. (2010). Local induction of adiponectin reduces lipopolysaccharide-triggered

skeletal muscle damage. *Endocrinology*, *151*(10), 4840-4851. https://doi.org/10.1210/en.2009-1462

Joseph, G., Arviv-Eliashiv, R., & Tesler, R. (2020). A comparison of diet versus diet + exercise programs for health improvement in middle-aged overweight women. *Womens Health (Lond)*, *16*, 1745506520932372. https://doi.org/10.1177/1745506520932372

Juge-Aubry, C. E., Somm, E., Giusti, V., Pernin, A., Chicheportiche, R., Verdumo, C., . . . Meier, C. A. (2003). Adipose tissue is a major source of interleukin-1 receptor antagonist: upregulation in obesity and inflammation. *Diabetes*, *52*(5), 1104-1110. https://doi.org/10.2337/diabetes.52.5.1104

Kahleova, H., Matoulek, M., Malinska, H., Oliyarnik, O., Kazdova, L., Neskudla, T., . . . Pelikanova, T. (2011). Vegetarian diet improves insulin resistance and oxidative stress markers more than conventional diet in subjects with Type 2 diabetes. *Diabet Med*, *28*(5), 549-559. https://doi.org/10.1111/j.1464-5491.2010.03209.x

Kahleova, H., Tura, A., Hill, M., Holubkov, R., & Barnard, N. D. (2018). A Plant-Based Dietary Intervention Improves Beta-Cell Function and Insulin Resistance in Overweight Adults: A 16-Week Randomized Clinical Trial. *Nutrients*, *10*(2). https://doi.org/10.3390/nu10020189

Kahleova, H., Tura, A., Klementova, M., Thieme, L., Haluzik, M., Pavlovicova, R., . . . Pelikanova, T. (2019). A Plant-Based Meal Stimulates Incretin and Insulin Secretion More Than an Energy- and Macronutrient-Matched Standard Meal in Type 2 Diabetes: A Randomized Crossover Study. *Nutrients*, *11*(3). https://doi.org/10.3390/nu11030486

Kanda, H., Tateya, S., Tamori, Y., Kotani, K., Hiasa, K., Kitazawa, R., . . . Kasuga, M. (2006). MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. *J Clin Invest*, *116*(6), 1494-1505. https://doi.org/10.1172/JCI26498

Kany, S., Vollrath, J. T., & Relja, B. (2019). Cytokines in Inflammatory Disease. *Int J Mol Sci*, *20*(23). https://doi.org/10.3390/ijms20236008

Kapiotis, S., Holzer, G., Schaller, G., Haumer, M., Widhalm, H., Weghuber, D., . . . Wagner, O. F. (2006). A proinflammatory state is detectable in obese children and is accompanied by functional and morphological vascular changes. *Arterioscler Thromb Vasc Biol*, *26*(11), 2541-2546. https://doi.org/10.1161/01.ATV.0000245795.08139.70

Karstoft, K., & Pedersen, B. K. (2016). Exercise and type 2 diabetes: focus on metabolism and inflammation. *Immunol Cell Biol*, *94*(2), 146-150. https://doi.org/10.1038/icb.2015.101

Kelishadi, R., Hashemi, M., Mohammadifard, N., Asgary, S., & Khavarian, N. (2008). Association of changes in oxidative and proinflammatory states with changes in vascular function after a lifestyle modification trial among obese children. *Clin Chem*, *54*(1), 147-153. https://doi.org/10.1373/clinchem.2007.089953

Kelly, A. S., Ryder, J. R., Marlatt, K. L., Rudser, K. D., Jenkins, T., & Inge, T. H. (2016). Changes in inflammation, oxidative stress and adipokines following bariatric surgery among adolescents with severe obesity. *Int J Obes (Lond)*, *40*(2), 275-280. https://doi.org/10.1038/ijo.2015.174

Kelsey, M. M., & Zeitler, P. S. (2016). Insulin Resistance of Puberty. *Curr Diab Rep*, *16*(7), 64. https://doi.org/10.1007/s11892-016-0751-5

Khan, I. M., Perrard, X. Y., Brunner, G., Lui, H., Sparks, L. M., Smith, S. R., . . . Ballantyne, C. M. (2015). Intermuscular and perimuscular fat expansion in obesity correlates with skeletal muscle T cell and macrophage infiltration and insulin resistance. *Int J Obes (Lond)*, *39*(11), 1607-1618. https://doi.org/10.1038/ijo.2015.104

Khodabandehloo, H., Gorgani-Firuzjaee, S., Panahi, G., & Meshkani, R. (2016). Molecular and cellular mechanisms linking inflammation to insulin resistance and β-cell dysfunction. *Transl Res*, *167*(1), 228-256. https://doi.org/10.1016/j.trsl.2015.08.011

Kim, J. J., & Sears, D. D. (2010). TLR4 and Insulin Resistance. *Gastroenterol Res Pract*, *2010*. https://doi.org/10.1155/2010/212563

Kim, J. Y., & Jeon, J. Y. (2020). Role of exercise on insulin sensitivity and beta-cell function: is exercise sufficient for the prevention of youth-onset type 2 diabetes? *Ann Pediatr Endocrinol Metab*, *25*(4), 208-216. https://doi.org/10.6065/apem.2040140.070

Kim, J. Y., Tfayli, H., Bacha, F., Lee, S., Gebara, N., & Arslanian, S. (2020). β-cell impairment and clinically meaningful alterations in glycemia in obese youth across the glucose tolerance spectrum. *Metabolism*, *112*, 154346. https://doi.org/10.1016/j.metabol.2020.154346

Kim, J. Y., Tfayli, H., Bacha, F., Lee, S., Michaliszyn, S. F., Yousuf, S., . . . Arslanian, S. (2020). β-cell function, incretin response, and insulin sensitivity of glucose and fat metabolism in obese youth: Relationship to OGTT-time-to-glucose-peak. *Pediatr Diabetes*, *21*(1), 18-27. https://doi.org/10.1111/pedi.12940

Kirovski, G., Dorn, C., Huber, H., Moleda, L., Niessen, C., Wobser, H., . . . Hellerbrand, C. (2011). Elevated systemic monocyte chemoattractrant protein-1 in hepatic steatosis without significant hepatic inflammation. *Exp Mol Pathol*, *91*(3), 780-783. https://doi.org/10.1016/j.yexmp.2011.08.001

Kitabchi, A. E., Temprosa, M., Knowler, W. C., Kahn, S. E., Fowler, S. E., Haffner, S. M., . . . Group, D. P. P. R. (2005). Role of insulin secretion and sensitivity in the evolution of type 2 diabetes in the diabetes prevention program: effects of lifestyle intervention and metformin. *Diabetes*, *54*(8), 2404-2414. https://doi.org/10.2337/diabetes.54.8.2404

Knowler, W. C., Barrett-Connor, E., Fowler, S. E., Hamman, R. F., Lachin, J. M., Walker, E. A., . . . Group, D. P. P. R. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*, *346*(6), 393-403. https://doi.org/10.1056/NEJMoa012512

Lawrence, J. M., Divers, J., Isom, S., Saydah, S., Imperatore, G., Pihoker, C., . . . Group, S. f. D. i. Y. S. (2021). Trends in Prevalence of Type 1 and Type 2 Diabetes in Children and Adolescents in the US, 2001-2017. *JAMA*, *326*(8), 717-727. https://doi.org/10.1001/jama.2021.11165

Lawrence, T. (2009). The nuclear factor NF-kappaB pathway in inflammation. *Cold Spring Harb Perspect Biol*, *1*(6), a001651. https://doi.org/10.1101/cshperspect.a001651

Lee, B. C., & Lee, J. (2014). Cellular and molecular players in adipose tissue inflammation in the development of obesity-induced insulin resistance. *Biochim Biophys Acta*, *1842*(3), 446-462. https://doi.org/10.1016/j.bbadis.2013.05.017

Lee, J., & Pilch, P. F. (1994). The insulin receptor: structure, function, and signaling. *Am J Physiol*, *266*(2 Pt 1), C319-334. https://doi.org/10.1152/ajpcell.1994.266.2.C319

Lee, J. M., Okumura, M. J., Davis, M. M., Herman, W. H., & Gurney, J. G. (2006). Prevalence and determinants of insulin resistance among U.S. adolescents: a population-based study. *Diabetes Care*, *29*(11), 2427-2432. https://doi.org/10.2337/dc06-0709

Lee, M. K., Jekal, Y., Im, J. A., Kim, E., Lee, S. H., Park, J. H., . . . Jeon, J. Y. (2010). Reduced serum vaspin concentrations in obese children following short-term intensive lifestyle modification. *Clin Chim Acta*, *411*(5-6), 381-385. https://doi.org/10.1016/j.cca.2009.12.003

Lee, S., Bacha, F., Hannon, T., Kuk, J. L., Boesch, C., & Arslanian, S. (2012). Effects of aerobic versus resistance exercise without caloric restriction on abdominal fat,

intrahepatic lipid, and insulin sensitivity in obese adolescent boys: a randomized, controlled trial. *Diabetes*, *61*(11), 2787-2795. https://doi.org/10.2337/db12-0214

Lee, S., Libman, I., Hughan, K., Kuk, J. L., Jeong, J. H., Zhang, D., & Arslanian, S. (2019). Effects of Exercise Modality on Insulin Resistance and Ectopic Fat in Adolescents with Overweight and Obesity: A Randomized Clinical Trial. *J Pediatr*, *206*, 91-98.e91. https://doi.org/10.1016/j.jpeds.2018.10.059

Lee, Y. S., Kim, J. W., Osborne, O., Oh, D. Y., Sasik, R., Schenk, S., . . . Olefsky, J. M. (2014). Increased adipocyte O2 consumption triggers HIF-1α, causing inflammation and insulin resistance in obesity. *Cell*, *157*(6), 1339-1352. https://doi.org/10.1016/j.cell.2014.05.012

Lee, Y. S., Li, P., Huh, J. Y., Hwang, I. J., Lu, M., Kim, J. I., . . . Kim, J. B. (2011). Inflammation is necessary for long-term but not short-term high-fat diet-induced insulin resistance. *Diabetes*, *60*(10), 2474-2483. https://doi.org/10.2337/db11-0194

Lenighan, Y. M., McNulty, B. A., & Roche, H. M. (2019). Dietary fat composition: replacement of saturated fatty acids with PUFA as a public health strategy, with an emphasis on α-linolenic acid. *Proc Nutr Soc*, *78*(2), 234-245. https://doi.org/10.1017/S0029665118002793

Leto, D., & Saltiel, A. R. (2012). Regulation of glucose transport by insulin: traffic control of GLUT4. *Nat Rev Mol Cell Biol*, *13*(6), 383-396. https://doi.org/10.1038/nrm3351

Li, J., Chen, L., Zhang, Y., Zhang, W. J., Xu, W., Qin, Y., . . . Zou, D. (2013). TLR4 is required for the obesity-induced pancreatic beta cell dysfunction. *Acta Biochim Biophys Sin (Shanghai)*, *45*(12), 1030-1038. https://doi.org/10.1093/abbs/gmt092

Liese, A. D., Schulz, M., Fang, F., Wolever, T. M., D'Agostino, R. B., Sparks, K. C., & Mayer-Davis, E. J. (2005). Dietary glycemic index and glycemic load, carbohydrate and fiber intake, and measures of insulin sensitivity, secretion, and adiposity in the Insulin Resistance Atherosclerosis Study. *Diabetes Care*, *28*(12), 2832-2838. https://doi.org/10.2337/diacare.28.12.2832

Lihn, A. S., Pedersen, S. B., & Richelsen, B. (2005). Adiponectin: action, regulation and association to insulin sensitivity. *Obes Rev*, *6*(1), 13-21. https://doi.org/10.1111/j.1467-789X.2005.00159.x

Lin, Y., Itani, S. I., Kurowski, T. G., Dean, D. J., Luo, Z., Yaney, G. C., & Ruderman, N. B. (2001). Inhibition of insulin signaling and glycogen synthesis by phorbol dibutyrate in rat skeletal muscle. *Am J Physiol Endocrinol Metab*, *281*(1), E8-E15. https://doi.org/10.1152/ajpendo.2001.281.1.E8

Lira, F. S., Rosa, J. C., Dos Santos, R. V., Venancio, D. P., Carnier, J., Sanches, P. e. L., . . . Oyama, L. M. (2011). Visceral fat decreased by long-term interdisciplinary lifestyle therapy correlated positively with interleukin-6 and tumor necrosis factor-α and negatively with adiponectin levels in obese adolescents. *Metabolism*, *60*(3), 359-365. https://doi.org/10.1016/j.metabol.2010.02.017

Lira, F. S., Rosa, J. C., Pimentel, G. D., Santos, R. V., Carnier, J., Sanches, P. L., . . . Dâmaso, A. R. (2012). Long-term interdisciplinary therapy reduces endotoxin level and insulin resistance in obese adolescents. *Nutr J*, *11*, 74. https://doi.org/10.1186/1475-2891-11-74

Liu, M., & Liu, F. (2014). Regulation of adiponectin multimerization, signaling and function. *Best Pract Res Clin Endocrinol Metab*, *28*(1), 25-31. https://doi.org/10.1016/j.beem.2013.06.003

Liu, Z., Xiao, T., Peng, X., Li, G., & Hu, F. (2017). APPLs: More than just adiponectin receptor binding proteins. *Cell Signal*, *32*, 76-84. https://doi.org/10.1016/j.cellsig.2017.01.018

Luciardi, M. C., Carrizo, T. R., Díaz, E. I., Áleman, M. N., Bazán, M. C., & Abregu, A. V. (2018). [Proinflammatory state in obese children]. *Rev Chil Pediatr*, *89*(3), 346-351. https://doi.org/10.4067/S0370-41062018005000501

Lumeng, C. N., Bodzin, J. L., & Saltiel, A. R. (2007). Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J Clin Invest*, *117*(1), 175-184. https://doi.org/10.1172/JCI29881

Mager, D. R., Iñiguez, I. R., Gilmour, S., & Yap, J. (2015). The effect of a low fructose and low glycemic index/load (FRAGILE) dietary intervention on indices of liver function, cardiometabolic risk factors, and body composition in children and adolescents with nonalcoholic fatty liver disease (NAFLD). *JPEN J Parenter Enteral Nutr*, *39*(1), 73-84. https://doi.org/10.1177/0148607113501201

Magge, S. N., Silverstein, J., Elder, D., Nadeau, K., & Hannon, T. S. (2020). Evaluation and Treatment of Prediabetes in Youth. *J Pediatr*, *219*, 11-22. https://doi.org/10.1016/j.jpeds.2019.12.061

Mao, T. (2021). Effects of dietary fiber on glycemic control and insulin sensitivity in patients with type 2 diabetes: A systematic review and meta-analysis. *Journal of Functional Foods*, *82*, 1-11. https://doi.org/https://doi.org/10.1016/j.jff.2021.104500

Marti, A., Morell-Azanza, L., Rendo-Urteaga, T., García-Calzón, S., Ojeda-Rodríguez, A., Martín-Calvo, N., . . . Azcona-San Julián, M. C. (2018). Serum and gene

expression levels of CT-1, IL-6, and TNF-α after a lifestyle intervention in obese children. *Pediatr Diabetes*, *19*(2), 217-222. https://doi.org/10.1111/pedi.12561

Martínez-Fernández, L., Laiglesia, L. M., Huerta, A. E., Martínez, J. A., & Moreno-Aliaga, M. J. (2015). Omega-3 fatty acids and adipose tissue function in obesity and metabolic syndrome. *Prostaglandins Other Lipid Mediat*, *121*(Pt A), 24-41. https://doi.org/10.1016/j.prostaglandins.2015.07.003

Mather, K. J., Funahashi, T., Matsuzawa, Y., Edelstein, S., Bray, G. A., Kahn, S. E., . . . Program, D. P. (2008). Adiponectin, change in adiponectin, and progression to diabetes in the Diabetes Prevention Program. *Diabetes*, *57*(4), 980-986. https://doi.org/10.2337/db07-1419

Mayerhofer, E., Ratzinger, F., Kienreich, N. E., Stiel, A., Witzeneder, N., Schrefl, E., . . . Hoermann, G. (2020). A Multidisciplinary Intervention in Childhood Obesity Acutely Improves Insulin Resistance and Inflammatory Markers Independent From Body Composition. *Front Pediatr*, *8*, 52. https://doi.org/10.3389/fped.2020.00052

McCurley, J. L., Crawford, M. A., & Gallo, L. C. (2017). Prevention of Type 2 Diabetes in U.S. Hispanic Youth: A Systematic Review of Lifestyle Interventions. *Am J Prev Med*, *53*(4), 519-532. https://doi.org/10.1016/j.amepre.2017.05.020

McLaughlin, T., Liu, L. F., Lamendola, C., Shen, L., Morton, J., Rivas, H., . . . Engleman, E. (2014). T-cell profile in adipose tissue is associated with insulin resistance and systemic inflammation in humans. *Arterioscler Thromb Vasc Biol*, *34*(12), 2637-2643. https://doi.org/10.1161/ATVBAHA.114.304636

McMurray, F., Patten, D. A., & Harper, M. E. (2016). Reactive Oxygen Species and Oxidative Stress in Obesity-Recent Findings and Empirical Approaches. *Obesity (Silver Spring)*, *24*(11), 2301-2310. https://doi.org/10.1002/oby.21654

Mezuk, B., & Allen, J. O. (2021). Rethinking the Goals of Diabetes Prevention Programs. *Diabetes Care*, *44*(11), 2457-2459. https://doi.org/10.2337/dci21-0038

Milajerdi, A., Saneei, P., Larijani, B., & Esmaillzadeh, A. (2018). The effect of dietary glycemic index and glycemic load on inflammatory biomarkers: a systematic review and meta-analysis of randomized clinical trials. *Am J Clin Nutr*, *107*(4), 593-606. https://doi.org/10.1093/ajcn/nqx042

Miller, G. D., Isom, S., Morgan, T. M., Vitolins, M. Z., Blackwell, C., Brosnihan, K. B., . . . Goff, D. (2014). Effects of a community-based weight loss intervention on adipose tissue circulating factors. *Diabetes Metab Syndr*, *8*(4), 205-211. https://doi.org/10.1016/j.dsx.2014.09.003

Miranda, D. N., Coletta, D. K., Mandarino, L. J., & Shaibi, G. Q. (2014). Increases in insulin sensitivity among obese youth are associated with gene expression changes in whole blood. *Obesity (Silver Spring)*, *22*(5), 1337-1344. https://doi.org/10.1002/oby.20711

Mirza, N. M., Palmer, M. G., Sinclair, K. B., McCarter, R., He, J., Ebbeling, C. B., . . . Yanovski, J. A. (2013). Effects of a low glycemic load or a low-fat dietary intervention on body weight in obese Hispanic American children and adolescents: a randomized controlled trial. *Am J Clin Nutr*, *97*(2), 276-285. https://doi.org/10.3945/ajcn.112.042630

Misciagna, G., Del Pilar Díaz, M., Caramia, D. V., Bonfiglio, C., Franco, I., Noviello, M. R., . . . Osella, A. R. (2017). Effect of a Low Glycemic Index Mediterranean Diet on Non-Alcoholic Fatty Liver Disease. A Randomized Controlled Clinici Trial. *J Nutr Health Aging*, *21*(4), 404-412. https://doi.org/10.1007/s12603-016-0809-8

Moon, Y. S., Kim, D. H., & Song, D. K. (2004). Serum tumor necrosis factor-alpha levels and components of the metabolic syndrome in obese adolescents. *Metabolism*, *53*(7), 863-867. https://doi.org/10.1016/j.metabol.2004.02.007

Morinaga, H., Mayoral, R., Heinrichsdorff, J., Osborn, O., Franck, N., Hah, N., . . . Oh, D. Y. (2015). Characterization of distinct subpopulations of hepatic macrophages in HFD/obese mice. *Diabetes*, *64*(4), 1120-1130. https://doi.org/10.2337/db14-1238

Morishita, R., Franco, M. o. C., Suano-Souza, F. I., Solé, D., Puccini, R. F., & Strufaldi, M. W. (2016). Body mass index, adipokines and insulin resistance in asthmatic children and adolescents. *J Asthma*, *53*(5), 478-484. https://doi.org/10.3109/02770903.2015.1113544

Narayan, K. M., Boyle, J. P., Thompson, T. J., Sorensen, S. W., & Williamson, D. F. (2003). Lifetime risk for diabetes mellitus in the United States. *JAMA*, *290*(14), 1884-1890. https://doi.org/10.1001/jama.290.14.1884

Nassis, G. P., Papantakou, K., Skenderi, K., Triandafillopoulou, M., Kavouras, S. A., Yannakoulia, M., . . . Sidossis, L. S. (2005). Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers in overweight and obese girls. *Metabolism*, *54*(11), 1472-1479. https://doi.org/10.1016/j.metabol.2005.05.013

Nemet, D., Wang, P., Funahashi, T., Matsuzawa, Y., Tanaka, S., Engelman, L., & Cooper, D. M. (2003). Adipocytokines, body composition, and fitness in children. *Pediatr Res*, *53*(1), 148-152. https://doi.org/10.1203/00006450-200301000-00025

Neumann, H. F., & Egert, S. (2022). Impact of Meal Fatty Acid Composition on Postprandial Lipemia in Metabolically Healthy Adults and Individuals with Cardiovascular Disease Risk Factors: A Systematic Review. *Adv Nutr*, *13*(1), 193-207. https://doi.org/10.1093/advances/nmab096

Ogden, C. L., Carroll, M. D., Lawman, H. G., Fryar, C. D., Kruszon-Moran, D., Kit, B. K., & Flegal, K. M. (2016). Trends in Obesity Prevalence Among Children and Adolescents in the United States, 1988-1994 Through 2013-2014. *JAMA*, *315*(21), 2292-2299. https://doi.org/10.1001/jama.2016.6361

Ogden, C. L., Fryar, C. D., Hales, C. M., Carroll, M. D., Aoki, Y., & Freedman, D. S. (2018). Differences in Obesity Prevalence by Demographics and Urbanization in US Children and Adolescents, 2013-2016. *JAMA*, *319*(23), 2410-2418. https://doi.org/10.1001/jama.2018.5158

Ohashi, K., Parker, J. L., Ouchi, N., Higuchi, A., Vita, J. A., Gokce, N., . . . Walsh, K. (2010). Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype. *J Biol Chem*, *285*(9), 6153-6160. https://doi.org/10.1074/jbc.M109.088708

Ohman-Hanson, R. A., Cree-Green, M., Kelsey, M. M., Bessesen, D. H., Sharp, T. A., Pyle, L., . . . Nadeau, K. J. (2016). Ethnic and Sex Differences in Adiponectin: From Childhood to Adulthood. *J Clin Endocrinol Metab*, *101*(12), 4808-4815. https://doi.org/10.1210/jc.2016-1137

Ojo, O., Ojo, O. O., Wang, X. H., & Adegboye, A. R. A. (2019). The Effects of a Low GI Diet on Cardiometabolic and Inflammatory Parameters in Patients with Type 2 and Gestational Diabetes: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Nutrients*, *11*(7). https://doi.org/10.3390/nu11071584

Orlando, A., Nava, E., Giussani, M., & Genovesi, S. (2019). Adiponectin and Cardiovascular Risk. From Pathophysiology to Clinic: Focus on Children and Adolescents. *Int J Mol Sci*, *20*(13). https://doi.org/10.3390/ijms20133228

Ottobelli Chielle, E., de Souza, W. M., da Silva, T. P., Moresco, R. N., & Moretto, M. B. (2016). Adipocytokines, inflammatory and oxidative stress markers of clinical relevance altered in young overweight/obese subjects. *Clin Biochem*, *49*(7-8), 548-553. https://doi.org/10.1016/j.clinbiochem.2016.01.003

Paltoglou, G., Schoina, M., Valsamakis, G., Salakos, N., Avloniti, A., Chatzinikolaou, A., . . . Mastorakos, G. (2017). Interrelations among the adipocytokines leptin and adiponectin, oxidative stress and aseptic inflammation markers in pre- and early-

pubertal normal-weight and obese boys. *Endocrine*, *55*(3), 925-933. https://doi.org/10.1007/s12020-017-1227-3

Parish, R. C., Todman, S., & Jain, S. K. (2016). Resting Heart Rate Variability, Inflammation, and Insulin Resistance in Overweight and Obese Adolescents. *Metab Syndr Relat Disord*, *14*(6), 291-297. https://doi.org/10.1089/met.2015.0140

Park, T. G., Hong, H. R., Lee, J., & Kang, H. S. (2007). Lifestyle plus exercise intervention improves metabolic syndrome markers without change in adiponectin in obese girls. *Ann Nutr Metab*, *51*(3), 197-203. https://doi.org/10.1159/000104137

Pedersen, B. K. (2017). Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. *Eur J Clin Invest*, *47*(8), 600-611. https://doi.org/10.1111/eci.12781

Pejsova, H., Hubacek, J. A., Zemankova, P., & Zlatohlavek, L. (2019). Baseline Leptin/Adiponectin Ratio is a Significant Predictor of BMI Changes in Children/Adolescents after Intensive Lifestyle Intervention. *Exp Clin Endocrinol Diabetes*, *127*(10), 691-696. https://doi.org/10.1055/a-0859-7041

Petersen, A. M., & Pedersen, B. K. (2005). The anti-inflammatory effect of exercise. *J Appl Physiol (1985)*, *98*(4), 1154-1162. https://doi.org/10.1152/japplphysiol.00164.2004

Peña, A., McNeish, D., Ayers, S. L., Olson, M. L., Vander Wyst, K. B., Williams, A. N., & Shaibi, G. Q. (2020). Response Heterogeneity to Lifestyle Intervention among Latino Adolescents. *Pediatr Diabetes*. https://doi.org/10.1111/pedi.13120

Piemonti, L., Leone, B. E., Nano, R., Saccani, A., Monti, P., Maffi, P., . . . Bertuzzi, F. (2002). Human pancreatic islets produce and secrete MCP-1/CCL2: relevance in human islet transplantation. *Diabetes*, *51*(1), 55-65. https://doi.org/10.2337/diabetes.51.1.55

Piercy, K. L., Troiano, R. P., Ballard, R. M., Carlson, S. A., Fulton, J. E., Galuska, D. A., . . . Olson, R. D. (2018). The Physical Activity Guidelines for Americans. *JAMA*, *320*(19), 2020-2028. https://doi.org/10.1001/jama.2018.14854

Punthakee, Z., Delvin, E. E., O'loughlin, J., Paradis, G., Levy, E., Platt, R. W., & Lambert, M. (2006). Adiponectin, adiposity, and insulin resistance in children and adolescents. *J Clin Endocrinol Metab*, *91*(6), 2119-2125. https://doi.org/10.1210/jc.2005-2346

Rainone, V., Schneider, L., Saulle, I., Ricci, C., Biasin, M., Al-Daghri, N. M., . . . Trabattoni, D. (2016). Upregulation of inflammasome activity and increased gut

permeability are associated with obesity in children and adolescents. *Int J Obes (Lond)*, *40*(6), 1026-1033. https://doi.org/10.1038/ijo.2016.26

Rambhojan, C., Bouaziz-Amar, E., Larifla, L., Deloumeaux, J., Clepier, J., Plumasseau, J., . . . Foucan, L. (2015). Ghrelin, adipokines, metabolic factors in relation with weight status in school-children and results of a 1-year lifestyle intervention program. *Nutr Metab (Lond)*, *12*, 43. https://doi.org/10.1186/s12986-015-0039-9

Reinehr, T. (2019). Inflammatory markers in children and adolescents with type 2 diabetes mellitus. *Clin Chim Acta*, *496*, 100-107. https://doi.org/10.1016/j.cca.2019.07.006

Reinehr, T., Karges, B., Meissner, T., Wiegand, S., Stoffel-Wagner, B., Holl, R. W., & Woelfle, J. (2016). Inflammatory Markers in Obese Adolescents with Type 2 Diabetes and Their Relationship to Hepatokines and Adipokines. *J Pediatr*, *173*, 131-135. https://doi.org/10.1016/j.jpeds.2016.02.055

Reinehr, T., Stoffel-Wagner, B., Roth, C. L., & Andler, W. (2005). High-sensitive C-reactive protein, tumor necrosis factor alpha, and cardiovascular risk factors before and after weight loss in obese children. *Metabolism*, *54*(9), 1155-1161. https://doi.org/10.1016/j.metabol.2005.03.022

Reyna, S. M., Ghosh, S., Tantiwong, P., Meka, C. S., Eagan, P., Jenkinson, C. P., . . . Musi, N. (2008). Elevated toll-like receptor 4 expression and signaling in muscle from insulin-resistant subjects. *Diabetes*, *57*(10), 2595-2602. https://doi.org/10.2337/db08-0038

Richter, E. A., & Hargreaves, M. (2013). Exercise, GLUT4, and skeletal muscle glucose uptake. *Physiol Rev*, *93*(3), 993-1017. https://doi.org/10.1152/physrev.00038.2012

Roberts, C. K., Izadpanah, A., Angadi, S. S., & Barnard, R. J. (2013). Effects of an intensive short-term diet and exercise intervention: comparison between normal-weight and obese children. *Am J Physiol Regul Integr Comp Physiol*, *305*(5), R552-557. https://doi.org/10.1152/ajpregu.00131.2013

Roche, J., Isacco, L., Perret, F., Dumoulin, G., Gillet, V., & Mougin, F. (2019). Beneficial effects of a lifestyle intervention program on C-reactive protein: impact of cardiorespiratory fitness in obese adolescents with sleep disturbances. *Am J Physiol Regul Integr Comp Physiol*, *316*(4), R376-R386. https://doi.org/10.1152/ajpregu.00309.2018

Rosenbaum, M., Nonas, C., Weil, R., Horlick, M., Fennoy, I., Vargas, I., . . . Group, C. D. P. (2007). School-based intervention acutely improves insulin sensitivity and

decreases inflammatory markers and body fatness in junior high school students. *J Clin Endocrinol Metab*, *92*(2), 504-508. https://doi.org/10.1210/jc.2006-1516

Rossato, M., Curtale, G., Tamassia, N., Castellucci, M., Mori, L., Gasperini, S., . . . Bazzoni, F. (2012). IL-10-induced microRNA-187 negatively regulates TNF-α, IL-6, and IL-12p40 production in TLR4-stimulated monocytes. *Proc Natl Acad Sci U S A*, *109*(45), E3101-3110. https://doi.org/10.1073/pnas.1209100109

Roth, C. L., Kratz, M., Ralston, M. M., & Reinehr, T. (2011). Changes in adipose-derived inflammatory cytokines and chemokines after successful lifestyle intervention in obese children. *Metabolism*, *60*(4), 445-452. https://doi.org/10.1016/j.metabol.2010.03.023

Rui, L., Aguirre, V., Kim, J. K., Shulman, G. I., Lee, A., Corbould, A., . . . White, M. F. (2001). Insulin/IGF-1 and TNF-alpha stimulate phosphorylation of IRS-1 at inhibitory Ser307 via distinct pathways. *J Clin Invest*, *107*(2), 181-189. https://doi.org/10.1172/JCI10934

Rull, A., Camps, J., Alonso-Villaverde, C., & Joven, J. (2010). Insulin resistance, inflammation, and obesity: role of monocyte chemoattractant protein-1 (or CCL2) in the regulation of metabolism. *Mediators Inflamm*, *2010*. https://doi.org/10.1155/2010/326580

Ryan, M. C., Itsiopoulos, C., Thodis, T., Ward, G., Trost, N., Hofferberth, S., . . . Wilson, A. M. (2013). The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease. *J Hepatol*, *59*(1), 138-143. https://doi.org/10.1016/j.jhep.2013.02.012

Rynders, C., Weltman, A., Delgiorno, C., Balagopal, P., Damaso, L., Killen, K., & Mauras, N. (2012). Lifestyle intervention improves fitness independent of metformin in obese adolescents. *Med Sci Sports Exerc*, *44*(5), 786-792. https://doi.org/10.1249/MSS.0b013e31823cef5e

Santiprabhob, J., Limprayoon, K., Aanpreung, P., Charoensakdi, R., Kalpravidh, R. W., Phonrat, B., & Tungtrongchitr, R. (2018). Impact of a group-based treatment program on adipocytokines, oxidative status, inflammatory cytokines and arterial stiffness in obese children and adolescents. *J Pediatr Endocrinol Metab*, *31*(7), 733-742. https://doi.org/10.1515/jpem-2018-0012

Saqib, U., Sarkar, S., Suk, K., Mohammad, O., Baig, M. S., & Savai, R. (2018). Phytochemicals as modulators of M1-M2 macrophages in inflammation. *Oncotarget*, *9*(25), 17937-17950. https://doi.org/10.18632/oncotarget.24788

Savalei, V. (2009). A two-stage approach to missing data: Theory and Application to Auxiliary Variables. In P. M. Bentler (Ed.), (Vol. 16, pp. 477-497): Structural Equation Modeling: A Multidisciplinary Journal.

Savoye, M., Caprio, S., Dziura, J., Camp, A., Germain, G., Summers, C., . . . Tamborlane, W. V. (2014). Reversal of early abnormalities in glucose metabolism in obese youth: results of an intensive lifestyle randomized controlled trial. *Diabetes Care*, *37*(2), 317-324. https://doi.org/10.2337/dc13-1571

Schwimmer, J. B., Ugalde-Nicalo, P., Welsh, J. A., Angeles, J. E., Cordero, M., Harlow, K. E., . . . Vos, M. B. (2019). Effect of a Low Free Sugar Diet vs Usual Diet on Nonalcoholic Fatty Liver Disease in Adolescent Boys: A Randomized Clinical Trial. *JAMA*, *321*(3), 256-265. https://doi.org/10.1001/jama.2018.20579

Schwingshackl, L., & Hoffmann, G. (2013). Long-term effects of low glycemic index/load vs. high glycemic index/load diets on parameters of obesity and obesity-associated risks: a systematic review and meta-analysis. *Nutr Metab Cardiovasc Dis*, *23*(8), 699-706. https://doi.org/10.1016/j.numecd.2013.04.008

Senn, J. J., Klover, P. J., Nowak, I. A., Zimmers, T. A., Koniaris, L. G., Furlanetto, R. W., & Mooney, R. A. (2003). Suppressor of cytokine signaling-3 (SOCS-3), a potential mediator of interleukin-6-dependent insulin resistance in hepatocytes. *J Biol Chem*, *278*(16), 13740-13746. https://doi.org/10.1074/jbc.M210689200

Seppä, S., Tenhola, S., & Voutilainen, R. (2018). Serum IL-1 Receptor Antagonist Concentrations Associate With Unfavorable Metabolic Features in 12-Year-Old Children. *J Endocr Soc*, *2*(8), 870-881. https://doi.org/10.1210/js.2018-00159

Sha, Y., & Markovic-Plese, S. (2011). A role of IL-1R1 signaling in the differentiation of Th17 cells and the development of autoimmune diseases. *Self Nonself*, *2*(1), 35-42. https://doi.org/10.4161/self.2.1.15639

Shaibi, G. Q., Cruz, M. L., Ball, G. D., Weigensberg, M. J., Salem, G. J., Crespo, N. C., & Goran, M. I. (2006). Effects of resistance training on insulin sensitivity in overweight Latino adolescent males. *Med Sci Sports Exerc*, *38*(7), 1208-1215. https://doi.org/10.1249/01.mss.0000227304.88406.0f

Shaibi, G. Q., Konopken, Y., Hoppin, E., Keller, C. S., Ortega, R., & Castro, F. G. (2012). Effects of a culturally grounded community-based diabetes prevention program for obese Latino adolescents. *Diabetes Educ*, *38*(4), 504-512. https://doi.org/10.1177/0145721712446635

Shaibi, G. Q., Ryder, J. R., Kim, J. Y., & Barraza, E. (2015). Exercise for obese youth: refocusing attention from weight loss to health gains. *Exerc Sport Sci Rev*, *43*(1), 41-47. https://doi.org/10.1249/JES.0000000000000034

Shapiro, H., Lutaty, A., & Ariel, A. (2011). Macrophages, meta-inflammation, and immuno-metabolism. *ScientificWorldJournal*, *11*, 2509-2529. https://doi.org/10.1100/2011/397971

Shapouri-Moghaddam, A., Mohammadian, S., Vazini, H., Taghadosi, M., Esmaeili, S. A., Mardani, F., . . . Sahebkar, A. (2018). Macrophage plasticity, polarization, and function in health and disease. *J Cell Physiol*, *233*(9), 6425-6440. https://doi.org/10.1002/jcp.26429

Shih, K. C., & Kwok, C. F. (2018). Exercise reduces body fat and improves insulin sensitivity and pancreatic β-cell function in overweight and obese male Taiwanese adolescents. *BMC Pediatr*, *18*(1), 80. https://doi.org/10.1186/s12887-018-1025-y

Shin, P. K., Park, S. J., Kim, M. S., Kwon, D. Y., Kim, M. J., Kim, K., . . . Choi, S. W. (2020). A Traditional Korean Diet with a Low Dietary Inflammatory Index Increases Anti-Inflammatory IL-10 and Decreases Pro-Inflammatory NF-κB in a Small Dietary Intervention Study. *Nutrients*, *12*(8). https://doi.org/10.3390/nu12082468

Siegrist, M., Rank, M., Wolfarth, B., Langhof, H., Haller, B., Koenig, W., & Halle, M. (2013). Leptin, adiponectin, and short-term and long-term weight loss after a lifestyle intervention in obese children. *Nutrition*, *29*(6), 851-857. https://doi.org/10.1016/j.nut.2012.12.011

Sindhu, S., Thomas, R., Kochumon, S., Wilson, A., Abu-Farha, M., Bennakhi, A., . . . Ahmad, R. (2019). Increased Adipose Tissue Expression of Interferon Regulatory Factor (IRF)-5 in Obesity: Association with Metabolic Inflammation. *Cells*, *8*(11). https://doi.org/10.3390/cells8111418

Singer, K., & Lumeng, C. N. (2017). The initiation of metabolic inflammation in childhood obesity. *J Clin Invest*, *127*(1), 65-73. https://doi.org/10.1172/JCI88882

Sirico, F., Bianco, A., D'Alicandro, G., Castaldo, C., Montagnani, S., Spera, R., . . . Nurzynska, D. (2018). Effects of Physical Exercise on Adiponectin, Leptin, and Inflammatory Markers in Childhood Obesity: Systematic Review and Meta-Analysis. *Child Obes*, *14*(4), 207-217. https://doi.org/10.1089/chi.2017.0269

Sjaarda, L. G., Bacha, F., Lee, S., Tfayli, H., Andreatta, E., & Arslanian, S. (2012). Oral disposition index in obese youth from normal to prediabetes to diabetes: relationship to clamp disposition index. *J Pediatr*, *161*(1), 51-57. https://doi.org/10.1016/j.jpeds.2011.12.050

Smallie, T., Ricchetti, G., Horwood, N. J., Feldmann, M., Clark, A. R., & Williams, L. M. (2010). IL-10 inhibits transcription elongation of the human TNF gene in

primary macrophages. *J Exp Med*, *207*(10), 2081-2088. https://doi.org/10.1084/jem.20100414

Soltero, E. G., Konopken, Y. P., Olson, M. L., Keller, C. S., Castro, F. G., Williams, A. N., . . . Shaibi, G. Q. (2017). Preventing diabetes in obese Latino youth with prediabetes: a study protocol for a randomized controlled trial. *BMC Public Health*, *17*(1), 261. https://doi.org/10.1186/s12889-017-4174-2

Soltero, E. G., Olson, M. L., Williams, A. N., Konopken, Y. P., Castro, F. G., Arcoleo, K. J., . . . Shaibi, G. Q. (2018). Effects of a Community-Based Diabetes Prevention Program for Latino Youth with Obesity: A Randomized Controlled Trial. *Obesity (Silver Spring)*, *26*(12), 1856-1865. https://doi.org/10.1002/oby.22300

Soltero, E. G., Ramos, C., Williams, A. N., Hooker, E., Mendez, J., Wildy, H., . . . Shaibi, G. Q. (2019). ¡Viva Maryvale!: A Multilevel, Multisector Model to Community-Based Diabetes Prevention. *Am J Prev Med*, *56*(1), 58-65. https://doi.org/10.1016/j.amepre.2018.07.034

Stoner, L., Beets, M. W., Brazendale, K., Moore, J. B., & Weaver, R. G. (2019). Exercise Dose and Weight Loss in Adolescents with Overweight-Obesity: A Meta-Regression. *Sports Med*, *49*(1), 83-94. https://doi.org/10.1007/s40279-018-01040-2

Stoner, L., Rowlands, D., Morrison, A., Credeur, D., Hamlin, M., Gaffney, K., . . . Matheson, A. (2016). Efficacy of Exercise Intervention for Weight Loss in Overweight and Obese Adolescents: Meta-Analysis and Implications. *Sports Med*, *46*(11), 1737-1751. https://doi.org/10.1007/s40279-016-0537-6

Stoppa-Vaucher, S., Dirlewanger, M. A., Meier, C. A., de Moerloose, P., Reber, G., Roux-Lombard, P., . . . Schwitzgebel, V. M. (2012). Inflammatory and prothrombotic states in obese children of European descent. *Obesity (Silver Spring)*, *20*(8), 1662-1668. https://doi.org/10.1038/oby.2012.85

Tateya, S., Tamori, Y., Kawaguchi, T., Kanda, H., & Kasuga, M. (2010). An increase in the circulating concentration of monocyte chemoattractant protein-1 elicits systemic insulin resistance irrespective of adipose tissue inflammation in mice. *Endocrinology*, *151*(3), 971-979. https://doi.org/10.1210/en.2009-0926

Tilg, H., & Wolf, A. M. (2005). Adiponectin: a key fat-derived molecule regulating inflammation. *Expert Opin Ther Targets*, *9*(2), 245-251. https://doi.org/10.1517/14728222.9.2.245

Vander Wyst, K. B., Hu, H. H., Peña, A., Olson, M. L., Bailey, S. S., & Shaibi, G. Q. (2021). Bone marrow adipose tissue content in Latino adolescents with

prediabetes and obesity. *Obesity (Silver Spring)*. https://doi.org/10.1002/oby.23279

Vander Wyst, K. B., Olson, M. L., Hooker, E., Soltero, E. G., Konopken, Y. P., Keller, C. S., . . . Shaibi, G. Q. (2020). *Yields and Costs of Recruitment Methods with Participant Phenotypic Characteristics for a Diabetes Prevention Research Study in an Underrepresented Pediatric Population.*

Villareal, D. T., Miller, B. V., Banks, M., Fontana, L., Sinacore, D. R., & Klein, S. (2006). Effect of lifestyle intervention on metabolic coronary heart disease risk factors in obese older adults. *Am J Clin Nutr*, *84*(6), 1317-1323. https://doi.org/10.1093/ajcn/84.6.1317

Visuthranukul, C., Sirimongkol, P., Prachansuwan, A., Pruksananonda, C., & Chomtho, S. (2015). Low-glycemic index diet may improve insulin sensitivity in obese children. *Pediatr Res*, *78*(5), 567-573. https://doi.org/10.1038/pr.2015.142

Vos, R. C., Wit, J. M., Pijl, H., & Houdijk, E. C. (2011). Long-term effect of lifestyle intervention on adiposity, metabolic parameters, inflammation and physical fitness in obese children: a randomized controlled trial. *Nutr Diabetes*, *1*, e9. https://doi.org/10.1038/nutd.2011.5

Wagenknecht, L. E., Palmer, N. D., Bowden, D. W., Rotter, J. I., Norris, J. M., Ziegler, J., . . . Langefeld, C. D. (2011). Association of PNPLA3 with non-alcoholic fatty liver disease in a minority cohort: the Insulin Resistance Atherosclerosis Family Study. *Liver Int*, *31*(3), 412-416. https://doi.org/10.1111/j.1478-3231.2010.02444.x

Wang, Y., Lam, K. S., Yau, M. H., & Xu, A. (2008). Post-translational modifications of adiponectin: mechanisms and functional implications. *Biochem J*, *409*(3), 623-633. https://doi.org/10.1042/BJ20071492

Weaver, J. R., Holman, T. R., Imai, Y., Jadhav, A., Kenyon, V., Maloney, D. J., . . . Taylor-Fishwick, D. A. (2012). Integration of pro-inflammatory cytokines, 12-lipoxygenase and NOX-1 in pancreatic islet beta cell dysfunction. *Mol Cell Endocrinol*, *358*(1), 88-95. https://doi.org/10.1016/j.mce.2012.03.004

Weickert, M. O., & Pfeiffer, A. F. H. (2018). Impact of Dietary Fiber Consumption on Insulin Resistance and the Prevention of Type 2 Diabetes. *J Nutr*, *148*(1), 7-12. https://doi.org/10.1093/jn/nxx008

Weiss, R., Taksali, S. E., Tamborlane, W. V., Burgert, T. S., Savoye, M., & Caprio, S. (2005). Predictors of changes in glucose tolerance status in obese youth. *Diabetes Care*, *28*(4), 902-909. https://doi.org/10.2337/diacare.28.4.902

Westerbacka, J., Cornér, A., Kolak, M., Makkonen, J., Turpeinen, U., Hamsten, A., . . . Yki-Järvinen, H. (2008). Insulin regulation of MCP-1 in human adipose tissue of obese and lean women. *Am J Physiol Endocrinol Metab*, *294*(5), E841-845. https://doi.org/10.1152/ajpendo.00653.2006

Westwell-Roper, C. Y., Chehroudi, C. A., Denroche, H. C., Courtade, J. A., Ehses, J. A., & Verchere, C. B. (2015). IL-1 mediates amyloid-associated islet dysfunction and inflammation in human islet amyloid polypeptide transgenic mice. *Diabetologia*, *58*(3), 575-585. https://doi.org/10.1007/s00125-014-3447-x

Wijesekara, N., Krishnamurthy, M., Bhattacharjee, A., Suhail, A., Sweeney, G., & Wheeler, M. B. (2010). Adiponectin-induced ERK and Akt phosphorylation protects against pancreatic beta cell apoptosis and increases insulin gene expression and secretion. *J Biol Chem*, *285*(44), 33623-33631. https://doi.org/10.1074/jbc.M109.085084

Willett, W. C. (2006). The Mediterranean diet: science and practice. *Public Health Nutr*, *9*(1A), 105-110. https://doi.org/10.1079/phn2005931

Winer, D. A., Winer, S., Chng, M. H., Shen, L., & Engleman, E. G. (2014). B Lymphocytes in obesity-related adipose tissue inflammation and insulin resistance. *Cell Mol Life Sci*, *71*(6), 1033-1043. https://doi.org/10.1007/s00018-013-1486-y

Winer, S., & Winer, D. A. (2012). The adaptive immune system as a fundamental regulator of adipose tissue inflammation and insulin resistance. *Immunol Cell Biol*, *90*(8), 755-762. https://doi.org/10.1038/icb.2011.110

Wolf, A. M., Wolf, D., Rumpold, H., Enrich, B., & Tilg, H. (2004). Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. *Biochem Biophys Res Commun*, *323*(2), 630-635. https://doi.org/10.1016/j.bbrc.2004.08.145

Yeckel, C. W., Weiss, R., Dziura, J., Taksali, S. E., Dufour, S., Burgert, T. S., . . . Caprio, S. (2004). Validation of insulin sensitivity indices from oral glucose tolerance test parameters in obese children and adolescents. *J Clin Endocrinol Metab*, *89*(3), 1096-1101. https://doi.org/10.1210/jc.2003-031503

Yu, N., Ruan, Y., Gao, X., & Sun, J. (2017). Systematic Review and Meta-Analysis of Randomized, Controlled Trials on the Effect of Exercise on Serum Leptin and Adiponectin in Overweight and Obese Individuals. *Horm Metab Res*, *49*(3), 164-173. https://doi.org/10.1055/s-0042-121605

Zeitler, P., Hirst, K., Pyle, L., Linder, B., Copeland, K., Arslanian, S., . . . Group, T. S. (2012). A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med*, *366*(24), 2247-2256. https://doi.org/10.1056/NEJMoa1109333