Diet Diversity and Health Value in Children with Non-alcoholic Fatty Liver Disease and Prader-Willi Syndrome: Association with Cardio-metabolic Risk

by

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Abstract

In Canada, the obesity prevalence rate in children and adolescents has increased significantly during the last four decades resulting in increased incidence of obesity- related health conditions, lower quality of life and greater health care cost. Patients with non-alcoholic fatty liver disease (NAFLD) or Prader-Willi syndrome (PWS) present two different forms of pediatric obesity with cardio-metabolic dysregulation (CMD) being a common feature among them. Few studies have examined whether this is related to poor diet quality (DQ) and lack of diet diversity (DD). DD is the variation of food intake across and within food groups and may be an important contributor to improved DQ if the observed diversity comes from healthy food choices which is the concept of dietary health value (HV). In the present study, DD, HV and overall healthy food diversity of patients with NAFLD (n= 12), PWS (n=8) and controls (n= 16) and their relation to CMD were studied using an adapted version of Healthy Food Diversity Index (HFD-I) and WHO definition for CMD. The results indicated that DD, HV and HFD-I scores were higher in children with higher scores for DQ. It also showed a significantly lower DD and HV in children with NAFLD, CMD, obesity and hyperinsulinemia/ insulin resistance (IR) while PWS patients had the highest scores for HFD-I. It was also displayed that higher scores of DD and HV were associated with higher intake of some relevant nutrients and food groups such as fiber, carbohydrate, protein, vitamin D and E, fruits and vegetables, milk and alternatives and lower intake of MUFA, meat and alternatives. The results of the present study show that increasing DD together with HV may improve the diets in children with NAFLD, CMD and obesity.

Preface

This thesis is a secondary data analysis of an original work done by Dr Mager's group. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name: "Vitamin D and body composition in children and adolescents with non-alcoholic fatty liver disease and Prader-Willi syndrome", No. Pro00056649.

No part of this thesis has been previously published. I (Maryam Beheshti Beglar MSc) was responsible for data analysis including adapting the HFD Index, data interpretation and thesis write up and secondary statistical analysis related to thesis hypothesis and objectives under the supervision of Dr Diana Mager PhD RD. Krista MacDonald MSc was responsible for subject recruitment and data collection for all data; data analysis for dietary intake food groups and Healthy Eating Index and data auditing: HV, BI and HFD calculations. Leslie Seto RD MSc RA contributed to data analysis/data auditing for BI, HFD and HV, data interpretation and method development/adaptation. Kristin Harms BSc RA was responsible for data analysis for Food groups and Healthy Eating Index. Dr Catherine Field PhD RD was on supervisory committee; contributed to study interpretation and provided feedback to thesis preparation. Dr Jason Yap MD FRCPC assisted with subject recruitment (KM), data interpretation and study design. Dr Andrea Haqq MD FRCPC assisted with subject recruitment (KM), data interpretation and study design. She was also Co-PI on grant. Dr Diana Mager PhD RD (Supervisor) was responsible for and supervised all phases of research: study design, data collection and data analysis, data interpretation, thesis preparation and feedback for MB and KM. She was Co-PI on grant funding for this project: Food and Health Innovation Fund, University of Alberta.

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My wonderful dad Mohammad Beheshti and my beloved mother Zahra Tabasi, I would like to dedicate this thesis to you and to my great sisters and brother, Masoume, Maral and Mahdi. Without your love, support and encouragements I would have not been able to make it. Words are not enough to express my appreciation towards you. I also need to thank you Hossein and my uncle Mahmoud for your care and help.

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List of Abbreviations

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ADC; American Diagnostic Corporation

AHS; Alberta Health Services

AI; Adequate Intake

ALP; Alkaline Phosphatase

ALT; Alanine Aminotransferase

AMDR; Acceptable Macronutrient Distribution Range

ANGCY; Alberta Nutrition Guidelines for Children and Youth

ANOVA; analysis of variance

APDQS; A Priori Diet Quality Score

AST; Aspartate Aminotransferase

BI; Berry Index

BMI; body mass index

BMR; basal metabolic rate

BP; blood pressure

BUN; blood urea nitrogen

CCHS; Canadian Community Health Survey

C-DHQ II; Canadian Diet History Questionnaire

CHO; carbohydrate

CMD; cardio-metabolic Dysregulation

CRP; C-reactive protein

DBP; diastolic blood pressure

DD; diet diversity

DDS; Diet Diversity Score

DED; Dietary Energy Density

DFE; dietary folate equivalents

DGI-CA; Dietary Guideline Index for Children and Adolescents

DNL: de novo lipogenesis

DQ; diet quality

DQI-I; Diet Quality Index-International

DRI; Dietary Reference Intakes

DS; Down syndrome

EAR; Estimated Average Requirement

FFA; free fatty acids

FFQ; food frequency questioner

FVS; Food Variety Score

FXR; Farnesoid X receptor

ɣGT; gamma-glutamyl transferase

GI; glycemic index

GL; glycemic load

HDL-C; high density lipoprotein cholesterol

HEI-C; Healthy Eating Index-Canada

hf; health factor

HFCS; high fructose corn syrup

HFD-I; Healthy Food Diversity- Index

HI; hyperinsulinemia

HV; health value

HiC; hip circumference

HOMA-IR; homeostasis model assessment for insulin resistance

HuSKY; Healthy Nutrition Score for Kids and Youth

IBW; ideal body weight

IDEFICS; Identification and prevention of Dietary- and lifestyle-induced health EFfects In Children and infantS

IDF; International Diabetes Institute

IFI; Indicator Food Index

IGF; insulin-like growth factors

IL-1β: interleukin-1β

IL-6: interleukin-6

IQR; inter- quartile range

IR; insulin resistance

LBM; lean body mass

LDL-C; low density lipoprotein cholesterol

LGI: low glycemic index

LPS: lipopolysaccharide

MAR; mean adequacy ratio

MRE; magnetic resonance elastography

MRI; magnetic resonance imaging

MRS; magnetic resonance spectroscopy

MUFA; mono- unsaturated fatty acid

NACTRC; Northern Alberta Clinical Trials Centre

NAFLD; non-alcoholic fatty liver disease

NASH; non-alcoholic steatohepatitis

NEFA; non-esterified free fatty acids

OMD; Optimized Mixed Diet

PPARα; Peroxisome proliferator-activated receptor alpha

PUFA; poly- unsaturated fatty acid

PWS; Prader–Willi syndrome

QR; quartile range

RDA; Recommended Dietary Allowance

ROS; reactive oxygen species

SBP; systolic blood pressure

SCFA; short chain fatty acid

SFA; saturated fatty acid

SOCS; suppressors of cytokine signaling

TC; total cholesterol

TG; triglycerides

TNF; tumor necrosis factor

TSH; thyroid stimulating hormone

UA; uric acid

VLDL; very low-density lipoprotein

WC; waist circumference

WHO; World Health Organisation

WHtR; waist to height ratio

WHR; waist to hip ratio

WS; Williams syndrome

Presentation of Work within Thesis

Poster presentation and abstract

Beheshti M, MacDonald K, Seto L, Harms K, Field CJ, Yap J, Haqq A, Mager D. Diet Diversity in Children with Non-alcoholic Fatty Liver Disease and Prader Willi Syndrome: Association with Cardio-metabolic Risk. ADI Research Day, October 2018.

Chapter 1: Literature Review

1.1 Introduction

Several nutritional guidelines across the world emphasize the necessity of having a varied and diverse diet. Some relationships have been shown between diet diversity (DD) score values with nutrient intake and anthropometric parameters, chronic diseases such as cardio- vascular disease, metabolic syndrome, obesity, cancer and non-alcoholic fatty liver disease and all-cause mortality (1-14). However, there are some controversies regarding the relationships between DD and cardio-metabolic dysregulation (CMD) and/or chronic disease in children and youth (7, 15). For instance, some researchers have found greater BMI or waist to hip ratio in children with higher DD (7, 16) while others observed lower BMI and smaller waist circumference (WC) in children with higher DD (15). Diversity is the variation of food intake across and within food groups (17). When measuring diet diversity, what is equally important is to know if that diversity comes from food choices with a higher health value (HV) (Figure 1.1) or with lower HV.

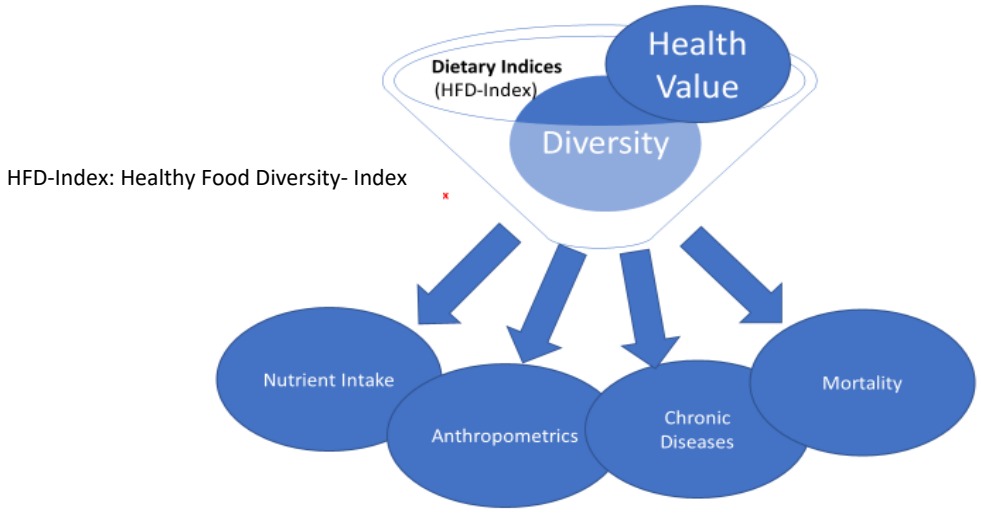


Figure 1.1 Diet Diversity and Health Value. *Diversity and health value of the diet, measured by indices such as Healthy Food Diversity (HFD) Index has been linked to nutrient intake, anthropometrics, chronic diseases and mortality*. Sources: (1, 3, 17).

HV, in general, refers to the proportion of the overall dietary consumption that comes from healthy food choices and is an important component of the associations that have been observed between dietary intake and chronic disease prevention (1). This is particularly important to study as obesity rates in children and adults globally have increased exponentially over the past few decades leading to an increased risk of chronic diseases such as diabetes, cardiovascular and liver diseases. In Canada, the obesity prevalence rate in children and adolescents has increased significantly during the last four decades resulting in increased incidence of obesity-related health conditions such as type 2 diabetes, dyslipidemia, hypertension, depression, joint problems, sleep apnea and non-alcoholic fatty liver disease (NAFLD) in this population (18, 19). These conditions are considered a burden on individual's quality and quantity of life and health care cost and the higher risk of obese children to become obese adults adds to the burden (18, 19). In 2013, 27% of Canadian children were either overweight or obese (20). A group of obese patients are those with syndromic obesity like Prader Willi Syndrome (PWS) which if left unmanaged, will lead to morbid obesity and increased mortality rate (21). There are controversial results regarding the association between obesity and DD in children and adolescents depending on the tool used and the location of the study (4, 7, 22, 23). Some researchers such as Fernandez and Vakili and their colleagues reported a positive association between diet diversity (DD) and BMI and waist to hip ratio in children and youth (7, 16). On the other hand, higher DD score was associated with lower BMI, waist circumference and lower prevalence of overweight/obesity among a group of Iranian adolescents (15).

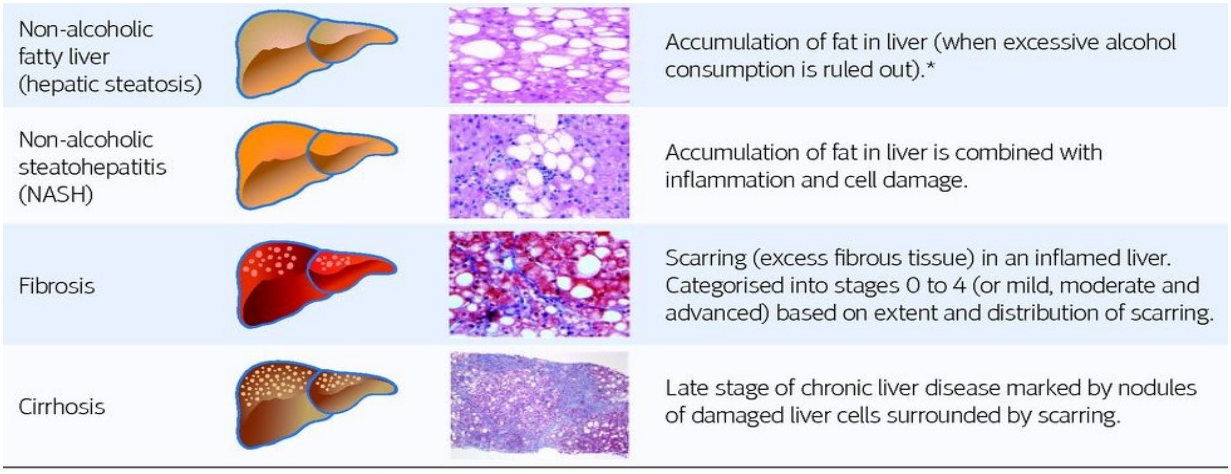
The objective of this literature review is to critically examine the concepts of DD and overall healthy eating in obese children and adolescents with non-alcoholic fatty liver disease

and children with Prader-Willi syndrome. A secondary objective is to evaluate the existing literature regarding the associations of DD with anthropometric and cardio-metabolic dysregulation in these populations.

1.2 Study Population

1.2.1 Non-Alcoholic Fatty Liver Disease (NAFLD)

About 10- 20% of overweight and obese children are affected by non-alcoholic fatty liver disease (NAFLD)(24) . NAFLD is a term used to address a spectrum ranging from accumulation of fat in hepatocytes (fatty liver) to inflammation ± fibrosis (non-alcoholic steatohepatitis or NASH), and cirrhosis (14, 25) (Figure 1.2). The prevalence of obesity and NAFLD is increasing in such an alarming rate that one would anticipate a "tsunami" of NAFLD-related complications in future (26). The pathophysiology and natural course of the disease is complex, some aspects have been recognized but there are so many hidden corners awaiting to be elucidated (27).



Reproduced from [Non-alcoholic fatty liver disease (NAFLD): summary of NICE guidance], Glen J, Floros L, Day C, Pryke R, 354, 2-7, 2018] with permission from BMJ Publishing Group Ltd (28).

Figure 1.2 NAFLD Progression and Pathogenicity. *NAFLD is a term used to address a spectrum ranging from accumulation of fat in hepatocytes (fatty liver) to inflammation ± fibrosis (non-alcoholic steatohepatitis or NASH).*

1.2.2 Clinical/ cardio-metabolic characteristics in NAFLD

The etiology of pediatric NAFLD and NASH is suggested to have a "multi hit" model including hepatic fat accumulation, insulin resistance (IR), oxidative stress, gut microbiota, unhealthy life style (physical inactivity, high saturated fat/simple sugar intake) and gut liver axis dysfunction (figure 1.3) (29). The sex and the ethnicity differences in prevalence rate (more prevalent in males and Hispanics, the progression of the disease and the responsiveness to treatment and the fact that not all obese patients develop NAFLD, suggests the involvement of some hereditary predispositions in the etiology (26, 27, 30-34). The gene variants whose association has been fully confirmed in pediatric population are: PNPLA3 rs738409, GCKR rs1260326, and TM6SF2 rs58542926 (30). IR and hyperinsulinemia are important factors that have been shown to play a fundamental role in NAFLD etiology (25, 27, 31, 35, 36). Insulin is an anabolic hormone which blocks lipolysis (37). Therefore in IR state, the continued lipolysis in adipose tissue leads to efflux of non-esterified free fatty acids (NEFA) to the liver which may potentially contribute to excessive fat accumulation in the liver (37). Reduced hepatic secretion of triglycerides in form of VLDL and impaired fatty acid oxidation can also add to fat accumulation (27, 38). Accumulated fatty acids activates some signalling pathways which are related to steatosis and inflammation (38). NEFA may be toxic and damage hepatocellular mitochondria leading to decreased beta-oxidation of free fatty acids, increased oxidative stress and consequent exacerbation of the liver inflammation and damage (38). Beta oxidation can be suppressed by insulin as well (38). Insulin and certain SOCS (suppressors of cytokine signaling) proteins upregulate SREBP-1c (sterol regulatory element binding protein-1c) which is involved in hepatic fat and glucose metabolism, resulting in hypertriglyceridemia observed in NAFLD (38). Insulin can

also upregulate hepatocellular SOCS-3 which in turn downregulates hepatocellular insulin receptors, adding to hepatic resistance to insulin (38). Impaired fatty acid oxidation ends in the production of an excessive amount of reactive oxygen species causing even more damage to the liver (31).

Obesity, particularly central obesity has been confirmed as an important risk factor for NAFLD in children and adolescents (29-31). In IR status, uptake of TG-rich chylomicrons by peripheral adipose tissue may be reduced due to inhibited lipoprotein lipase (29). Excess visceral fat is effluxed directly to the liver through portal vein in form of FFA (27). Metabolites of FFA relocate protein kinase C from cytoplasm to the cell membrane, causing the phosphorylation and unresponsiveness of Insulin receptors and thereby worsening of IR and Inflammation (27). Moreover, in presence of excessive FFA in adipose tissue, adiponectin is suppressed while leptin, tumor necrosis factor-alpha (TNF-α) and some other pro-inflammatory adipocytokines are increased, worsening the liver damage (29, 38). The oxidative stress observed in fatty liver might be partly derived from mitochondria, peroxisomes and microsomes (29). IR can trigger lipid peroxidation and reactive oxygen species (ROS) production by inhibiting cytochrome P450 4A (29, 38). This can induce the synthesis of several pro-inflammatory and fibro-genic cytokines leading to NASH and cirrhosis (29). Abnormal glutathione–related pathways and elevated plasma oxidised glutathione has also been reported in pediatric NASH (39).

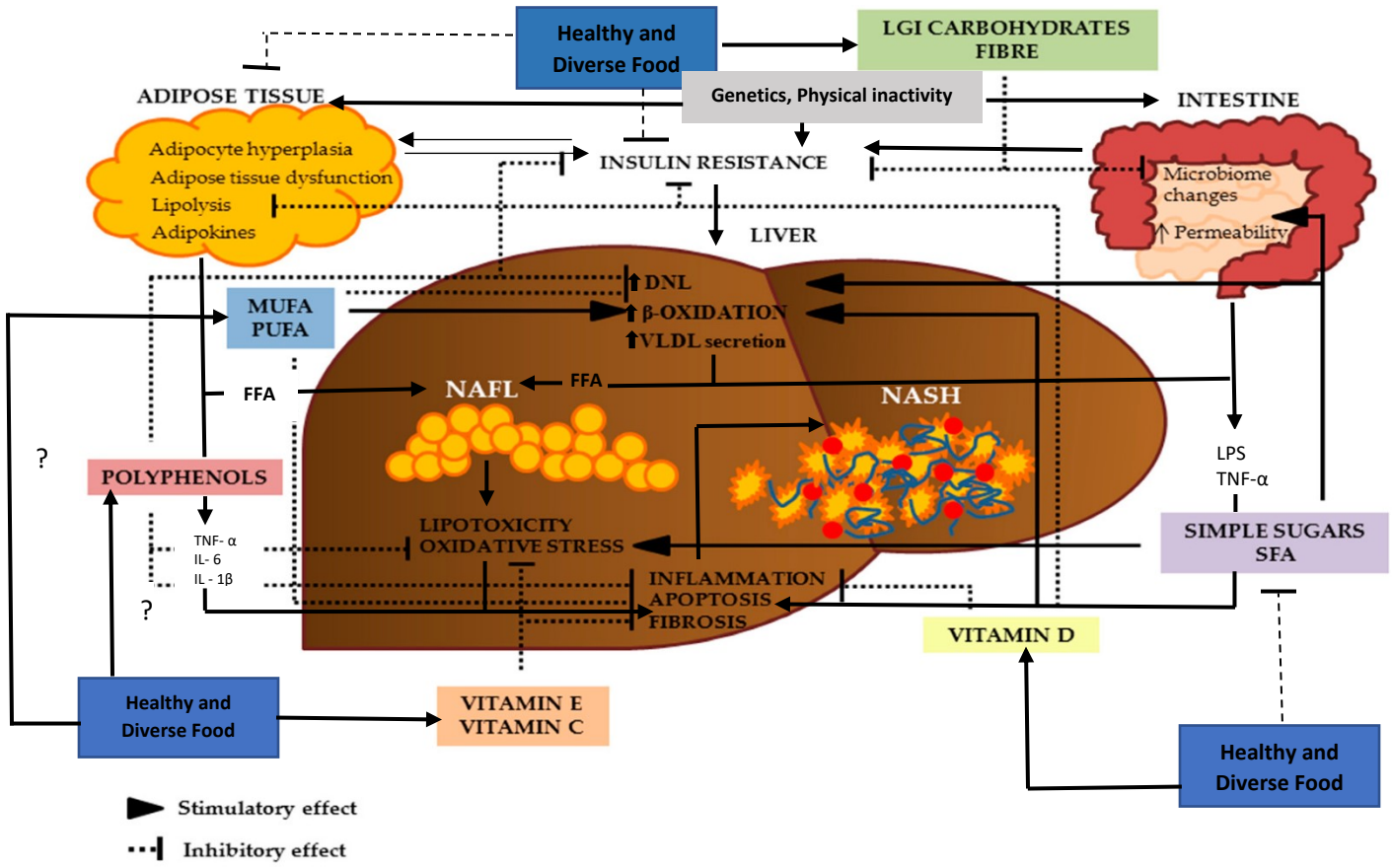


Figure 1.3 NAFLD pathogenesis Based on the "Multiple Hit" Model and Possible Sites of Action of Dietary Nutrients in the Nutritional Treatment and Prevention of NAFLD. *Nutrients and dietary composition can modulate many key aspects in the pathophysiology of NAFLD: simple sugars promote DNL, produce inflammation and activate cellular stress pathways. Contrarily, LGI meals can improve insulin resistance and can positively modulate the microbiome. SFA could induce lipogenesis, oxidative stress, and apoptosis of hepatocytes; conversely, MUFA and PUFA can improve FFA β-oxidation and can reduce DNL, improve insulin sensitivity and reduce inflammation. Polyphenols could inhibit DNL and increase FFA β-oxidation. Furthermore, polyphenols can improve insulin sensitivity, reduce the transcription of inflammatory cytokines, and can mitigate the oxidative stress involved in NAFLD progression. Vitamin C and vitamin E could avoid the progression of NAFLD and improve NASH acting as powerful antioxidants; furthermore, vitamin E could reduce plasma levels of cytokines involved in inflammation and liver fibrosis. Vitamin D can reduce the transcription of inflammatory cytokines and improve FFA β-oxidation. Furthermore, it has been observed that vitamin D increases adiponectin secretion, decreases lipolysis in adipose tissue, and improves IR. The possible action site of healthy food diversity has also been shown. DNL: de novo lipogenesis; IL-6: interleukin-6; IL-1β: interleukin-1β; LGI: low glycemic index; LPS: lipopolysaccharide; MUFA: monounsaturated fatty acids; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; PUFA: polyunsaturated fatty acids; SFA: saturated fatty acids; TNF-α: tumor necrosis factor-α.*

Adapted with permission from: Della Pepa G et al. Isocaloric Dietary Changes and Non-Alcoholic Fatty Liver Disease in High Cardiometabolic Risk Individuals. Nutrients. 2017;9(10):1065 (40).

There is evidence showing a role of dysbiosis (imbalance between different bacteria species in the intestine) in etiology of NAFLD (27, 29, 31). Dysbiosis might increase the permeability of the gut allowing the toxins to pass through the barrier into the portal blood which leads to inflammation and injury of the liver (29, 31). Microbiota breaks down non-absorbable polysaccharides into monosaccharides and short chain fatty acids (SCFAs) and add to the calorie intake (29, 41). Monosaccharides might increase hepatic lipogenesis and fat accumulation through activation of hepatic carbohydrate response element binding protein (27, 29). Additionally, SCFAs may increase leptin production (27, 29). These may be the potential mechanism through which dysbiosis takes part in NAFLD etiology. Bile acids composition might also be subject to change at the presence of dysbiosis (27, 29, 42). There is evidence showing that bile acids play a role in regulation of carbohydrate and lipid metabolism and insulin sensitivity through Farnesoid X receptor (FXR), the mechanism by which bile acid might be involved in NAFLD pathophysiology (27, 29, 31, 42). Another possible mechanism of the gut microbiota impact on NAFLD is the decreased phosphatidylcholine metabolism leading to decreased VLDL export from the liver and increased endogenous production of ethanol due to bacterial overgrowth (27, 29). Endogenous ethanol yields acetaldehyde which can generate liver damage ranging from fatty infiltration to inflammation and fibrosis (29, 43). However, the elevated blood ethanol levels could be rather attributed to insulin-dependent impairment of alcohol dehydrogenase activity in the liver (29).

There are several studies reporting a lower physical activity level in obese youth with NAFLD when compared to healthy lean controls (44-48). The relationship between transaminases levels and physical inactivity have also been displayed (44). Mager et al. have also shown that

youth with fatty liver spend the majority of their leisure time doing sedentary activities such as watching TV and video games (46). Apart from obesity and hyperinsulinemia which are also considered the key factors in NAFLD etiology, elevated liver function enzyme (increased alanine aminotransferase, aspartate transaminase, alkaline phosphatase, gamma-glutamyl transferase), dyslipidemia (high plasma triglyceride and low levels of high density lipoprotein cholesterol), hypertension and elevated blood urea nitrogen (BUN) are other manifestations of the disease (49-51). However, there are a considerable number of patients who have normal liver function tests, lipid profile, blood pressure and uric acid (33, 51-54).

Regarding the manifestations, it is not surprising that the prevalence of characteristics of cardio-metabolic dysregulation (CMD) is as high as 84.61% in patients with NAFLD (55). The progression of the disease to a more severe cirrhosis and cardiovascular disease occur faster in these patients (56, 57). Therefore, it is important to understand the lifestyle factors that may contribute to CMD.

1.2.3 NAFLD and dietary factors

Several dietary factors have been associated with NAFLD etiology in children and adolescents (Figure 1.3). It has been shown that these patients have increased intake of total and saturated fat, simple carbohydrate, fructose and high fructose corn syrup (HFCS) and a lower intake of fiber, vitamin D and vitamin E (25, 27, 58-61).

HFCS and Saturated fat

HFCS and glucose upregulate the de-novo lipogenesis that leads to oxidative stress and liver injury which is further exacerbated by some vitamin deficiencies (62, 63). Antioxidant deficiency may increase lipid peroxidation and cell death due to mitochondrial compromise (64-69). Glucose can enhance liver lipogenesis through activation of a carbohydrate response element binding protein (60). Excessive fat intake directly leads to excess free fatty acids which their accumulation enhances peroxidation and consequent injury (70, 71). Saturated fat enhances de-novo lipogenesis. The involved mechanism depends on PPARα and the eminence of this effect is determined by the content of sucrose in the diet (29). Saturated fat also triggers endoplasmic reticulum stress and apoptosis in hepatocytes and cause more injury (72). Diets high in saturated fat have been associated with lower DD and HV in some studies in adults; contributing to increased expression of CMD components (1). However, little information is available regarding its contribution to NAFLD disease etiology and/or NAFLD disease expression.

Vitamin D and E

As evident in animal studies, this injury could even worsen by vitamin D deficiency-through reduced expression of IGF-1 and the resulting inflammation in the liver (73). It is now evident that low plasma concentrations of 25(OH)D are associated with obesity, metabolic syndrome, NAFLD and its progression (29). In human subjects, vitamin D supplementation has also resulted in decreased secretion of inflammatory cytokines (74). However, evidences on supplementation of vitamin D in NAFLD are controversial. Sharifi and Amani systematically and critically reviewed the clinical trials available in this area (75). Of 6 articles included, only 2

reported significant decrease in grade of hepatic steatosis and one reported changes in IR after vitamin D supplementation. One in 3 studies that measured biomarkers of inflammation and oxidative stress revealed a significant decrease in these biomarkers after vitamin D supplementation. Vitamin E insufficiency has been related to higher grade of hepatic steatosis in children (59, 76). Nobili et al. have also shown the favourable effect of vitamin E supplementation on transaminases and liver histology in children with NAFLD (76, 77). In another study, vitamin E (600 IU/day) and ascorbic acid (500 mg/day) supplementation in addition to dietary changes and physical activity, have shown to improve liver function and metabolism of glucose in children (78).

1.2.4 Diagnosis of NAFLD

Pediatric NAFLD usually has no clinical symptoms except for malaise or fatigue in some patients (79). A complaint of a vague pain in upper right quadrant of abdomen may be present which may be linked to a more advanced non-alcoholic steatohepatitis (NASH) (79). NAFLD in pediatrics is usually considered a "diagnosis of exclusion" which means several conditions that could have caused a steatosis should be ruled out (Table 1.1) after a positive imaging (usually ultrasonography or fibroscan) or liver function tests (primarily ALT and ɣGT)(52, 79).

Other imaging methods are also available such as unenhanced computed tomography (CT), MRI, 1H-MR spectroscopy (1H-MRS) and Magnetic resonance elastography (MRE or fibroscan). While liver biopsy has been historically regarded as the gold standard for NAFLD diagnosis, more recent approaches to clinical practice have been to delay liver biopsy in favor of less invasive methods such as elastography, however there are some cases that the biopsy should

be done right away (Appendix A, Table A1)(38, 53, 79). The specificity and sensitivity of the NAFLD diagnosis criteria are displayed in Appendix A (Table A2) (33). The cut-off value of ALT for diagnosis of NAFLD in children is ALT levels> 20 U/L (80).

Table 1.1 Causes of Fatty Liver Disease in Children

General or systemic	Genetic-metabolic causes	Other rare hereditary genetic disorders	Drugs' hepatotoxicity
Acute systemic disease	Cystic fibrosis and Shwachman	AlstrÖm syndrome	Ethanol
Acute starvation	syndrome	Bardet-Biedl syndrome	Ecstasy, cocaine
Protein energy malnutrition	Wilson disease	Prader-Willi syndrome	Nifedipine
Total parenteral nutrition	a1-Antitrypsin deficiency	Cohen syndrome Cantu	Diltiazem
Obesity/metabolic syndrome	Galactosemia	syndrome (1p36 deletion)	Estrogens
Polycystic ovary syndrome	Fructosemia	Weber-Christian disease	Corticosteroids
Obstructive sleep apnea	Cholesteryl ester storage disease		Amiodarone
Rapid weight loss	Glycogen storage disease (types I &VI)		Perhexiline
Anorexia nervosa	Mitochondrial and peroxisomal		Coralgil
Cachexia	defects of fatty acid oxidation		Tamoxifen
Inflammatory bowel disease	Madelung lipomatosis		Methotrexate
Celiac disease	Lipodystrophies		Prednisolone
Hepatitis C	Dorfman-Chanarin syndrome		Valproate
Nephrotic syndrome	Abeta or hypobetalipoproteinemia		Vitamin
Type 1 diabetes mellitus	α and β-oxidation defects		L- asparaginase
and Mauriac syndrome	Porphyria cutanea tarda		Zidovudine and
Thyroid disorders	Homocystinuria		HIV treatments
Hypothalamo-pituitary	Familial hyperlipoproteinemias		Solvents
disorders	Tyrosinemia type 1		Pesticides
Blind loop (bacterial	Bile acids synthesis defects		
overgrowth)	Congenital disorders of glycosylation		
	Turner syndrome		
	Organic acidosis		
	Citrin deficiency		
	HFE (hemochromatosis)		

Adapted with permission from Vajro P, Lenta S, Socha P, et al. Diagnosis of Nonalcoholic Fatty Liver Disease in Children and Adolescents: Position Paper of the ESPGHAN Hepatology Committee. Journal of Pediatric Gastroenterology and Nutrition, 2012,54 (5): 700- 713 (79).

1.2.5 Treatment of NAFLD

The main treatment for NAFLD is life style change with weight loss being one of the main goals (25). Loosing 3-5% of weight has been associated with improvements in steatosis, while a 10% reduction may improve inflammatory activity (53). For a systemic metabolic benefit to be achieved, a 0.25 BMI SDs change is typically necessary (53). However, achieving a sustainable weight loss on a long run is a hard task (53, 81). Currently, there are no specific evidenced based guidelines on the most effective way to promote weight loss in both children and adults with NAFLD (79, 82, 83). Traditionally, the approaches have included weight loss induced by hypocaloric diets and increased physical activity; both of which have illustrated that improvements in hepatic steatosis can be obtained with weight reduction (53, 84). However, sustainability of these approaches has been low in both adults and children (25, 53, 85). More recently, interest in examining the influence of iso-caloric approaches with alterations in saturated fat and simple sugar intake have shown promising results (25, 84). There are evidences of the favorable effects of iso-caloric nutritionally modulated diets on liver fat content and IR (25, 81). It has been shown that iso-caloric low fat- high carbohydrate diets, low SFA- high PUFA diets and high MUFA diets can decease the liver fat content but not IR in adults (81). In a pilot study done by Mager et al. in 12 children and adolescents with NAFLD, an iso-caloric diet with modest reductions in fructose content and glycemic index/load was associated with a significant decrease in IR, ALT, percentage body fat and systolic blood pressure (SBP) (25). However, more work needs to be done to examine the potential effectiveness of these strategies. It has also been shown that vitamin E supplementation at a dosage of 800 IU/day could resolve NASH in 8-17

year-old children with NAFLD, but in adults with NAFLD the data has been equivocal (86). A summary of some lifestyle interventions to treat NAFLD is presented in table 1.2.

Table 1.2 A Summary of Some Lifestyle Interventions to Treat NAFLD in Children and Adolescents.

References	Location	Subjects (N)	Age (SD)	Type of Intervention	Weekly Frequency	Exercise Duration (min)	Duration (W)	Nutrition	Results
Van der Heijden GJ, 2010	EUA	15	12.6 (0.4)	Exercise	4	30	12	n/a	Decrease in hepatic and visceral fat and IR
Farris JW,2011	EUA	23	6- 12	Exercise and Diet	3	60	12	n/d	Decrease in BMI, Body Fat, WC, TC, BS, BUN, ALT, SBP, ALT and increase in fitness
Verduci E, 2013	Italy	46	6- 14	Exercise and diet	7	30-45	12	55% CHO, 25% Fat, 12% protein	Decrease in liver fat
Gronbaek, 2012	Denmark	117	12.1 (1.3)	Exercise and diet	7	60	10	60% CHO, 24% Fat, 16% protein, 1.547 Kcal/day	Weight loss, decreased steatosis, transaminases and IR
Antunes BDMM,2013	Brazil	34	13.7 (1.17)	Exercise	3	60	20	n/a	Decrease in body fat, liver lobes size, TC, LDL-C, lower prevalence of fatty liver and increase in LBM.
Togashi K, 2010	Japan	33	10.1 (1.7)	Exercise and diet	7	60	12	55% CHO, 25% Fat, 20% Protein 1.400-1.900 Kcal/day	Significant decrease in substances fat and visceral fat. Notable decrease in TG, TC, insulin, AST, ALT, and UA

Table 1.2 A Summary of Some Lifestyle Interventions to Treat NAFLD in Children and Adolescents, Continued.

References	Location	Subjects (N)	Age (SD)	Type of Intervention	Weekly frequency	Exercise Duration (min)	Duration (W)	Nutrition	Results
Wang CL, 2008	China	76 (19 in diet group)	13.4 (2.5)	Exercise and diet	3	30	4	50% CHO, 10% Fat, 20% Protein, 1300-1600 Kcal VS vitamin E (100mg/d)	Improvement of BMI, ALT, AST, TG, TC and HOMA-IR in both groups but less significantly in vitamin E group
Nobili V, 2006	Italy	90 (43 in placebo)	12.4 (3.02)	Exercise and diet	7	45	52	50-60% CHO, 23-30% Fat, 15-20% Protein, 25-30 Kcal/Kg+ placebo vs Vitamin E 600 IU + 500 mg/d+ diet	Decrease in ALT, HOMA-IR and weight in both groups. Antioxidants supplements did not add to the effect.
Tazawa Y, 1997	Japan	73	10	Exercise and diet	n/d	n/d	12	n/d	Normalisation of AST/ALT in 70% of patients
Vajro P, 2000	Italy	11	8.5 (2.8)	Exercise and diet	n/d	n/d	26	65% CHO, 23% Fat, 12% Protein, 30 Kcal/ Kg	Weight loss and resolved biochemical liver abnormalities
Tock L, 2010	Brazil	14	15-18	Exercise and diet	3	60	52	n/d	Metformin plus intervention produced more improvement in IR and visceral fat

Table 1.2 A Summary of Some Lifestyle Interventions to Treat NAFLD in Children and Adolescents, Continued.

References	Location	Subjects (N)	Age (SD)	Type of Intervention	Weekly frequency	Exercise Duration (min)	Duration (W)	Nutrition	Results
Nobili V, 2006	Italy	84	3-18.8	Exercise and diet	3	45	52	50-60% CHO, 23-30% Fat, 15-20% Protein, 25-30 KCal	significant decrease in BMI, fasting glucose, insulin, lipids, and liver enzymes, liver echogenicity
Tock L, 2006	Brazil	73	17	Exercise and diet	2	60	52	n/d	Reduction in visceral fat and NAFLD prevalence
Reinehr T, 2009	London	109	6-16	Exercise and diet	1	n/d	52	55% CHO, 30% Fat, 15-20% Protein	significant decrease of transaminases and overweight
Pozzato C, 2010	Italy	26	6- 14	Exercise and diet	7	45	52	55-60% CHO, 25-30% Fat, 12-15% Protein	Decrease in steatosis prevalence, BMI, WC, TG, TC, Apo A1, ApoB, ApoA1/ApoB ratio, and ɣGT
Santomauro M, 2012	Venezuela	24	7- 18	Exercise and diet	3	30	52	n/d	NAFLD resolving in 37.5%, decreased severity in 12.5%, Decrease in BMI, fat area, basal insulin, IR lipid profile and transaminases

Table 1.2 A Summary of Some Lifestyle Interventions to Treat NAFLD in Children and Adolescents, Continued.

References	Location	Subjects (N)	Age (SD)	Type of Intervention	Weekly frequency	Exercise Duration (min)	Duration (W)	Nutrition	Results
Akcam M, 2011	Turkey	22	11.3 (2.6)	Exercise and diet	7	30	26	50% CHO, 30% Fat, 20% Protein, 30 Kcal/kg	Significant decrease in BMI, Fasting insulin and IR.
Nadeau KJ, 2009	USA	13	15.1	Exercise and diet	n/d	n/d	26	n/d	significantly Decrease in ALT, ɣGT and fasting insulin
Koot BG, 2011	Holland	144	14.1 (2.3)	Exercise and diet	3	60	26	n/d	Decrease in steatosis and high ALT and AST prevalence
Mager D, 2015	Canada	12	7- 18	Diet	7	n/d	24	low GI (45-55), GL (<80), and fructose (<7% of total EI), 45-50% CHO, 25-30% Fat, 15-20% protein, 1600- 2300 kcal	Decrease in SBP, body fat, Apo B-100, ALT and HOMA-IR

Abbreviations: ALT, Alanine Transaminase; AST, Aspartate Transaminase; BS, Blood Sugar; BMI, Body Mass Index; BUN, Blood Urea Nitrogen; CHO, Carbohydrates; EI, energy intake; ɣGT, Gamma-Glutamyl Transferase; GI, Glycemic Index; GL; Glycemic Load; IR, Insulin Resistance; LBM, Lean Boddy Mass; LDL-C, Low Density Lipoprotein Cholesterol; SBP, Systolic Blood Pressure; TC, Total Cholesterol; TG, Triglycerides; UA, Uric Acid; W, Week; WC, waist circumference.

Modified with permission from: Utz-Melere M, Targa-Ferreira C, Lessa-Horta B, Epifanio M, Mouzaki M, Mattos AA. Non-Alcoholic Fatty Liver Disease in Children and Adolescents: Lifestyle Change - a Systematic Review and Meta-Analysis. Annals of Hepatology. 2018;17(3):345-54 (87).

1.2.6 Prader Willi syndrome (PWS)

PWS is a genetic disorder resulting from the absent expression of the paternal active genes in chromosome 15 at the locus q11_q13 (88). It is the most common form of genetic obesity with the prevalence rate of 1 in 10,000 to 1 in 20,000 live births (89, 90).

1.2.7 Clinical and cardio-metabolic characteristics of PWS

The syndrome is manifested by neonatal hypotonia and failure to thrive at early phases and morbid obesity in later phases (89, 91). Regarding nutrition, patients with PWS experience 5 different distinct phases with the first phase occurring in utero. The second phase (from birth to 25 months of age) which has two sub- phases is typically defined as a phase where children have "normal Appetite". Weight gain without an increase in appetite is the characteristic of the first sub- phase of phase 3 followed by a sub- phase of increased interest in food and continued weight gain. This happens around the age 4.5-8 years but may vary in presentation (89, 91). At phase 4, hyperphagia starts which subsides at phase 5 in adulthood (89, 91). Other manifestations are endocrine defects and hypogonadism, scoliosis, developmental delay, sleep abnormalities, cognitive impairment, characteristic facial appearance and short stature due to insufficient growth hormone (90, 92).

Patients with PWS typically have a higher fat mass but lower visceral fat and lower lean body mass than the individuals with simple obesity and the same degree of excess weight both in children and adults (21, 90, 93). This might be the reason why BMI is not an appropriate indicator of body composition in these patients and might explain the 20- 40% lower calorie needs of patients with PWS in comparison to others (89, 90). Other explanations might be lower spontaneous physical activity and reduced metabolic rate (89, 94). Lower visceral fat might also

explain lower than expected prevalence of cardio-metabolic dysregulation characteristics such as IR in PWS patients compared to healthy individuals with the same BMI (21, 90). However, several cardiovascular risk factors have been observed in pre-pubertal children with PWS and many PWS children die early due to complications related to obesity like type 2 diabetes mellitus (DM2) and hypertension (21). Brambilla et al. have demonstrated that although non-obese PWS patients have lower frequency of metabolic syndrome and its components, obese PWS patients have almost the same frequency levels compared to non-syndromic obese controls. This shows the importance of preventing or treating obesity in PWS patients (21).

Some studies have shown that the dietary intake of PWS patients might be low in calcium, vitamin D, tocopherol, iron and fiber (89, 94-96). In a study in Canadian children and adolescents with PWS, it was shown that mean intake of macronutrients, saturated fat, calcium, vitamin D, vitamin K and food groups (grains, milk, meat, fruit and vegetables) was within the recommended range, however vitamin D intake from food (excluding supplemented vitamin D) was far below the recommendations (33). PWS patients had significantly lower intake from grains and higher intake from fruits and vegetables compered to healthy controls (33). Overall diet quality was also significantly higher in these children suggesting a higher dietary HV. However, no information regarding food diversity and/or the overall HV of these children was available (33).

Individuals with PWS have been shown to have reduced physical activity and motor skills explained partly by lower lean mass (97, 98). It has been shown that children with PWS have reduced lean mass and maximal jump power compared to age/gender matched healthy controls (99). Similarly, 9 Canadian children and adolescent with PWS studied by MacDonald et al. had significant reduced handgrip strength and shorter 6-minute walk test distances compared to

healthy controls and children with NAFLD (33). A comparison of NAFLD and PWS characteristic is displayed in table 1.3.

Table 1.3 Pathophysiology, Anthropometric and Laboratory Differences between NAFLD and PWS

	Obese child with NAFLD	Obese child with PWS
Pathophysiology	-More common in males -Non-syndromic: life style induced and some genetic component	-No gender differences -Syndromic: genetic, hyperphagia
Height	-Normal	- Short stature due to growth hormone deficiency
Body Composition	<u>Adipose Tissue</u> ↑Total body fat ↑ Primarily visceral fat/ subcutaneous fat↑or within normal range <u>Lean Mass</u> -Lean mass normal/↓lean mass possible	<u>Adipose Tissue</u> ↑ Total body fat ↑ Primarily subcutaneous fat/visceral fat likely in normal range <u>Lean Mass</u> ↓Lean mass
Lipid Panel	↑Blood lipids (TG, TC, LDL) ↓HDL -Could be normal	-Could be normal ↑Blood lipids (TG, TC, LDL) possible
Liver Dysfunction	↑Liver enzymes (ALT, AST, ɣGT)	↓Prevalence of NAFLD in PWS ↑Liver enzymes possible
Insulin resistance /hyperinsulinemia	↑Insulin resistance/ hyperinsulinemia	-Possible insulin resistance/ hyperinsulinemia -Literature suggest children with PWS are more insulin sensitive compare to obese controls with similar BMI-z scores

Abbreviations: NAFLD, non-alcoholic fatty liver disease; PWS, Prader-Willi syndrome; TG, triglycerides; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; ALT, alanine aminotransferase; AST, aspartate transaminase; ɣGT, gamma-glutamyl transferase

Adapted with permission from McDonald K. Vitamin D Status and Markers of Cardiometabolic and Liver Disease Risk in Childhood Obesity: University of Albert; 2017 (33).

1.2.8 Diagnosis of PWS

Before molecular genetic testing become available for the diagnosis of PWS, a numerical scale (table 1.4) was invented as clinical diagnostic criteria which have proven to be accurate, however molecular genetic testing is necessary for confirmation (92). When there is a clinical indication (Table A3 in Appendix A), the DNA methylation analysis technic is a good point to start (92).

Table 1.4 Clinical Diagnostic Criteria for PWS

	Major criteria (1 point each)	**Minor criteria (1/2 point each)**
1	Neonatal/infantile hypotonia and poor suck	Decreased fetal movement and infantile lethargy
2	Feeding problems and failure to thrive as infant	Typical behavior problems
3	Weight gain at 1-6 years; obesity; hyperphagia	Sleep apnea
4	Characteristics dysmorphic facial features	Short stature for family by 15 years
5	Small genitalia; pubertal delay and insufficiency	Hypopigmentation for the family
6	Developmental delay/ intellectual disability	Small hands and feet for height
7	-	Narrow hands, straight ulnar border
8	-	Esotropia, myopia
9	-	Thick, viscous saliva
10	-	Speech articulation defects
11	-	Skin picking

Clinical diagnosis requires five points (at least four of them major) at age < 3 years; eight points (at least five of them major) at age 3 years or older.

Adapted with permission from Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. Genetics in medicine : official journal of the American College of Medical Genetics. 2012;14(1):10-26 (92).

1.2.9 Treatment of PWS

It has been shown that early PWS diagnosis can prevent obesity. However, weight control seems a challenge in these patients due to their decreased energy needs. 10-14 and 7-9 Kcal /cm ht energy intake are recommended for weight maintenance and reduction in these patients respectively (89). However, it has been shown that an energy-restricted diet with a well-balanced macronutrient composition and fiber intake created a greater improvement in body weight and body composition in PWS patients in comparison to a simple energy-restricted diet (95). The lifelong weight management goals would be achieved through a multidisciplinary approach including tight supervision on food access and intake, a balanced food intake and regular exercise (94). Nevertheless, over restriction may result in energy and nutrients deficiency and impair growth and development (94). Some studies have shown that the dietary intake of PWS patients might be low in calcium, vitamin D, tocopherol, iron, fiber and fat (89, 94, 95). Hormone therapy (growth hormone replacement) has been used as standard of care to normalize height, increase lean body mass, mobility and activity level, and reduce fat mass (92).

1.3 Diet Diversity

Although there is a global agreement on the importance of dietary diversity, there is no consensus on what it exactly demonstrates about overall nutritional intake and how to measure it (17). For instance, the source of dietary data for calculating the DD ranges from a 1-day food recall to different food frequency questionnaires with different time courses (i.e. assessing last year or last six months). There is also inconsistency in the amount (1 serving, half serving or 10 grams) of food counted as a score in dietary diversity scoring system (7). These factors affect the

comparison of tools used to assess DD and the decision on the appropriate model to use for any given population.

1.3.1 Count Measures

There are several tools for measuring the DD of individuals, with count measures being the most prevalent ones (1, 17, 100-103). The definition of count measures varies according to their type: Food Variety Score or FVS is simply counting each different food consumed whereas Dietary Variety Score is the cumulative number of different food items consumed over a 15-d period (17, 104). Dietary Diversity Score (DDS) invented by Kant et al. counts the number of food groups consumed daily while consumption of each food group contributes 1 point to a maximum possible DDS of 5 (6). More than 10 different versions of this tool have been applied by different investigators, each one differing in grouping, scoring system and reference time periods (4, 8, 17, 101, 102, 105). Those with more food groups and longer reference time periods can give us a more accurate picture of the person's usual intake. Many of these tools examine diversity of food intake as the differences in variety between food group intake while few also consider the variety of food intake within a food group: Mirmiran et al. divided the 5 food groups into 23 subgroups according to US Food Guide Pyramid (3). In their study, each main group received a maximum diversity score of 2 multiplied by the number of subgroups consumed in that group divided by the number of subgroups available in that group hitting a maximum score of 10.

There are some limitations with count indices: They do not show the quantity of the share of each food item in the overall consumption (distribution), neither they show up to what extent an individual's observed food variety is concordant with the healthy eating recommendations. Both

factors are important to consider in terms of nutritional adequacy and overall quality of food intake. One may have a very diverse diet in terms of number of food items consumed however if all that diversity come from less healthy food, then that diet cannot be considered of good quality.

1.3.2 Diet Quality Indices

Some dietary indices which have a variety component have tried to overcome the latter obstacle: Dietary Score developed by Guthrie and Scheer and its modified version, "Serving Score" consider the concordance of the number of servings consumed from each food group with the dietary guidelines (17). The two scoring systems mentioned above, look in to the within group diversity as well. Some similar approaches are dietary quality indices such as Healthy Eating Index- Canada (HEI-C), Diet Quality Index-International (DQI-I) and Dietary Guideline Index for Children and Adolescents (DGI-CA) which add some more healthy eating-related issues like macro and micronutrients intake, fiber and fatty acids ratios in comparison to DRI (23, 106, 107). However, each of these tools looks only into some aspect of healthy eating indices and they still fail to show the within group diversity (except for Guthrie and Scheer's scoring system and "Serving Score") and the complete distribution of food quantities. If two food products are consumed in equal shares, they add more diversity to the diet in comparison to a situation in which they are consumed in a different proportion e.g. 90% to 10% (1). This is the meaning of distribution. It is worthy to note that dietary quality indices are not particularly designed to measure diversity and they usually only address a simple question of variety.

1.3.3 The Berry Index and Healthy Food Diversity Index

Recently some new tools using Berry-Index have been introduced to include both the number and distribution of food items consumed, the two concepts highlighted in various nutritional guidelines (1). Drescher et al. employed the Berry index ($BI = 1-\sum s_i^2$) to determine the number and diversity of food items where s_i is the share of food item i in the total amount of food consumed. The BI is bounded between 0 and 1- 1/n which BI=0 refers to the instance that one has consumed only one product and BI= 1-1/n to the circumstance that one has consumed equal shares of all products considered (1). To enable the equation to show the extent to which the diet consumed is in accordance to recommendations, it was multiplied by a total HV components. To calculate the HV of a given food recall, first a health factor for each food item (hf_i) had to be calculated. The basis for the calculation of the health factor (hf_i) was the German nutritional guideline which is illustrated through a circle and a pyramid. The circle, which displays the shares of food groups that should be consumed in terms of weight, was used to calculate the HV of the main food groups or G_b as they named it. The nutritional pyramid presents a graded order of foods divided in 3 groups:plant foods, animal foods and fats and oils and was used to calculate the HV for each food subgroups (G_W). The health factor for each food subgroups was computed as ($hf = G_w \cdot G_b$). To calculate the total HV, the share of each food item in the food basket was multiplied by its corresponding health factor (hf_i) and summed up: $HV = hf_i W_i$. W_i was the weight of the food item divided by the total weight of the all foods consumed. The final equation or the Healthy Food Diversity Index (HFD-I) is as follows: $HFD = (1-\sum s_i^2) HV$. BI and HV calculations for a sample meal is presented in Appendix (Table A4 and A5 in Appendix A). In order to get a high score in this index, one's diet must be both diverse and healthy. One advantage of their approach

is that unlike other scoring systems, all quantity of the food consumed takes part in calculation of DD score. They validated their tool using retrospective data from a large population representative of German adults. Their validation results demonstrated that the HFD-I had better correlation with the nutrient intake and the biochemical indices and so it was a better indicator of DD in comparison to Count Index and the Berry Index (BI) (1). However, since their calculations are based on the German guidelines for adults it is critical to take some adaptation measures before one can consider applying their indices in Canadian youth (1). In German guidelines, food portions in food groups recommended to be consumed are presented in a circle in terms of weight instead of serving sizes. Another difference is that in their guidelines, meat and dairy products are generally considered as having high fat concentration and hence receive a low score while in Canadian guidelines, fat-reduced dairy and meat products are given a high weight.

Strength and limitations of some diversity tools and diet quality indices with a variety component are presented in table 1.5. HFD-I is the best tool for determining DD because it is the only tool capable of simultaneously considering number, distribution and HV of food items available in a basket at a subgroup level. HFD-I is also easy to use and has shown good correlation with both nutrient supply and biochemical parameters.

Table 1.5 Strength and Limitations of Dietary Diversity Tools and Diet Quality Indices with a Variety Component

DQ tool	Strengh	Limitations
HFD-I (1)	-It was validated in a large study population -Has been validated by both nutrient intake and biochemical parameters. -Unlike other scoring systems, all quantity of the food consumed takes part in calculation of DD score -Considers number, distribution and the HV of the food baskets at the same time -Components: moderation and variety	-Needs to be adapted according to Canadian guidelines. -An individual omitting one or more food group but with healthy and diverse intake from other groups may still get a good score -Low correlation of the index with nutrients with animal sources e.g. vitamin B12 due to German guidline characteristics
DDS 23 (3)	-Considers diversity in subgroups -Has been validated against micronutrients -Components: variety	-DDS has no correlation with macronutrients -Has not been validated by biochemical parameters - no difference between healthy and unhealthy foods) -Does not show the distribution
HEI (106)	-Adapted for Canadian children based on the Canadian recommendations -Reports intake in comparison with recommendations -Consider some aspect of healthy eating such as cholesterol Components: adequacy and variety	-Does not consider distribution -Does not consider the variety in subgroups -Scoring of the variety component is dichotomous -Consider only some aspects of healthy eating -Was not validated by nutrient supply or biochemicals -Failure to assess micronutrients (vitamin K, folate, sodium), omega-3 fatty acids and the quality of carbohydrate (GI, GL, fructose, added sugar)

Abbreviations: DDS: Diet Diversity Score, DGI-CA, Dietary Guideline Index for Children and Adolescents; DQ, Diet quality; DQI-I, Diet Quality Index-International; GI, Glycemic Index; GL, Glycemic Load, HEI-C, Healthy Eating Index-Canada, HFD-I: Healthy Food Diversity Index.

Table 1.5 Strength and Limitations of Dietary Diversity Tools and Diet Quality Indices with a Variety Component; Continued

DQ tool	Strengh	Limitations
DQI-I (107)	-Used to measure DQ internationally -Considers within group diversity (only in Meat group) -Considers some aspect of healthy eating like quality of fat intake -Can be used Internationally and enables the cross- national comparisons -Shows target intervention points. Components: adequacy (macro and micronutrients), moderation, variety and overal balance	-Based on old dietary recommendations -Not validated against nutrient biomarkers -Not validated for children -Does not show the distribution of the food basket. -Does not consider the variety within food groups (except for Meat group) -Considers only some aspects of healthy eating -The scoring procedure is complex & time consuming -Failure to assess micronutrients (vitamin K, folate, sodium), omega-3 fatty acids and the quality of carbohydrate (GI, GL, fructose, added sugar) -Cut-off values based on old recommendation (World Health Organization 1996 and U.S. Department of Agriculture1992)
DGI-CA (23)	-Based on the new Australian dietary recommendations -Validated against nutritional biomarker -Used to measure the association between overall DQ and socioeconomic variables, cardio-metabolic risk, and nutritional status in children	-Components: the majority are food based and can be difficult to adapt for therapeutic diets -Not used in other countries -Variety: does not evaluate within food groups -Failure to assess micronutrients (vitamin K, folate, sodium), omega-3 fatty acids and the quality of carbohydrate (GI, GL, fructose, added sugar)

Abbreviations: DDS: Diet Diversity Score, DGI-CA, Dietary Guideline Index for Children and Adolescents; DQ, Diet quality; DQI-I, Diet Quality Index-International; GI, Glycemic Index; GL, Glycemic Load, HEI-C, Healthy Eating Index-Canada, HFD-I: Healthy Food Diversity Index.

1.4 Diet Diversity and Cardio-metabolic Dysregulation

Cardiometabolic dysregulation markers referrer to a group of parameters related to obesity (BMI and central obesity), elevated blood pressure, dyslipidemia (low HDL-C, elevated triacylglycerol and LDL-C) and impaired glucose homeostasis (hyperinsulinemia and IR) (108).

There are different definitions for cardio-metabolic dysregulation in children and youth (Table 1.5) with no statistically significant agreement between them (109). Since each definition has its own strength and limitations (Appendix A, Table A7), there is no consensus on which one is the most appropriate one (109). Most criteria are adapted from the adult versions in spite of the fact that growth and puberty stage affect several CMD components such as adiposity and IR; this underlines the need for age-dependent cut-off points (109). Additionally these criteria have not been tested with "clinical outcomes" such as morbidity and mortality (109). The clinical value of the diagnosis of the metabolic syndrome in children and adolescents is still under question (109, 110).

Evidence on the association between CMD risk factors and diet diversity/ quality are inconsistent (Table 1.6). There are only two studies in children and adolescents using HFD-I and neither of them had participants with NAFLD or PWS. Fernandez et al. reported that higher HFD-I score was prospectively associated with higher BMI Z-scores (7). However, their calculation of HFD-I was different from the calculations in the study which introduced the index for the first time (1): Instead of using a calculated health factor for multiplication by BI, they used the percentage of concordance with American dietary guidelines serving recommendations for each food group. This might be due to the fact that unlike German nutritional guidelines and Alberta

Nutrition Guidelines for Children and Youth (ANGCY), US guidelines do not have a rating system, so their tool could not distinguish between healthy and unhealthy foods when calculating diversity. This might partly explain the difference observed between the two study results. They tried to examine the effect of food health value by creating "Variety" scores for healthy food using Count index which was also significantly and positively correlated with changes in BMI Z-Score. However, when assessing the association of food variety with BMI, healthy food and unhealthy or "Moderation food" variety must be considered together, since one with a high "healthy foods variety" score, can also have a high score for "Moderation food variety". Truthmann et al. who compared the different dietary indices- including HFD-I- in terms of their association with biomarkers of dietary exposure and cardiovascular status reported a non-significant trend for higher prevalence of obese adolescents in higher quantiles of indices scores (99). They mentioned that their 45-item food frequency questionnaire and their HFD tool which was based on Optimized Mixed Diet [OMD] for German children and adolescents, was not successful in reflecting the intakes of fiber, sodium and saturated fat which are dietary parameters relevant to CMD risk factors and obesity (24, 25, 111, 112). Marshal et al. reviewed the literature on diet quality indices and their associations with health-related outcomes in children and adolescents (113). In terms of weight status, they concluded that significant relationships observed are inconsistent. Some researchers believe that the sign (negative or positive) of the association between the DDS and the anthropometric measures is defined by the calorie density of the foods that make the DDS (3). It means if the diversity comes from food choices with a high HV, the association between DD score and anthropometric indices such as BMI would be negative and vice versa.

Table 1.6 Definition of Cardio-metabolic Dysregulation in Children and Adolescents by Different Criteria.

Definitions	Excess adiposity	Elevated Blood Pressure	Dyslipidemia	Impaired glucose metabolism and insulin resistance
Cook et al. ⊥(114)	WC ⩾90th percentile	SBP or DBP ⩾90th percentile	Triglycerides ⩾1.24 mmol l − 1 (110mg dl − 1) or HDL cholesterol ⩽1.03 mmol l − 1 (40mg dl − 1)	Impaired fasting glucose ⩾6.11 mmol l – 1 (110mg dl − 1)
Viner et al. § (115)	BMI ⩾95th percentile	SBP ⩾95th percentile	Triglycerides ⩾1.69 mmol l − 1 (150mg dl − 1) or HDL cholesterol <0.91 mmol l − 1 (35mg dl − 1) or high total cholesterol ⩾95th percentile	Hyperinsulinemia ⩾104.2 pmol l − 1 (15mU l − 1) or impaired fasting glucose ⩾6.11 mmol l – 1 (110mg dl − 1) or Impaired glucose tolerance: glucose at 120 min >7.8 mM/l
IDF‡ (116)	WC ⩾90th percentile	SBP ⩾17.3 kPa (130mmHg) or DBP ⩾11.3 kPa (85mmHg)	Triglycerides ⩾1.69 mmol l − 1 (150mg dl − 1) HDL cholesterol <1.03 mmol l − 1 (40mg dl − 1)	Impaired fasting glucose ⩾5.55 mmol l – 1 (100mg dl − 1)
WHO †(109)	Obesity (BMI ≥ 95%) or Waist ≥ 102 cm(M), 88 cm (F)	Hypertension (diastolic ≥ 85 mm Hg, systolic ≥ 130 mm Hg)	HDL ≤ 35mg/dL (M), 39 mg/dL (F) or Triglycerides ≥ 150 mg/dL	Glucose ≥ 110 mg/dL or known diabetes or Hyperinsulinemia
IDEFICS -monitoring Level (117)	WC ⩾90th percentile	SBP ⩾90th percentile or DBP ⩾90th percentile	Triglycerides ⩾90th percentile or HDL cholesterol ⩽10th percentile	HOMA-IR ⩾90th percentile or fasting glucose ⩾90th percentile

⊥presence of at least 3 of the following 5 criteria (elevated blood pressure, low HDL-C high TG, high fasting glucose and abdominal obesity) was necessary for CMD definition. §CMD was defined as having three or more components. ‡IDF: For CMD definition, presence of central obesity plus any two of other criteria (increased TG, decreased HDL-C, increased blood pressure, increased glucose) is required. †For CMD definition, impaired fasting glucose, known diabetes, or hyperinsulinemia was required plus 2 of the additional 3 parameters. Abbreviations: BMI, Body Mass Index; DBP, Diastolic Blood Pressure; (F), Female; HDL, High Density Lipoprotein; HOMA-IR, homeostasis model assessment (for insulin resistance); (M), Male; SBP, Systolic Blood Pressure; WC, waist circumference; WHO, World Health Organisation.

Table 1.7 Some Association between CMD Risk Factors and Diet Diversity/ Quality Scores.

Reference	Number of participants	Age	DD/DQ tool	CMD component studied	Results
Fernandez et al. 2016 (7)	340	Mean :4.2 SD: 0.5	HFD-I	BMI, BMI change	Higher HFD-Index score was prospectively associated with higher BMI Z-scores
Truthmann et al. 2012 (118)	5,198	12-17 years	HFD-I, HuSKY, IFI, simple fruit/ vegetable intake index	Total cholesterol, HDL-C and BMI, SBP, DBP	Non-significant trend for higher prevalence of obese adolescents in higher quantiles of indices scores. Significant positive association between diastolic blood pressure in girls and Indicator Food Index (IFI) as well as fruit and vegetable consumption.
Vakili et al. 2013 (16)	506	15 to 18 years	DDS	BMI, WC, WHR	Slightly greater BMI, waist circumference and waist to hip ratio in those adolescents with higher DDS
Chan She Ping-Delfos et al. 2015 (22)	1608	14 and 17 years	DGI-CA	BMI- Z-scores, SBP, DBP, lipid profile, insulin, HOMA-IR	A weak positive relationship was found between the index score and the BMI Z-scores. No association between systolic or diastolic blood pressure and DGI-CA score. A significant negative association between DGI-CA scores and TG but not with other lipids. Inverse association between DGI-CA scores and insulin levels and HOMA-IR

Table 1.7 Some Association between CMD Risk Factors and Diet Diversity/ Quality Scores, Continued.

Reference	Number of participants	Age	DD/DQ tool	CMD component studied	Results
Azadbakht et al. 2015 (15)	265	11-13 years	DDS, HEI and MAR	BMI, WC, HiC and abdominal adiposity	BMI, WC, HiC and abdominal adiposity values and the prevalence of overweight or obesity were significantly lower in those with higher DDS scores. No significant associations between HEI score and BMI, central or abdominal obesity and blood pressure
Hu et al. 2016 (119)	2656	Mean: 15 years	APDQS	Weight	Higher diet quality in and after adolescence is associated with reduced weight gain in the following 10 years
Jennings et al. 2011 (120)	1700	9-10 years old	DQI, Healthy Diet Indicator	Body composition, WC	Lower body fat and WC was associated with higher scores
Li et al. 2011, (121)	13770	2-17 years	DDS	Weight/height, height/age, BMI, lipid profile	DD and high energy dense diets are related to both being stunted and overweight. Children with stunting as well as overweight children had greater odds for having dyslipidemia

Abbreviations: APDQS, A Priori Diet Quality Score; BMI, Body Mass Index, CMD, Cardio-metabolic Dysregulation; DD, Diet Diversity; DDS, Diet Diversity Score; DGI-CA, Dietary Guideline Index; DQ: Diet Quality; DQI, Diet Quality Index; DBP, Diastolic Blood Pressure; HiC, hip circumference; HDL-C High Density Lipoprotein Cholesterol; HEI, Healthy Eating Index; HFD-I, Healthy Food Diversity Index; HOMA-IR, homeostasis model assessment (for insulin resistance); HuSKY, Healthy Nutrition Score for Kids and Youth; IFI, Indicator Food Index; MAR, Mean Adequacy Ratio; SBP, Systolic Blood Pressure, WC, waist circumference; WHR, waist to hip ratio

Regarding blood pressure, a systematic review by Marshal et al. showed a weak negative association between some quality indices and diastolic blood pressure (113). However, Truthmann et al. found a significant positive association between diastolic blood pressure in girls and Indicator Food Index (IFI) as well as fruit and vegetable consumption (118). The association for other indices including HFD-I was not significant. IFI rates and scores the frequency of intake of seven food groups according to dietary guidelines. They justified their results by mentioning that milk and milk products, that are believed to lower hypertension risk, are not involved in IFI. Chan She Ping-Delfos et al. did not find any association between systolic or diastolic blood pressure and DGI-CA score in 1608 adolescents studied in Australia and related it to the low scoring accuracy of the tool in terms of salt intake (22). In adults, HEI has been shown to have a weak inverse relationship with systolic blood pressure (122).

Truthman et al. did not find any association between HDL-C levels and dietary indices including HFD Index. They reasoned that their indices which were based on a Food Frequency Questionnaire (FFQ) with only 45 food items and did not estimate the intake of some nutrients such as fiber, sodium and saturated fat very well. One example they mentioned was that the fat content of dairy product was not considered in their index scores. However, when HFD-I was first introduced in 2007, it showed a significant positive association with serum HDL-C and a significant negative association with serum TG (1). It is worth mentioning that their participant reported consuming 2678 different foods which were then categorized into 133 food items and they were all adults. Chan She Ping-Delfos et al. reported that DGI-CA was not able to detect the changes in total cholesterol, LDL-C and HDL-C levels according to food intake (22). In a group of elderly

Iranian individuals, a significant positive association was found between HEI scores and HDL-C levels while no significant association was found for TG, LDL-C and total cholesterol (123).

The inverse association observed between DD or DQ scores and insulin levels/ HOMA-IR is particularly important since IR plays a fundamental role in NAFLD etiology and is considered the "primary defect" in CMD (16, 22, 25, 27, 31, 35, 123).

1.4.1 Diet Diversity and Cardio-metabolic Dysregulation in NAFLD

In a cohort of healthy adults, a higher consumption of vegetables, legumes and fruits and a higher Diet Quality Index (DQI) but not Mediterranean Diet Score was associated with a reduced likelihood of having NAFLD (124). Adult NAFLD patients have also been reported to have low quality nutrition with high energy density and low intakes of calcium, magnesium, zinc, iron, vitamin A, B1 and B2 (125). In one of a few studies assessing the relation between dietary indices and CMD risk factors in NAFLD patients, Hashemi Kani et al. reported that participants with higher HEI scores had significantly lower odds ratio for elevated LDL (14). For TG, only a non-significant trend ($p= 0.05$) was observed. They also reported a significant negative correlation between overweight and obesity with Healthy Eating Index (HEI) in adult NAFLD patients and healthy controls (14). There are some studies showing the effect of different diets on CMD risk factors in NAFLD patients. Browing et al. showed that both a low calorie and a low carbohydrate diets were successful in reducing the BMI and TG in these patients, but they could not affect total plasma cholesterol (126). In another study by Kani et al. three different dietary approaches (low calorie, low calorie- low carbohydrate and low calorie-low carbohydrate-soy containing) were all effective at reducing BMI and TG and increasing HDL-C (127). Razavi-Zade et al. reported that

following the DASH diet for 8 weeks resulted in reduction in BMI, fasting serum insulin levels, TG, total cholesterol/HDL-C and HOMA-IR (128). Currently there is no study reporting the associations between childhood NAFLD, CMD and diet diversity. However, a recent analysis by Alzaben et al. showed that obese youth with NAFLD had lower DQ compared to healthy controls and poor DQ was associated with obesity and cardio-metabolic dysregulation (129). They assessed the relationships between variety components of 3 different Diet Quality tools: DGI-CA, DQI and HEI. It was shown that higher variety scores (total and within some food groups such as milk and grain) measured as a component of diet quality tools was associated with lower ɣGT, glucose, HOMA-IR, TG levels, weight z-scores, BMI Z-scores and body fat mass. They could not assess the interrelationships between HEI-C (variety) score and anthropometric and biochemical markers since the majority of their participants had 100% of the maximum score for the Variety component (129).

1.4.2 Diet Diversity and Cardio-metabolic Dysregulation in PWS

To best of our knowledge, there is no published article studying the association between DD and CMD risk factors in PWS patients. Nordstrom et al. studied the intake frequencies of selected foods (fruits, fruit juice, and vegetables; fish and omega-3 supplements; soft drinks and precooked meal) in participants with Prader-Willi syndrome (PWS), Down syndrome (DS), and Williams syndrome (WS)(130). Their results suggested that PWS patients better meet dietary recommendations for fruits, vegetables, fish and omega 3 intake when compared to patients with WS and DS group. It was also shown that the percentages of normal weight and overweight PWS patients who consumed fruits four or more times a week were significantly higher than the

percentage of obese PWS participants. No other significant association between BMI and other food frequency was observed for PWS patients. In another study done by Miller et al. it was shown that children who complied to a low-calorie diet and tried to meet the prescribed goals for fiber and macronutrients, had larger loss of weight and body fat than those who only restricted their energy intakes (95).

1.5 Conclusion

DD is the variation of food intake across and within food groups and may be an important contributor to improved diet quality (DQ) if the observed diversity comes from healthy food choices (17). There is convincing evidence associating a low DD to chronic diseases however, data on DD in NAFLD patients are scarce and currently there are no data available in children with PWS (1, 9, 14). This is important to examine as dietary intake has been shown to influence the metabolic environment in children with NAFLD; contributing to higher risk for CMD and increasing disease severity in childhood NAFLD. An important consideration in the evaluation of DDS include the need to examine the HV of dietary intake in the overall context of food intake. Current literature utilizes a variety of different tools to evaluate DD and HV, but do not consistently apply these to the pediatric populations. In addition, a variety of outcomes (anthropometric, dyslipidemia, IR) have been used to study the association between DD and risk for CMD, but few studies have examined the associations of CMD with low DD in obese children with chronic diseases such as NAFLD or in syndromic forms of obesity such as PWS. This is important as both conditions rely on lifestyle interventions to prevent and treat the

complications due to CMD. The purpose of this thesis was to evaluate diversity and HV of the diet in children with NAFLD and PWS and to compare it to children with body weights within normal reference ranges. This information is needed to design more effective dietary interventions for obese children with NAFLD and PWS to prevent CMD.

Chapter 2: Research Plan

2.1 Study Rational

Pediatric obesity is endemic in North America leading to an increased risk for chronic diseases such as non-alcoholic fatty liver disease (NAFLD), diabetes and cardio-metabolic dysregulation (18, 19, 33, 131). Poor diet quality (DQ) is thought to be a major contributor to the onset and progression of these co- morbidities (13, 14, 22, 129). While DQ addresses major components of the diet including the concepts of nutritional adequacy, variety and moderation , it does not necessarily address the diversity of food intake within individual food groups or the proportion of foods within the diet that come from healthier food choices (129). The latter defines the concept of HV (1). Recent evidence indicates some relationships between DD and features of HV with anthropometric parameters and chronic diseases such as cardio-metabolic dysregulation (CMD) and non-alcoholic fatty liver disease in children and adults (7-10, 12, 14, 118). DD has also been associated with nutrient intake (1-6). This is important since high intake of some nutrients such as saturated fat and sugar and low intake of fiber and micronutrients like vitamin D and E has been related to obesity, CMD and NAFLD etiology and progression (25, 27, 33, 58, 59, 101, 132-136). Despite high prevalence of obesity and obesity- related health conditions in children and adolescents in Canada, the data regarding the relationship between DD with obesity and other CMD risk factors in children with chronic diseases such as NAFLD is scarce and controversial (7, 15, 18-20). This may be partly due to variation in tool used and population studied (7, 15). In addition, no data are available regarding DD in syndromic forms of childhood obesity such as Prader Willi Syndrome (PWS). This is important since obese children

with PWS have predominantly subcutaneous and total body adiposity, when compared to other obese children who experience predominantly visceral adiposity (NAFLD). Lower ratio of visceral /subcutaneous adipose tissue is suggestive of a better metabolic profile (137). Studying two obese populations with different pathogenicity, body composition and cardio-metabolic risk (PWS and NAFLD) (Table 1.3) creates a unique opportunity to examine the relationship between these factors and the dietary diversity. The overall goal would be to use this information to design more effective dietary interventions to treat and prevent obesity in childhood.

2.2. Overall Objectives and Overall Hypothesis

Overall Objective: To assess potential associations between DD, HV and HFD-I scores with CMD risk factors in children with either PWS or NAFLD.

Overall Hypothesis: Greater DD, HV and HFD-I scores is associated with lower CMD risk in children with either PWS or NAFLD.

2.3 Objectives and Hypothesis

Objective #1: To assess the potential associations between DD, HV and HFD-I scores with micro-and-macronutrient intake and overall DQ in children with NAFLD, PWS and controls.

Hypothesis #1: Lower DD, HV and HFD-I scores are associated with higher intake of energy, fat, saturated fat, polyunsaturated fatty acid, and sugar and a lower intake of fiber and several key micronutrients (vitamin D, E, folate).

Objective #2: To compare DD, HV and HFD-I scores amongst patients with PWS, NAFLD and controls.

Hypothesis #2: DD, HV and HFD-I scores are lower in patients with NAFLD than in PWS patients and controls.

Objective #3: Assessing the potential associations between DD, HV and HFD-I scores with anthropometric, physiologic and serum markers of CMD risk in children with NAFLD, PWS and children with body weights within healthy reference range.

Hypothesis #3: DD, HV and HFD-I scores are lower in patients with CMD/ CMD markers than in children without CMD/ CMD markers.

Chapter 3: Diet Diversity in Children with Non-alcoholic Fatty Liver Disease and Prader Willi Syndrome: Association with Cardio-metabolic Risk

3.1 Introduction

About one third of overweight and obese children are affected by non-alcoholic fatty liver disease (NAFLD) and it is becoming the most common chronic liver disease in North America with prevalence rate of 20- 30% (56, 138). NAFLD is a term used to address a spectrum of liver disease ranging from accumulation of fat in hepatocytes (fatty liver) to inflammation± fibrosis (non-alcoholic steatohepatitis or NASH), and cirrhosis (14, 25). Obese children with NAFLD tend to have more visceral fat/centrally located subcutaneous fat (36). Elevated liver function enzymes, hyperlipidemia, hyperinsulinemia and IR are the other manifestations of the disease with the latter being the core of the pathogenesis (14, 35, 36). The prevalence of cardio-metabolic dysregulation and its components, obesity, hypertension, dyslipidemia, hyperglycemia or hyperinsulinemia and IR, are significantly higher in children with NAFLD (55, 139). Feldstein et al. reported the prevalence of at least one characteristic of cardio-metabolic dysregulation (CMD) as high as 83% and the incidence of CMD, 29% in youth with NAFLD (139). In China, the prevalence of CMD in a group of obese children with NAFLD was 37.6% and significantly higher than their non-NAFLD obese counterparts (55). Progression of the disease to a more severe cirrhosis and cardiovascular disease occurs faster in pediatric NAFLD patients with features of CMD (56, 57, 140). CMD components are also present in obese patients with Prader- Willi Syndrome (PWS)(21). PWS is a genetic disorder resulting from the absent expression of the paternal active genes in chromosome 15 at the locus q11_q13 (88). These patients experience

hyperphagia and severe obesity. However, unlike NAFLD patients, their excess fat is more subcutaneously distributed rather than viscerally, a characteristic that might explain the lower IR and cardio-metabolic risk factors observed in these patients (90). Some studies have shown that the dietary intake of PWS patients might be low in calcium, vitamin D, potassium, tocopherol, iron and fiber (89, 94-96).

Since nutrients have interactional effects on each other, the evaluation of dietary intake as a whole entity using dietary indices reflective of overall nutritional quality may provide a more accurate estimation of overall nutritional value of the diet rather than approaches that examine individual nutrient content of the diet (14). Some studies have shown lower DQ in patients with NAFLD, obesity or cardiometabolic dysregulation characteristics and higher adherence to guidelines in children with PWS (14, 15, 22, 96, 119, 141). While DQ addresses major components of the diet including the concepts of nutritional adequacy, variety and moderation, it does not necessarily consider the diversity of food intake within individual food groups or the proportion of foods within the diet that come from healthier food choices (129). DD is the variation of food intake across and within food groups and may be an important contributor to high DQ if the observed diversity comes from healthy food choices (1, 17). However, it is possible that lower DQ could occur even in the presence of high DD if food selection choices come from foods with a lower HV (Table 3.1). Hence, including a HV component in the evaluation of an individual's diet is important in the overall evaluation of DD and DQ.

The study purpose was to assess potential associations between DD and overall HV of food intake with macronutrient/micronutrient intake (with relation to NAFLD etiology) and

total/subcomponents of a DQ tool called the Healthy Eating Index- Canada (HEI-C) (**Objective 1**). In addition, the differences between DD and overall HV of the diet was evaluated between groups (NAFLD, PWS, Control) and in children with and without CMD risk factors (**Objectives 2 and 3**). Macro-and-micronutrient intake was also compared between NAFLD, PWS and controls. We hypothesised that greater DD and HV of food intake is associated with lower CMD risk in obese children with PWS and NAFLD.

Table 3.1 Sample Meals with Different Diversity/ Health Value Combination

Sample Lower diversity/ Lower HV meal:	**Sample higher diversity/ Lower HV meal:**	**Sample lower diversity/ higher HV meal:**	**Sample higher diversity/ higher HV meal:**
2 rolls, white 150 g deli meat, high fat	1 roll, white 75 g deli meat, high fat 1 slice cheddar cheese 1 pickled cucumber (high salt) 1 cup cola 1 table spoon jelly	2 roll, whole wheat 150 g chicken breast	1 roll, whole wheat 75 g chicken breast 2 slices of tomato 0.5 cup lettuce 2 tea spoon mayo 1 cup natural orange juice

3.2 Methods

3.2.1 Subjects

This is a secondary data analysis of a previous cross-sectional study on vitamin D status and markers of cardio-metabolic and liver disease risk in childhood obesity (33). In that prospective study vitamin D status, body composition, markers of metabolic dysregulation in obese children with non-alcoholic fatty liver disease (NAFLD) and Prader-Willi syndrome (PWS) were examined (33). Children and adolescents (7–18 - years) with NAFLD and PWS were recruited while attending visits at Gastroenterology or Endocrinology clinics of Stollery Children's Hospital, Edmonton, Alberta from October 2015 to October 2016. The exclusion criteria were 1) A known history of primary liver disease, 2) Having a diagnosis of type 2 diabetes or receiving insulin, 3) Being on medications that are known to cause hepatic steatosis, 4) Having a history of comorbid conditions known to affect vitamin D metabolism including other liver disorders or gastrointestinal disorders such as inflammatory bowel disease or celiac disease. NAFLD was confirmed in overweight/obese children by elevated liver enzymes [gamma- glutamine transferase (ɣGT) and Alanine aminotransferase (ALT)], hyperinsulinemia and dyslipidemia, and the presence of an echogenic liver ultrasound and fibroscan evaluation and/or liver biopsy (where available) and by eliminating the other known causes of steatosis (e.g. inborn errors of metabolism, Wilson Disease, viral hepatitis). PWS was diagnosed via genetic tests (methylation studies and looking for the deleted region (q11-q13) of chromosome 15 (88). The control group consisted of children with BMI within healthy reference ranges and were recruited from the community with flyers. Children in the control group and their caregivers were asked to fill out a

health history questionnaire and were excluded from this analysis if they had any clinical evidence of CMD (e.g. acanthosis nigricans) or their lab tests [triglycerides (TG), cholesterol: total, LDL or HD, ALT, AST, insulin and glucose] were out of normal reference range (142, 143).

Informed consent/assent was obtained by participants and responsible caregivers/parents. The study was approved by Human Research Ethics Board, University of Alberta (Pro: 00056649).

3.2.2 Anthropometric and Blood Pressure Measurements

Height was measured without shoes to the nearest 0.1 cm, with a digital stadiometer (Measurement Concepts and QuickMedical, Washington, USA). Weight was measured to the nearest 0.1 kg with light clothes and without shoes, using a Health o meter® Professional digital scale (Illinois, USA). Body mass index (BMI) was calculated as weight (kg) / height (m^2). Weight, height and body mass index (BMI) were converted into Z-scores/percentiles using the WHO growth charts for Canada (2014 revision) (144). Waist circumference (WC) was measured to the nearest 0.1 cm using a steel flexible tape (Rosscraft Innovations Incorporated, USA), according to the WHO criteria (midpoint between the highest point of the iliac crest and the bottom of the rib cage)(145). Waist to height ratio (WHtR) was calculated as WC/ height. Waist circumference (WC) and waist to height ratio (WHtR) were converted into Z-scores/percentiles using the WHO growth charts for Canada (2014 revision)(144). Hip circumference (HiC) was measured at the maximum posterior protuberance of the buttocks (146). Waist to hip ratio (WHR) was calculated as WC/ HiC. Blood pressure (BP) was measured using an Adview®9000 modular diagnostic station (American Diagnostic Corporation (ADC), NY, USA). Blood pressure was converted to Z-

scores/percentiles and classified as normal or elevated according to the National High Blood Pressure Education Program Working group standards (147).

3.2.3 Biochemical Variables

Biochemical variables studied were serum triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), total cholesterol (TC), insulin, glucose, thyroid stimulating hormone (TSH), alkaline phosphatase (ALP), alanine aminotransferase (ALT), gamma-glutamyl transferase (ɣGT), aspartate aminotransferase (AST), creatinine, ferritin and C reactive protein (CRP). The blood work was part of routine procedure of clinical care and was performed fasted in the Core Laboratory at Alberta Health Services (AHS) according to standard methodologies (148). ALT values >20 U/L were considered abnormal (149). The homeostasis model assessment for IR (HOMA-IR) (glucose mmol/L x insulin mU/L /22.5) was used as an index of IR (150).

3.2.4 Dietary Intake Analysis

Food records

A three-day food record (2 weekdays and 1 weekend day) was employed to estimate food and beverage intake and then analyzed using Food Processor (2015 ESHA® Research, version 10.15.4, Salem, OR, USA) to determine micro-and macronutrient intake. The food intake analysis was performed by two students (MB and KM) and the percentage of inter-operator difference and CV were calculated as the standard operating procedure to avoid possible errors. Possibilities for over or under reporting were evaluated by calculating the ratio of energy intake on basic

metabolic rate (151). Basic metabolic rate was estimated employing Schofield equation. If body weight was <90% or >120% of IBW, ideal body weight was used (152). Those with ratios below or over 95% confidence intervals were considered as under and over-reporters respectively (Goldberg criteria) (153). The number of serving sizes consumed from each food group was calculated using Canada's Food Guide serving sizes (154, 155). Standardized operating procedures were based on Canada serving system which included evaluating the nutritional composition of mixed foods, recipe portions and ingredient listing (155, 156).

Healthy Eating Index – Canada (HEI-C)

HEI-C is a DQ scoring system adapted for Canadian children and adolescents which measures the number of servings consumed from each food group and the fat, saturated fat and cholesterol. It considers three aspects of healthy eating: Adequacy, Moderation and Variety (106). The adaptation of the tool for the present study and the calculation procedure are presented in table 3.2. Recent evidence has shown that lower Adequacy and Moderation scores were associated with obesity and cardio-metabolic dysregulation (129). For Variety, HEI-C only evaluates the overall food groups and not within food groups and the scoring of this component is dichotomous. HEI-C scores are categorized as 'poor' (≤50 HEI-C score), 'needs improvement' (HEI-C score 50-80), or 'good' (HEI-C score >80) (106). For evaluating the degree of agreement between HEI-C and HFD-I, the scores for HEI-C was divided into two groups: Low (HEI-C score ≤ 80) and High (HEI-C score > 80).

Table 3.2 The Adaptation of Healthy Eating Index-Canada

Components (not Adapted)	Maximum- Minimum	Rational/ Source
Grain: Meet the recommended intakes of based on CFG	10-0	Based on ANGCY
F/V: Meet the recommended intakes of F/V based on CFG	20-0	Based on ANGCY
Milk: Meet the recommended intakes of milk based on CFG	10-0	Based on ANGCY
Meat: Meet the recommended intakes of meat based on CFG	10-0	Based on ANGCY
Other foods	10-0	Servings in between the min and max = 5
Fat1,[4] ≤ 30% energy to ≥45% energy	10-0	Based on Health Canada recommendations
Saturated fat[2,4] ≤ 10% energy to ≥15 % energy	10-0	Based on the DRI
Cholesterol[3,4] <300 mg to ≥450 mg	10-0	Based on the DRI
Variety At least 1 serving from each food group to failure to eat a serving from any food group	10-0	Based on ANGCY

1The original paper (Not Adapted) scored this component as proportional and the cut-off point was 30-45(106).
2The original paper (Not Adapted) scored this component as proportional and the cut-off point was 10-15% (106).
3The original paper (Not Adapted) scored this component as proportional and the cut-off point was 300-450 mg (106).
4Dietary Reference Intakes for Energy, Carbohydrate, Fibre, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids (2002); Interim Summary of Conclusions (157). Dietary Recommendations on Total Fat & Fatty Acids from the Joint FAO/WHO Expert Consultation on Fats and Fatty Acids in Human Nutrition, 10-14. November 2008, WHO, Geneva (158). Garriguet, D. Diet quality in Canada. Health Reports, 2009 Sep;20(3):41-52 (159).
5The original paper (Not Adapted) scores at least 1 serving from each food group to max score or min score for no serving of at least 1 food group (106).
Abbreviations: ANGCY, Alberta Nutrition Guideline for Children and Youth; CFG, Canadian Food Guide; F/V, Fruits and Vegetables. Adapted with permission from (129)

Diet Diversity, Health Value and HFD-Index

DD was measured using a modified version of the HFD-Index (1). HFD-Index, a tool first introduced by Drescher et al. mixes a DD score calculated using Berry-Index with a quantitative measure of the HV of the diet to get a measurable estimate of "Healthy Food Diversity". There are three steps in the calculation of the HFD-I score. These include the calculation of the BI, HV of the individual's diet and finally the calculation of the HFD-I.

a) *Berry Index:* BI is defined as $BI = 1 - \sum S_i^2$ (1), where in the present study, S_i was the share of product i in the total amount of foods consumed both in terms of serving sizes consumed (S_i = number of serving sizes consumed from food item or product i /number of all serving sizes consumed). The BI is bounded between 0 and 1- 1/n which BI=0 refers to the instance that one has consumed only one product and BI= 1-1/n to the circumstance that one has consumed equal shares of all products considered (1).

To define food items or products, the Canadian Diet History Questionnaire (C-DHQ II) was employed (160). The C-DHQ II food list is based on analyses of 24-hour dietary recalls reported by adults surveyed in the Canadian Community Health Survey (CCHS), Cycle 2.2, Nutrition (2004), Statistics Canada (161). After omitting the questions on mixed dishes and supplements, the questionnaire yielded 164 food items (products). The amount consumed from each food item was converted to serving sizes according to Canada Serving System and was put under the appropriate subgroup (food item or product) (160). The S_i for each subgroup was calculated by dividing the number of servings consumed from that subgroup by total number of servings consumed from all subgroup.

b) *Health Value:* To calculate the HV, Drescher et al. derived a health factor (hf) for each food subgroup according to their recommended consumption prioritisation (1). Since their derived hf was based on guidelines from German Nutrition Society, calculation of new hf and HV for Canadian population was necessary. Adapted health factors were derived by calculating the HV of the Alberta Nutrition Guidelines for Children and Youth (ANGCY) food groups (G_b) and Alberta Health and Wellness' Food Rating System (G_w) through a 6- step process)(162, 163)(Table 3.3).

Table 3.3 Step by Step Health Factor (hf) Calculations.

Step 1	The number of servings recommended by Food Guide Serving Sizes (ANGCY) for each food group (A) was determined.
Step 2	A representative serving size weight for each food group (B) was calculated.
Step 3	(A) was multiplied by (B) and summed up to get a total weight of what a person is recommended to eat in a day (C).
Step 4	Share of each food group in the total weight (C) was calculated: (A) * (B)/ (C). This value was called $G_{b.}$
Step 5	G_w was determined according to Alberta Health and Wellness' Food Rating System (162) which classifies the foods into 3 different categories in terms of their HV: "Choose most often group", "Choose sometimes" and "Choose Least often" with each group having a defined recommended number of servings in a week.
Step 6	The final health factor (hf) value for each subgroup i.e. "Choose most often", "Choose sometimes" and "Choose Least often" in each food group, was calculated by multiplying G_b by G_w.

When reviewing a child's diet in regards of HV, for each food item its quantitative share in terms of weight on total quantities (w_i) (i.e. the weight of the food item divided by the total weight of the foods consumed) was calculated and it was decided to which subgroup it belongs in order to know its corresponding hf_i. This decision was made based on the criteria provided by ANGCY when describing the characteristic of each category and after some adaptation (162).

The HV of an individual's diet was assessed by multiplying w_i with the corresponding health factor (hf_i) for each food item and summing them all up. The output is called HV: $hv = \sum hf_i \, . \, w_i$. Dividing HV by the maximum HV one can get (which is equal to the highest health factor among health factors related to food subgroups according to the individual's age and sex) ensures that the HV is limited between 1 and nearly 0 and makes it possible to compare the HV and HFD-I values across age groups in the present study (1).

c) *HFD-I:* The overall HFD-I score is calculated as: BI* hv or $HFD = (1 - \sum S_i^2)hv$ (1). The final HFD-I is limited between 0 and 1-1/N. BI and HV calculations for a sample meal is presented in Appendix A (Table A4 and A5).

<u>Evaluation of potential associations of BI, HV and HFD-I with macro-and-micronutrients intake, overall DQ (HEI-C), sub-components of HEI-C (adequacy, variety and moderation) and Food Guide Servings (**Objective 1**).</u>

The nutrients for which intake were evaluated were chosen based on their potential contribution to pediatric NAFLD etiology, obesity and CMD (total and saturated fat, PUFA, MUFA, carbohydrate, total sugar, protein, fiber, vitamin D, vitamin E, folate) (25, 27, 58, 59, 101, 132-136). Relevant nutrient intake [absolute, %recommendations and per 1000 kcal basis], intakes from food groups (servings and %recommendations) and total/subcomponents HEI-C (Adequacy, Moderation and Variety) scores were compared between participants with higher than median BI, HV and HFD-I scores and those with lower than median scores. The recommendations were either Adequate Intake (AI), Estimated Average Requirement (EAR) or Acceptable Macronutrient Distribution Range (AMDR) for nutrients and Alberta Nutrition Guidelines for Children and Youth

(ANGCY) recommendations for food groups (162, 164, 165). The recommendations for sugar intake (< 10% of energy intake) was driven from WHO and for SFA (<10% energy intake), MUFA (<15% energy intake) and PUFA (<10% energy intake) from American Heart Associations (166, 167). The degree of agreement between BI, HV and HFD-I with HEI-C was also studied.

3.2.5 Cardiometabolic Dysregulation Markers

Cardio-metabolic dysregulation was defined using an adapted version of WHO criteria for assessing metabolic syndrome in adults (168). According to this definition, CMD is defined as having impaired fasting glucose (fasting glucose > 6.1mmol/L), known diabetes, hyperinsulinemia (insulin > 20 mU/L) or IR (HOMA-IR ≥ 3) plus 2 of the additional 3 parameters: 1) excess body fat and obesity (BMI ≥ 95^{th} percentile), 2) elevated blood pressure (BP ≥ 95^{th} percentile) and 3) dyslipidemia (HDL-C <5^{th} percentile or TG ≥ 95^{th} percentile). Blood lipids percentiles (5^{th} and 95^{th}) were determined using data from the study done by Daniels and Greer (169).

BI, HV and HFD-I mean scores (or median if scores were not normally distributed) were compared between a) groups (NAFLD, PWS and Control) (**Objective 2**) and b) those with and without CMD risk/risk factors (**Objective 3**).

3.3 Statistical Analysis

Data were analysed using SAS software version 9.4 (SAS institute). Data were tested for normality using the Shapiro-Wilks test and were expressed as mean ± standard deviation (range) or median (QR) for variables demonstrating parametric or non-parametric distributions respectively. For testing the differences between groups for mean values of normal variables such as waist circumference Z-scores, height, weight, BMI or some lab parameters (TC, LDL-C, urate) and while testing for the potential effect of sex (sex-variable interaction), two- way ANOVA including a post-hoc Bonferroni correction was employed. For data that were not normally distributed such as BI, WHtR Z-scores, ALT, AST, glucose, insulin and TG, non-parametric analysis (Kruskal- Wallis) and Dunn's test as post- hoc analysis was used. A p-value ≤0.05 (p- value≤ 0.025 for post-hoc Bonferroni) was considered significant.

Participants were divided according to their BI, HV and HFD- I scores using medians as the cut-off points. An independent sample t-test (or Man-Whitney test if the variable was not normally distributed) was employed to compare related nutrients (as % macronutrient distribution and EAR for individual micronutrients, absolute, on a per 1000 kcal basis,), food group intakes (servings and % ANGCY recommendations) and HEI-C and its subcomponents scores between those with higher than median and lower than median scores for BI, HV and HFD-I (**Objective 1**). Cohen's κ was run to test the agreement of BI, HV, HFD-I with HEI-C. The degree of agreement was defined according to Altman's criteria (170) (Table 3.4). A p-value ≤0.05 was considered significant.

Table 3.4 Strength of Observed Agreement in Cohen's Test Based on κ Value.

Value of K	Strength of agreement
< 0.20	Poor
0.21 - 0.40	Fair
0.41 - 0.60	Moderate
0.61 - 0.80	Good
0.81 - 1.00	Very good

Adapted with permission from: Altman D. Practical statistics for medical research. London: Chapman and Hall; 1991 (170).

To compare BI, HV and the overall HFD-I scores between groups (PWS vs NAFLD vs Control) (**Objective 2**), two-way ANOVA including a post-hoc Bonferroni correction (or Kruskal-Wallis and post- hoc Dunn's test accordingly) was performed. An independent sample t-test (or Man-Whitney test if the variable was not normally distributed) was employed to compare BI, HV and the overall HFD-I scores between those who were defined as having CMD risk according to WHO definition with those who were not (**Objective 3**). Using independent sample t-test (or Man- Whitney test, accordingly), BI, HV and overall HFD-I scores were compared between people who suffered each CMD risk factor (obesity, dyslipidemia, hypertension and impaired fasting glucose or IR) (see section 3.2.5) and who did not. A p-value≤ 0.05 (p- value≤ 0.025 for post-hoc Bonferroni) was considered significant.

Binomial logistic regression models (logistic regression models) were performed to evaluate the association between CMD risk factors and nutrient intake with BI, HV and HFD-I scores (**Objectives 1 and 3**). BI, HV and HFD-I were treated as dichotomous variables (> and < median). The models were created to predict likelihood of having lower/ higher than median BI, HV and HFD-I scores according to different selected variables. A p-value <0.05 was considered significant. Post- hoc Power Analysis and Effect sizes (Cohen's d) are presented in Appendix B (Tables B4- B10).

3.4 Results

3.4.1 Anthropometric and Demographic Data

Anthropometric, demographic and blood pressure data are illustrated in table 3.5. A total of 41 children (n=18 Control, n=9 PWS and n=14 NAFLD) were recruited. Five children were excluded from this analysis due to abnormal serum ALT/total cholesterol (N=2 Control), and incomplete food records (n=1 PWS, n=2 NAFLD), respectively. Final analysis included 36 youth (n=16 Control, n=8 PWS and n=12 NAFLD) between 7-18 years.

Eight children (n=4 Control, n= 4 PWS) had BMIs between the 85th- 97th percentile. BMI > 97th percentile was observed in 14 (n= 2 PWS, n= 12 NAFLD) and BMI ≥ 95th percentile in 16 (n=2 Control, n= 2 PWS, n= 12 NAFLD) children. Fifteen participants (n= 1 Control, n= 2 PWS and n= 12 NAFLD) had waist circumferences greater than 85th percentile. Blood pressure was elevated (pre-hypertension or hypertension) in 31 participants (n= 6 Control, n= 3 PWS and n= 12 NAFLD). Thirteen children (n=3 Control, n= 3 PWS and n= 7 NAFLD) had blood pressure ≥95th percentile.

Table 3.5 Demographic, Metabolic and Anthropometric Measures.

	Control (n=16)[1]	**PWS (n= 8)[1]**	**NAFLD (n=12)[1]**	**P-value[2]**
Sex (M: F)	9:7	1:7	8:4	0.051
Age (years)	12.6 ± 3.6 (7.2 – 18.0)	12.3 ± 3.6 (7.5 – 18.7)	13.9 ± 3.0 (8.4 – 17.5)	0.5
Weight (kg)	46.5 ± 17.3 [a] (22.4 – 77.8)	46.3 ± 20 [a] (22.5 – 86.9)	88.5 ± 25.1[b] (46.1 – 125.6)	<0.001
Height (cm)	155.8 ± 21.5 [a,b] (124.4 – 190.1)	139.9 ± 16.9 [a] (112.3 – 164.1)	162.6 ± 10.9 [b] (146.1 – 179.2)	0.03
BMI (kg/m^2)	18.4 ± 3.1[a] (14.3– 24.6)	22.9 ± 6.6 [a] (17.9 – 38.2)	33.1 ± 7.6 [b] (21.6 – 46.0)	<.0001
Weight z-score[3]	0.5 [a] (-0.5-1.1)	0.4 [a] (-0.2-1.0)	3.0 [b] (2.4-3.0)	<.0001
Height z-score[3]	0.8 ± 1.2 [a] (-1.0 – 3.2)	-1.2 ± 1.0 [b] (-1.95 – 0.84)	0.8 ± 1.4 [a] (-0.7 – 3.5)	0.002
BMI z-score[3]	-0.1 [a] (-1.1-0.9)	1.1 [a] (0.9-1.8)	2.9 [b] (2.5-3.0)	<.0001
Waist (cm)	65.7 [a] (60.6-70.5)	73.4 [a] (60.8-83.2)	96.8 [b] (91.4-125.0)	<0.0001
Waist z-score[3]	-0.1 ± 0.7 [a] (-1.1 – 1.2)	0.7 ± 0.7 [b] (0 – 1.8)	1.9 ± 0.4 [c] (1.1 – 2.4)	<0.0001
WHtR[3]	0.4 ± 0.04 [a] (0.4 – 0.5)	0.5 ± 0.1 [b] (0.5 – 0.7)	0.6 ± 0.1 [b] (0.5 – 0.9)	<0.0001
WHtR z-score[3]	-0.7 [a] (-1.2-0.1)	0.9 [b] (0.6-1.3)	1.8 [b] (1.4-2.2)	<0.0001
WHR	0.80 ± 0.06 [a] (0.70 – 0.92)	0.86 ± 0.06 [a,b] (0.80 – 0.99)	0.95 ± 0.09 [b] (0.80 – 1.12)	<0.0001
SBP Percentile	78.0 [a] (54.0-82.0)	84.0 [a,b] (65.5-95.5)	94.5 [b] (83.0-96.3)	0.01
DBP Percentile	56.0 ± 22.4 [a] (15.0 – 95.0)	80.3 ± 12.6 [a,b] (63.0 – 97.0)	81.3 ± 12.1[b] (56.0 – 97.0)	0.001

[1]Values are expressed as mean ± SD (range) for normal values and median (IQR) for non- normal values except for sex which the ratio is shown. [2] p-values <0.05 shows there is a significant difference between the groups. [3]Determined using World Health Organization (WHO) anthropometric calculator (Canada, 2014 revision) (144). [4] WHtR calculated as waist circumference (cm)/height (cm). [5]WHR calculated as waist circumference (cm)/hip circumference (cm). The difference in sex was tested by Freeman-Halton extension of Fisher's exact test. Data on BMI, weight and height Z-score and systolic blood pressure was analyzed using Kruskal – Wallis and Dunn's test as post hoc. For other variables ANOVA was employed with Bonferroni as a post hoc test. [a,b,c] values with unlike superscript letters were significantly different between groups (P≤ 0·025, post- hoc analysis). Abbreviations; NAFLD, Non-alcoholic fatty liver disease; BMI, body mass index; WHtR, waist to height ratio.

3.4.2 Laboratory Data

Biochemical measures are shown in table 3.6. Thirteen patients (n=1 PWS, n= 12 NAFLD) had ALT levels above 20 U/L. Elevated Insulin (> 20 mU/L) was observed in n=1 PWS and n=10 NAFLD patients, respectively. Controls had serum ALT and insulin values within reference ranges (171). Fourteen participants (n=1 Control, n=2 PWS and n= 11 NAFLD) had HOMA-IR values greater than 3. Serum triglyceride levels were high [≥0.85 in 0-9 years and ≥1.16 mmol/L in 10-17 years (172)] in 31.25% (n=5), 62.5% (n=5) and 66.7% (n=8) in Control, PWS and NAFLD children, respectively. Twelve children (n= 3 Control, n= 3 PWS and p= 6 NAFLD) had TG ≥ 95th percentile. Elevated serum TC (≥ 4.4 mmol/L) was observed in 25% (n= 4), 37.5% (n= 3) and 58.3% (n= 7) of Control, PWS and NAFLD participants respectively. In 12.5% (n= 2), 37.5% (n= 3) and 25% (n= 3) of Control, PWS and NAFLD children, serum LDL cholesterol levels were high (> 2.8 mmol/L) respectively. Total cholesterol/ HDL cholesterol ratio was elevated (> 2.8 mmol/L) in 6.25% (n= 1), 37.5% (n= 3) and 25% (n= 3) of Control, PWS and NAFLD children, respectively. Low serum HDL cholesterol (<1.16 mmol/L) was observed in 18.8% (n=3), 37.5% (n=3) and 83.3% (n=10) of Control, PWS and NAFLD children, respectively. Only one child (NAFLD) had serum HDL levels < 5th percentile.

Table 3.6 Biochemical Measures of Liver and Cardio-metabolic Dysfunction.

	Control (n=16)[1]	**PWS (n= 8) [1]**	**NAFLD (n=12)[1]**	**P-value [2]**	**Reference Values [3]**
ALT (U/L)	15 [a] (13.0-16.3)	18 [a] (16.5-20.0)	41[b] (30.5-64.3)	<0.0001	<20
AST(U/L)	23 [a] (20.0-25.3)	25.5 [a,b] (22.0-27.3)	27.5 [b] (25.8-35.3)	0.011	2-9 Y: <50 ≥10 Y: <40
ALP (U/L)	229.5 (191.8-240.8)	169.5 (145.3-197.8)	156.0 (103.8-243.3)	0.211	9-12 Y (M) :160-525 12-14 Y (M): 110- 430 14-16 Y (M): 80- 315 16-19 Y (M): 55- 150 9-11 Y (F): 160- 455 11-16 (F): 160- 525 16-19 (F): 90-225
ɣGT (U/L)	5 [a] (5.0-5.0)	5 [a,b] (5.0-5.3)	6 [b] (5.0-23.5)	0.004	M: <70 F: <55
Glucose (mmol/L)	5.1 (4.8-5.2)	4.9 (4.7-5.1)	5.0 (4.7-5.2)	0.505	3.3-6.0
Insulin (mU/L)	5.9 [a] (3.1-9.9)	13.5 [a] (11.2-15.3)	29.5 [b] (21.9-36.5)	<0.0001	5.0-20.0
HOMA-IR	1.2 [a] (0.7-2.2)	2.9 [b] (2.5-3.2)	6.4 [c] (4.8-7.8)	<0.0001	<3
TG (mmol/L)	0.7 (0.4-1.0)	1.1 (0.7-1.5)	1.2 (0.9-2.1)	0.046	0-9 Y: <0.85 10-17 Y: < 1.02
TC (mmol/L)	3.9 ± 0.6 (2.9 – 4.9)	4.6 ± 1.1 (3.3 – 6.2)	4.3 ± 0.7 (3.2 – 5.2)	0.098	<4.4
HDL-C (mmol/L)	1.4 [a] (1.2-1.6)	1.2 [a] (1.2-1.3)	1.0 [b] (1.0-1.1)	0.002	>1.16
LDL-C (mmol/L)	2.1 ± 0.5 (1.2 – 3.1)	2.7 ± 1.1 (1.2 – 4.3)	2.4 ± 0.4 (1.9 – 3.1)	0.075	<2.8
Urate (umol/L)	253 ± 75 [a] (137 – 409)	314 ± 79 [a,b] (158 – 395)	372 ± 75 [b] (263 – 545)	0.001	9 Y 100-300, 10-17 Y (M): 135-510 10-17 Y (F): 180-450 ≥18 Y: (M): 180-500 ≥18 Y: (F): 150-400

[1]Values are expressed as mean ± SD (range) for normal values and median (IQR) for non-normal values. [2] p-values <0.05 shows there is a significant difference between groups. [3]Pediatric reference ranges obtained from Alberta Health Services(171); For ALT, ALP, Albumin, TC and LDL-C, ANOVA plus post hoc Bonferroni test and for other variables, Kruskal Wallis (+ Dunn's test as post hoc) were used. There were missing values for ɣGT in the NAFLD group (n=1). [a,b,c] values with unlike superscript letters were significantly different between groups (P≤ 0·025 for post- hoc analysis). Abbreviations: NAFLD, Non-alcoholic fatty liver disease; ALT, alanine aminotransferase; AST, aspartate transaminase; ALP, alkaline phosphatase; ɣGT, gamma-glutamyl transferase; HOMA-IR, homeostatic model assessment of IR; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CRP, C-reactive protein; 25(OH)D, 25 hydroxyvitamin D; Y, years old; F, Female; M, Male.

3.4.3 Dietary Intake Data

Nutrient intake data are shown in table 3.7. Thirty participants (n= 11 Control, n= 7 PWS and n= 12 NAFLD) had energy intakes lower than their calculated energy requirements (BMR*1.5 in girls and BMR*1.6 in boys) while 10 (n= 8 Control, n= 2 PWS) exceeded that (33, 173). All subjects met the EAR for carbohydrate as expected and only 5 participants (n=1 Control, n= 4 NAFLD) failed to meet the EAR for protein (164). Two controls, four PWS and three NAFLD participants had total sugar intake above recommendations (25% energy intake). All children exceeded the World Health Organization (WHO) recommended cut-off (10% energy intake) for free sugar intake (167). Twelve participants (n= 5 Control, n= 1 PWS and n= 6 NAFLD) had high fat intake according to AMDR (> 30% Cal)(164). Percentage of energy derived from MUFA and PUFA intake were above the American Heart Association (AHA) recommendations (166) in 4 (NAFLD) and 3 (PWS) participants, respectively. Saturated fat limit as % energy according to AHA was only met in 6 participants (n= 2 Control, n= 3 PWS and n= 1 NAFLD) (166). Only 1 participant (Control) met the recommendations (Adequate Intake) for fiber (g)(164). Lower than recommendation vitamin E intake was prevalent across groups: n= 14 Control, n= 7 PWS, n= 9 NAFLD. Only 2 participants (n= 1 Control and n= 1 NAFLD) achieved the EAR for vitamin D from food (165). Six participants (n= 3 NAFLD and n= 3 PWS) had folate (DFE) intake lower than EAR (165). Fifteen, twenty-three, eight and twenty-three participants fail to meet the ANGCY recommended servings for grains, fruits and vegetables, meat and alternatives and milk and alternatives, respectively (162).

Table 3.7 Dietary Intake of Energy, Nutrients and Food Groups in Control, PWS and NAFLD.

	Control (n=16)[1]	PWS (n= 8)	NAFLD (n=12)[1]	P-value[2]	DRI
Energy (kcal)	2108 ± 597 (1205-3172)	1584 ± 359 (985- 2128)	1777 ± 439 (1119-2627)	0.050	8-9 Y: (M) 1750, (F) 1600 [3] 10-11 Y: (M) 2000, (F) 1800 12-13 Y: (M) 2250, (F) 2000 14-16 Y: (M) 2700, (F) 2100 17-18 Y: (M) 2900, (F) 2100
Protein (g)	88.5 ± 28.5 (33.1- 148.3)	69.5 ± 18.7 (43.3- 90.5)	75.5 ± 27.1 (42.9 – 142.4)	0.206	9-12Y: 34 g [4] 13-18 (F): 46 g 13-18 (M) 52 g
% Protein	17.3 ± 3.5 (10.0 – 24.2)	17.6 ± 3.1 (13.9 – 23.1)	17.3 ± 4.5 (8.2 – 24.6)	0.982	10-30%[5]
Carbohydrate (g)	272.9 ± 64.3 [a] (196.1- 400.0)	220. 4 ± 42.0 [b] (163.5-282.6)	219.5 ± 60.0 [b] (102.1- 319.9)	0.038	100 [6] (digestible)
%Carbohydrate	53.0 ± 8.4 (35.8 – 67.4)	56.6 ± 4.9 (50.2 – 66.4)	49.9 ± 7.7 (36.7 – 59.5)	0.161	45-65% [5]
Fat (g)	76.8 ±34.5 (25.8 – 155.7)	51.4 ± 18.2 (21.9 – 77.0)	68.6 ± 23.2 (38.2 – 108.0)	0.130	ND
% Fat	31.3 ± 6.7 (18.8 – 44.2)	28.3 ± 5.4 (19.9 – 36.8)	34.1 ± 6.4 (24.7 – 45.2)	0.148	25-35% [5]
Saturated Fat (g)	28.0 ± 13.4[a] (10.3 – 57.8)	15.3 ± 6.0 [b] (6.7 – 25.3)	21.9 ± 7.6 [a,b] (7.3- 34.0)	0.047	ND
% Saturated Fat	11.5 ± 3.2 [a] (7.5 – 17.8)	8.4 ± 2.1 [b] (6.1 – 12.8)	11.1 ± 2.7 [a,b] (4.7 – 14.7)	0.049	10% [7]
% MUFA	10.6 ± 2.5 (6.0 - 15.0)	8.2 ± 1.5 (6.0- 10.9)	11.4 ± 4.4 (3.8 – 16.6)	0.087	15%[7]
% PUFA	5.01[a] (3.18- 5.39)	8.71[b] (6.05- 12.30)	5.46 [a,b] (3.81- 7.48)	0.012	10% [7]
Fiber (g)	19.9 ± 5.3 (10.9 – 30.7)	21.0 ± 3.8 (13.7 ± 25.1)	15.1 ± 5.2 (7.4 – 23.6)	0.021	9-12Y:31 [8] 13-18 (F): 26 13-18 (M): 38
Total Sugar (g)	96.49 (82.39- 114.11)	96.26 (80.42- 124.66)	91.12 (66.66- 100.84)	0.419	<10% total Energy [9]
Folate DFE (microg)	372.4 ± 99.5 (204.4 – 514.5)	298.4 ± 85.2 (188.3 – 469.8)	295.0 ± 92.4 (135.6 – 477.3)	0.074	9-12Y: 250 [6] 13-18Y: 330
Vitamin E (mg)	5.16 (3.49-7.48)	5.84 (4.03- 8.10)	4.60 (3.51- 7.71)	0.771	4-8 Y: 6[6] 9-13 Y: 9 14-18 Y: 12
Vitamin D (IU)	194.03 ± 112.14 (23.22- 438.73)	205.77 ±76.84 (93.67- 355.31)	157± 120.31 (25.11- 435.24)	0.561	400[6]
Grain products (servings)	7.31± 1.94 [a] (4.38- 10.14)	4.95± 1.15 [b] (3.48- 6.53)	5.24± 2.68 [a,b] (2.04- 11.38)	0.014	6-8 Y: 4[10] 9-12Y: 6 13-18 Y (M) 6-7, (F) 6
Fruit & Vegetable (servings)	5.06± 2.08 (1.77- 8.72)	6.91± 1.41 (5.08- 9.32)	4.99± 4.00 (0.45- 12.76)	0.253	6-8 Y: 5[10] 9-12Y: 6 13-18 Y (M) 6-8, (F) 6-7
Milk and alternatives (servings)	2.94± 1.35 (0.83- 5.58)	2.41± 1.22 (0.83- 3.95)	2.41± 1.45 (0.94- 4.91)	0.552	6-8 Y: 2[10] 9-18Y: 3-4
Meat and alternatives (servings)	2.24 (1.93- 2.64)	2.13 (1.60- 2.80)	2.85 (1.84- 4.24)	0.490	6-8 Y: 1[10] 9-12Y: 1-2 13-18 Y (M) 2-3, (F) 2

[1] Values are expressed as Mean ± SD (range) for normal values and median (IQR) for non- normal variables. [2] p- values ≤0.05 shows a significant difference between groups (ANOVA for normal values and Kruskal Wallis for non- normal values). [3] Reference Values are approximations calculated using Canadian median heights and weights that were derived from the median normal BMI for low level of physical activity: https://www.canada.ca/en/health-canada/services/food-nutrition/canada-food-guide/food-guide-basics/estimated-energy-requirements. html [4]RDA (164, 165), [5]AMDR (164), [6]EAR (164, 165), [7] from American Heart Association (166), [8]Adequate Intake (164), [9] Sugar intake for adult and children (by WHO) (167), [10] ANGCY (162). [a,b] values with unlike superscript letters were significantly different between groups [P≤ 0·025, post- hoc analysis (Bonferroni for normal and Dunn's test for non- normal values]. Since energy intake was different between groups, energy adjusted nutrients (per 1000 KCal) were compared between groups. This time the only significant difference was observed for fiber intake (p= 0.009). The difference was seen between PWS and Control (p= 0.038) and NAFLD and PWS (p= 0.015). Abbreviations: NAFLD: Non-alcoholic fatty liver disease; MUFA, Mono Unsaturated Fatty Acid; PUFA, Poly Unsaturated Fatty Acid; HFD, Healthy Food Diversity; Y, years old; F, Female; M, Male; AMDR, Acceptable Macronutrient Distribution Range U-AMDR, Upper value of Acceptable Macronutrient Distribution Range; FAO, Food and Agricultural Organisation, RDA: Recommended Dietary Allowance.

3.4.4 Dietary Diversity and Macro-and-Micronutrient Intake (Objective 1)

Nutrients with intakes significantly different between groups of lower/higher than median BI, HV and HFD-I scores are shown in table 3.8 and figures 1B- 2B (Appendix B). There was no difference between intakes (as absolute or % AMDR/%EAR/%AI) of protein, vitamin D, total fat, saturated fat, PUFA, total sugar, carbohydrate and folate between participants with higher than median scores for BI versus those with lower scores ($p > 0.05$). The intakes (as absolute or % AMDR/%EAR/%AI) of protein, vitamin E, total fat, saturated fat, PUFA, MUFA total sugar, carbohydrate and folate in children with higher than median scores for HV was not significantly different from those with lower than median scores. For vitamin D and HV, only a non-significant trend was observed (Table 3.8).

Considering HFD-I scores and absolute intake of nutrients, the only significant association was found for MUFA intake. The intakes (% AMDR/%EAR/%AI) of protein, vitamin E, total fat, saturated fat, PUFA, total sugar, carbohydrate and folate was not significantly different between children with higher versus lower than median scores for HFD-I. For MUFA, only a non-significant trend was observed (Table 3.8). The energy adjusted intake (as absolute or % AMDR/%EAR/%AI) of vitamin D, fat, saturated fat, PUFA, total sugar and folate were not significantly different between participants with higher than median scores for BI versus those with lower scores. The energy adjusted intake (as absolute or % AMDR/%EAR/%AI) of protein, vitamin E, fat, saturated fat, PUFA, total sugar, carbohydrate and folate was not significantly different between groups with lower/higher than median scores for HV and HFD-I. The energy adjusted absolute intake of MUFA was not significantly different between participants with lower versus higher than median scores for HFD-I.

Table 3. 8 Nutrients with Intakes Significantly Different Between Groups of Lower/Higher than Median Berry Index, Health Value and Healthy Food Diversity Index Scores.

Dependent Variable	Nutrient [a]: independent variables [b]	%AMDR/%EAR and %AI [a b c]	Adjusted for Energy [a b d]
BI > and < median	Macronutrients (Absolute) Fiber (0.005) [+] MUFA (0.044) [-] Micronutrients (Absolute) Vitamin E (0.014) [+]	Macronutrients Fiber (0.001) [+] [f] MUFA (0.002) [-] [f] Micronutrients Vitamin E (0.004) [+]	Macronutrients (Absolute) Fiber (0.01) [+] MUFA (0.002) [-] Carbohydrate (0.018) [+] [e] Protein (0.045) [+] [e] Macronutrients (%AMDR/%AI) Fiber (0.007) [+] MUFA (0.003) [-] Carbohydrate (0.018) [+] [e] Protein (0.023) [+] Micronutrients (Absolute) Vitamin E (0.022) [+] Micronutrients (% EAR) Vitamin E (0.008) [+] [e]
HV > and < median	Macronutrients (Absolute) Fiber (0.037) [+] Micronutrients (Absolute) Vitamin D (0.052) [+] (non-significant trend)	Macronutrients Fiber (0.013) [+] [f] Micronutrients Vitamin D [+] [f] (non-significant trend)	Macronutrients (Absolute) Fiber (0.007) [+] Macronutrients (%AMDR/%AI) Fiber (0.011) [+] Micronutrients (Absolute) Vitamin D (0.019) [+] Micronutrients (% EAR) Vitamin D (0.019) [+]
HFD-I > and < median	Macronutrients (Absolute) MUFA (0.035) [-] Micronutrients (Absolute) --------	Macronutrients Fiber (0.033) [+] [f] MUFA (0.052) [-] (non-significant trend) Micronutrients Vitamin D [+] [g]	Macronutrients (Absolute) Fiber (0.009) [+] MUFA (0.049) [-] Macronutrients (%AMDR/%AI) Fiber (0.015) [+] Micronutrients (Absolute) Vitamin D (0.017) [+] Micronutrients (% EAR) Vitamin D (0.017) [+]

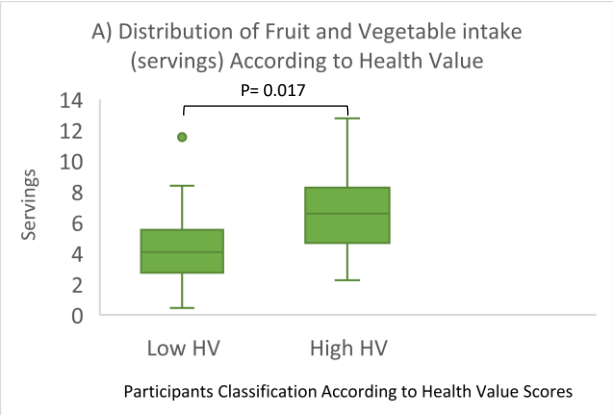
[a] P- values are stated in parenthesis. [b] Continuous variables. [c] Reference values for Macronutrients (164), American Heart Association: The Facts on Fats (166), Dietary Reference Intakes Tables (165), WHO: Sugars intake for adults and children (167). [d] Nutrient intake (absolute or as %AMDR/%EAR and %AI) were divided by energy intake and multiplied by 1000 KCal to adjust for energy.[+] The mean (or median) nutrient intake was higher in participants with higher than median scores for BI/HV/HFD-I; [-] The mean (or median) nutrient intake was lower in participants with higher than median scores for BI/HV/HFD-I. [e] A significant sex- variable interaction was observed. [f] Nutrients were also predictors of having a higher/lower than median BI/HV/ HFD scores in Logistic Regression Models. [g] only in Logistic Regression Analysis. Independent Sample t-test (or Man- Whitney test if data were not distributed normally) was used to compare variables between groups (below and above median). Abbreviations: AI, Adequate Intake; AMDR, Acceptable Macronutrient Distribution Range; BI, Berry Index; EAR, Estimated Average Requirement; HFD-I, Healthy Food Diversity Index; HV, Health Value; MUFA, Monounsaturated Fatty Acid.

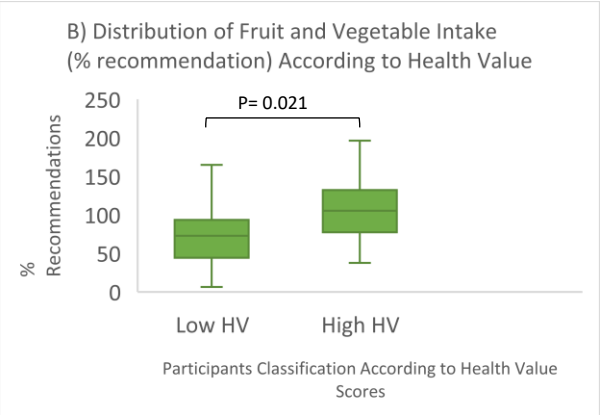
3.4.5 Food Groups, Dietary Diversity and Health Value (Objective 1)

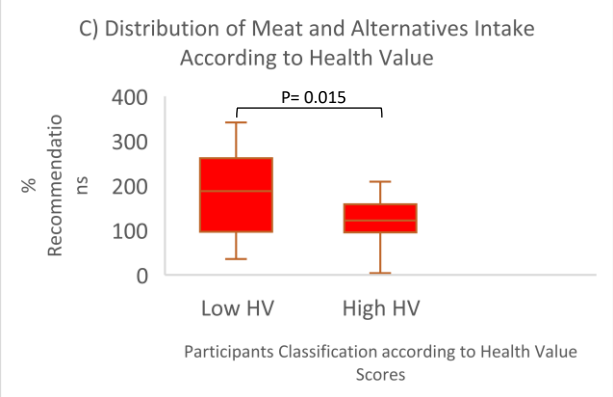
The significant differences in intakes from milk and alternatives, meat and alternatives, fruit and vegetables groups in children with lower than median and higher than median HV and HFD scores are displayed in figure 3.1. No significant difference was observed between participants with lower and higher than median BI scores or for grain group in terms of absolute intake or as % of recommendations according to ANGCY.

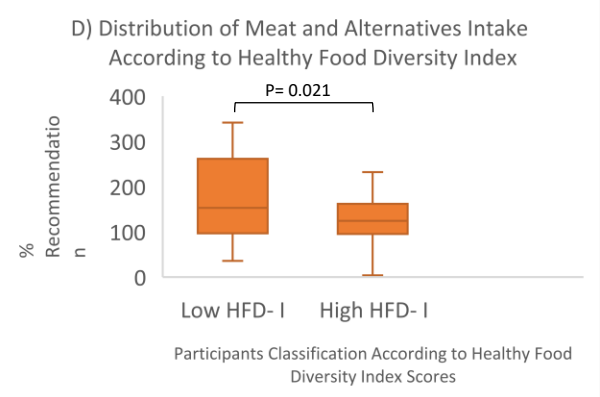
HV and HFD index scores were significantly lower in children who met the ANGCY recommendations for grain products intake ($p= 0.023$ and $p= 0.030$ respectively). On the contrary, in those who met the recommendations for fruit and vegetable intake, HV and HFD scores were higher ($p= 0.004$ and $p= 0.0048$, respectively). No significant difference was observed between BI scores or for meat and alternatives and milk and alternatives food groups.

Logistic regression analysis showed no significant association between food groups (% recommendations) and the likelihood of having a higher than median BI scores (Table B.1 in Appendix B). Regarding HV however, fruit and vegetable and meat and alternatives food groups (% recommendations) were significantly (negatively for meat and alternatives group) associated with higher than median scores when each of them were the only independent variable in the model ($p= 0.032$ and $p= 0.026$, respectively) or when assessed in combination with sex ($p= 0.038$ and $p= 0.025$, respectively) (Table B.2 in Appendix B). It is noteworthy that the overall models were not significant. No other significant association was observed for other food groups with one exception: intake from meat and alternatives group was significantly ($p= 0.031$) associated with likelihood of having higher than median HFD-I scores. The association was negative and remained significant when sex was added to the model ($p= 0.031$) (Table B.3 in Appendix B).









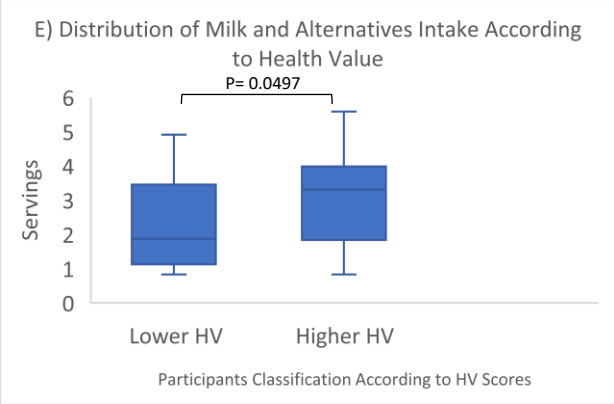


Figure 3.1 Distribution of Intakes from Different Food Groups According to Health Value and Healthy Food Diversity Index Scores. Distribution of intakes from Fruit and vegetable group in servings (3A, p= 0.017) and % of recommendations (3B, p= 0.021) according to HV scores. Distribution of intakes from meat and alternatives group (% of recommendations) according to HV (3C, 0.015) and HFD-I (3D, p= 0.021). Distribution of intake from milk and alternatives group (servings) according to HV scores (3E, p= 0.0497). Classification of participants into low and high HV or HFD-I scores was based on the median of scores. The dot in figure 3.1A is representing an outlier. Man- Whitney was used to compare intakes from milk group. For comparing intakes from fruit and vegetables and meat and alternatives groups Independent Sample t-test was used. Abbreviations: BI, Berry Index; HFD-I, Healthy Food Diversity; HV, Health Value.

Under- vs- Over Reporting, Dietary Diversity and Health Value

Participants considered to be over- reporter [energy intake (EI)/BMR> 95% CI], had significantly (p= 0.005) higher BI scores than participants considered to be "accurate-reporters" (EI/BMR within 95% CI). A significant sex interaction was also observed (0.049). No significant difference was observed between under-reporters (EI/BMR< 95% CI), with other two groups. HV and HFD-I scores were not different between groups and no sex interaction was observed. When BI, HV and HFD-I scores were compared between weekdays and weekends, no significant difference was observed.

3.4.6 Associations Between Healthy Eating Index and Healthy Food Diversity Index (HFD-I), Diet Diversity and Health Value (Objective 1)

Healthy Eating Index (HEI-C) in addition to Adequacy, Moderation and Variety (sub-components of HEI) scores were compared between participants with lower and higher than median BI, HV and HFD-I scores. HEI-C and Adequacy scores were higher in children with higher than median BI scores (p= 0.017 and p= 0.001, respectively), while no association was observed for other components (Moderation and Variety). HEI-C and Variety scores were higher in participants with higher than median HV scores (p< 0.001 and p= 0.025, respectively). Adequacy and Moderation scores were not significantly different between two groups with below/above median HV score. Children with higher than median HFD-I scores had greater scores for HEI-C and Moderation in comparison to those with lower than median HFD-I scores (p= 0.005 and p= 0.016, respectively). No significant difference was observed for Adequacy and Variety scores between two groups (i.e. groups with HFD-I scores above and below median).

Validation Analysis for HFD-Index by Total HEI-C and Its Sub- components

A fair agreement existed between total HEI-C scores and HV (κ= 0.33, p= 0.007) and HFD-I (κ= 0.28, p= 0.016) to detect children with lower/ higher scores for DQ, while there was no agreement between BI and HEI-C scores (p- value >0.05)(170).

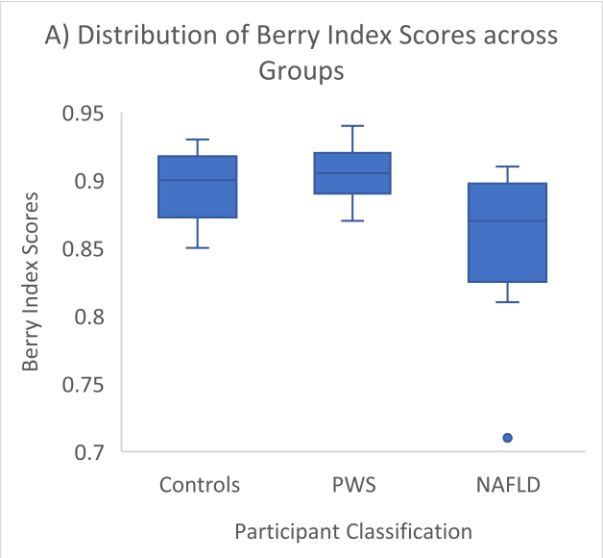
HEI-C and its components scores were put into simple/multiple models (in combination with each other and sex, age and group or individually) to predict the likelihood of having a higher than median BI, HV and HFD-I score (logistic regression, Tables B.2- B4 in Appendix B). HEI-C was significantly predictor of having a higher than median scores for BI, HV and HFD-I independently or in combinations with variables such as sex or group. Moderation was predictor of having a higher than median HV and HFD-I scores. Adequacy was predictor for the likelihood of having a higher than median BI or HV scores while Variety could only predict the likelihood of having a higher than median HV scores. More details are provided in Appendix B.

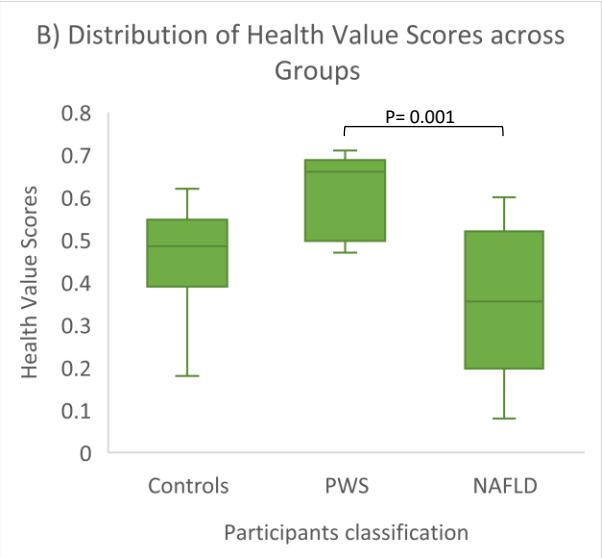
3.4.7 Dietary Diversity in healthy children and children with NAFLD and PWS (Objective 2) and Interrelationships between cardiometabolic risk (Objective 3).

Objective 2

Figure 3.2 shows the differences in BI, HV and HFD-I scores between Control, NAFLD and PWS groups. The corresponding p-values for BI between NAFLD patients with PWS and Control (0.032 and 0.038, respectively) showed only a non-significant trend. After adjusting BI scores for energy intake (scores per 1000 Kcal), no trend was observed. Children with PWS had higher un-adjusted scores for HV in comparison to patients with NAFLD (p= 0.001) and higher energy-adjusted HV scores in comparisons to Control (p= 0.011) and NAFLD (p= 0.006). Children with NAFLD had lower raw scores for HFD-I when compared to PWS patients and controls (p= 0.007

and p= 0.021, respectively). Energy- adjusted scores for HFD-I were significantly lower in PWS patients compared to the NAFLD patients (p=0.010) and controls (p= 0.007).





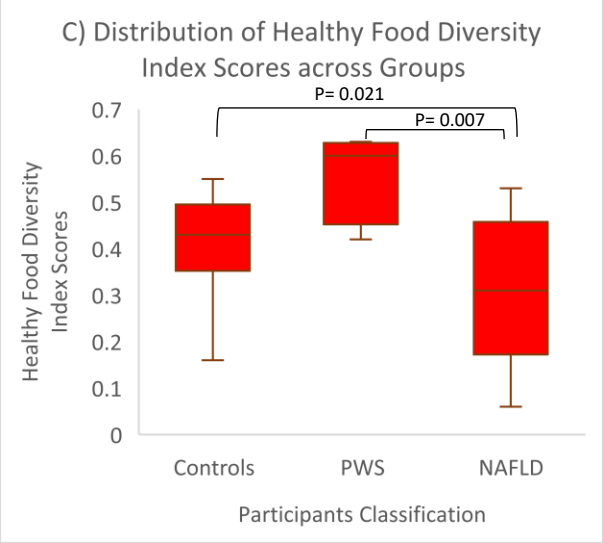


Figure 3.2 Distribution of Berry Index, Health Value and Healthy Food Diversity Index Scores Between Patients with NAFLD, PWS and controls. Distribution of BI (4A), HV (4B) & HFD-I (4C) scores between C (n= 16), PWS (n= 8) and NAFLD (n= 12) participants. The corresponding p- values for BI between NAFLD patients with PWS and controls (0.032 and 0.038, respectively) showed a non-significant trend. The p-value for HV between PWS and NAFLD were significant (p= 0.001). The corresponding p-values for HFD-I scores between NAFLD patients with PWS and Control were 0.007 and 0.021 respectively. There was no significant difference between PWS patients with Control for BI, HV and HFD-I (p- value >0.025). Data on BI and HFD were analysed using Kruskal- Wallis. ANOVA was used to analyse data on HV. Bonferroni correction and Dunn's were used as a post hoc. After repeating the analysis with energy adjusted BI, HV and HFD-I (scores per 1000 Kcal), no trend was observed for BI, and a significant difference was detected between PWS with Control (p= 0.011) and NAFLD (p= 0.006) for HV. Additionally, a significant difference was detected between PWS with Control (p= 0.007) and NAFLD (p= 0.010) for HFD-I. The association for HV was unchanged. The dot in figure 3.2A represents an outlier. Abbreviations: BI, Berry Index; HFD-I, Healthy Food Diversity; HV, Health Value; NAFLD, non-alcoholic fatty liver disease, PWS, Prader-Willi syndrome.

Objective 3: Associations between Diet Diversity and Expression of Cardio-metabolic dysregulation.

There was no significant difference in BI scores between participants with and without CMD, while a non-significant trend (p= 0.052) in HV scores was observed between the two groups with the children with CMD having lower HV scores. The HFD-I score was significantly different (p= 0.046) between the two groups (Figure 3.3).

Regarding the components of CMD definition (according to WHO definition), no difference was observed between groups with and without hypertension or dyslipidemia for BI, HV and HFD-I scores. Data on BI, HV and HFD-I scores in participants with and without BMI ≥ 95th percentile and either hyperinsulinemia or IR is presented in figures 3.4-3.5. No sex- variable interaction was observed.

Logistic regression analysis showed that insulin levels and having BMI ≥ 95th percentile could predict the likelihood of having a lower than median BI score (p= 0.05 and p< 0.001, respectively) (Table B.1 in Appendix B). However, HOMA and insulin levels showed a significant negative association with the likelihood of having a higher than median HV scores whether assessed as the only independent variable in the model (p= 0.035 and p= 0.044, respectively) or in combination with sex (p= 0.037 and p= 0.044, respectively), group (NAFLD, PWS and Control) (p= 0.036 and p= 0.028, respectively), sex and age group (cut off= 13 y) (p= 0.021 and p= 0.025, respectively), and sex, age group and group (p= 0.011 and p= 0.012, respectively) (Table B.2 in Appendix B). Having hyperinsulinemia or IR and having BMI≥ 95th percentile was negatively associated with the likelihood of having higher than median HV scores (p= 0.010 and p= 0.049). The overall model for the association of HDL-C with the likelihood of having a higher than median

HV scores was significant (p= 0.026). This was also true for the combination of HDL-C and group (NAFLD, PWS and Control) (p= 0.030). However, the p-values for the variables inside the models were not significant. The p- values for the models consisting of HDL-C and sex or age were not significant. No significant association was found for other CMD-related variables such as TG and blood pressure and the likelihood of having a higher/lower than median HV scores. The pattern observed by logistic regression analysis for HFD-I scores were similar to what was found for HV (Table B.3 in Appendix B) except for 3 cases: 1) Having a BMI ≥ 95^{th} percentile was not a predictor of a lower than median HFD-I score. 2) The p-value for the model consisting of HDL-C and age for predicting the likelihood of having a below or above median score for HFD-I was significant (p= 0.023) despite the non-significant p-values for the variables inside the model. 3) The p-value for the combination of systolic blood pressure, sex and age as a model was significant (p= 0.016). However, none of these variables (blood pressure, sex and age) were considered predictors since the p- value for none of the variables inside the model was significant.

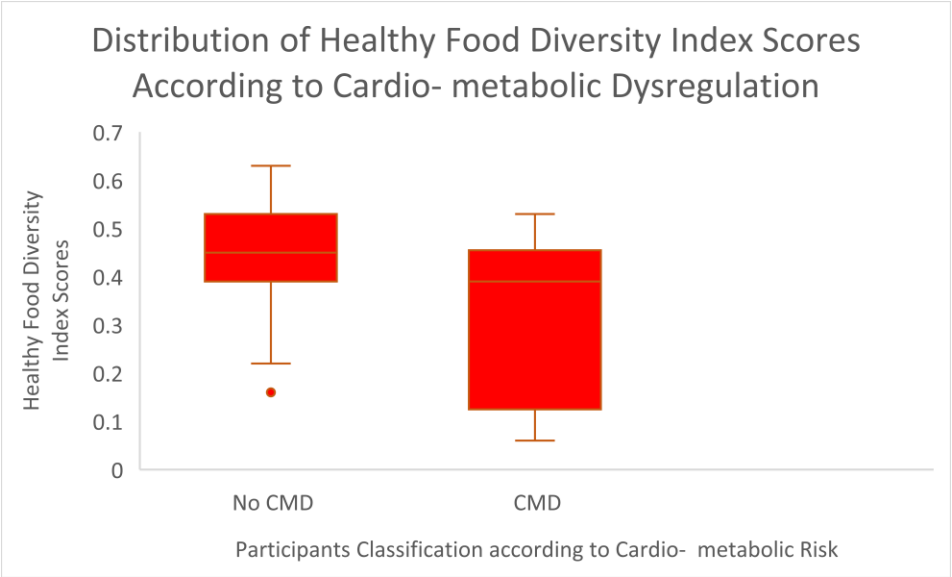
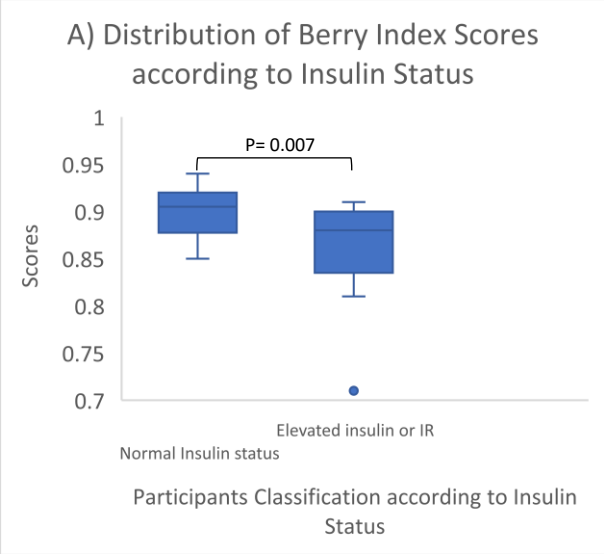
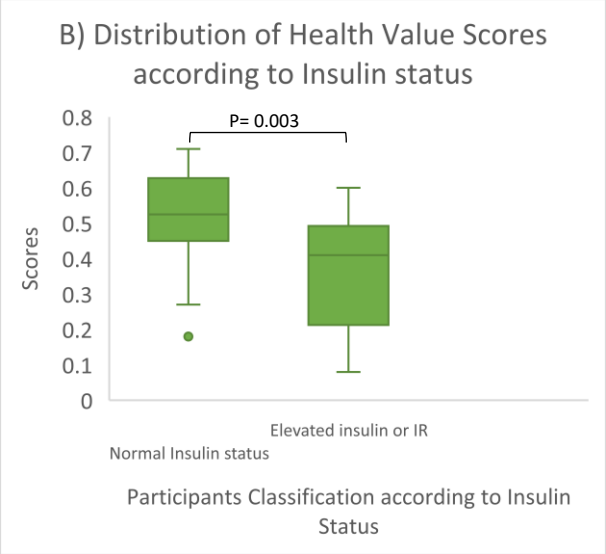


Figure 3.3 Distribution of Healthy Food Diversity Index Scores According to Cardio-metabolic Dysregulation (p= 0.046). Abbreviations: CMD, cardio-metabolic dysregulation. Scores were compared using Independent Sample t-test. The dot in the figure represents an outlier.





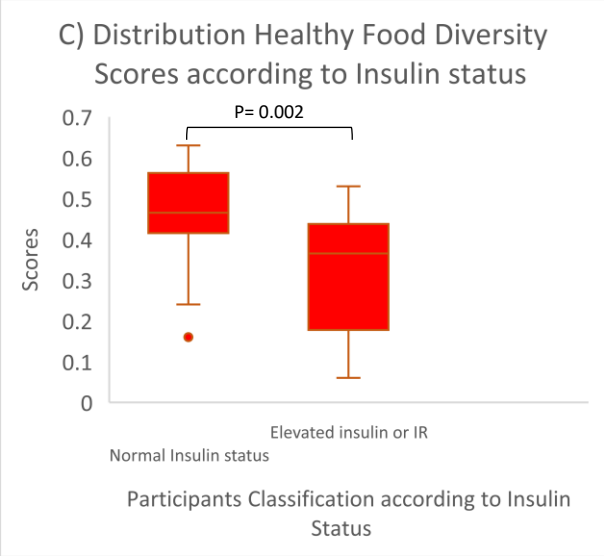
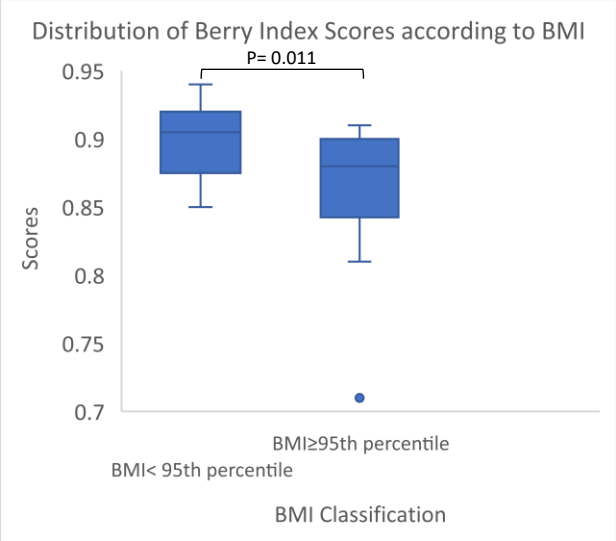
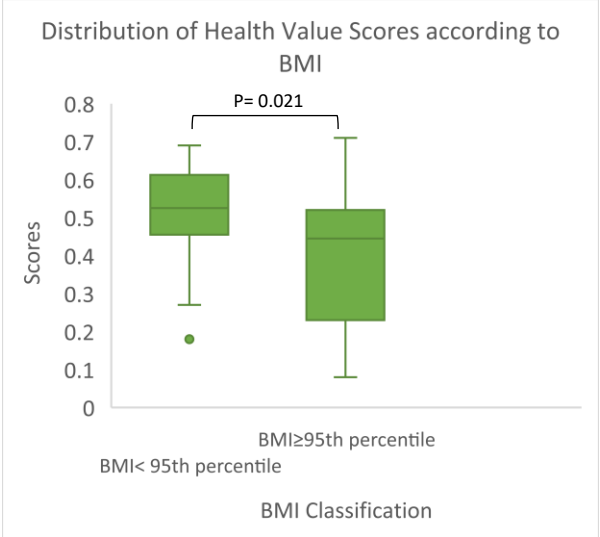


Figure 3.4 Distribution of Berry Index, Health Value and Healthy Food Diversity Index Scores According to Insulin Status. Distribution of BI (6A, p= 0.007), HV (6B, p= 0.003) and HFD-I (6C, p= 0.002) scores according to insulin status (normal insulin and insulin sensitivity versus either insulin levels > 20 mU/ I or HOMA ≥3) (169). Independent Sample t-test was used to compare HV and HFD-I scores between groups. For comparing BI scores, Man-Whitney test was employed. The dot in the figure represents an outlier. Abbreviations: BI, Berry Index; HFD-I, Healthy Food Diversity; HV, Health Value; IR, insulin resistance.





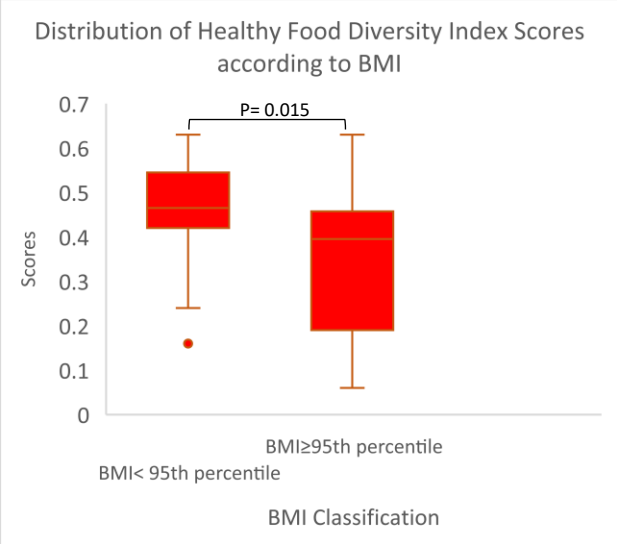


Figure 3.5 Distribution of Berry Index, Health Value and Healthy Food Diversity Index Scores According to BMI Classification. Distribution of BI (7A, p= 0.011), HV (7B, p= 0.021) and HFD-I (7C, p= 0.015) scores according to BMI status (cut-off= 95th Percentile). Independent Sample t-Test was used to compare HV and HFD-I scores between groups. For comparing BI scores, Man- Whitney test was employed. The dots in figures represent outliers. Abbreviations: BI, Berry Index; BMI: Body Mass Index; HFD-I, Healthy Food Diversity; HV, Health Value.

3.5 Discussion

This study confirmed that there are important associations between DQ (HEI-C total scores) and subcomponent scores of the HEI-C tool related to Adequacy, Variety, and Moderation with DD, HV and Healthy Food Diversity (HFD-I) (**Objective 1**). Specifically, we were able to demonstrate that while HV and HFD-I classified individuals similar to HEI-C, there were differences in the associations of HV and HFD-I with the sub-component HEI-C (Adequacy, Variety and Moderation). For example, DD was related to the concept of Adequacy, HV related to the concept of Variety, Adequacy and Moderation and HFD-I to the concept of Moderation within the total HEI-C score. These are important findings because they illustrate that a high score for overall DD does not necessarily translate to improved overall DQ score. Recent evidence suggests that increasing DD in the presence of low HV, can be associated with adverse metabolic biomarkers as it may be associated with a higher consumption/variety of high energy/low nutrient dense foods; a practise that would be translated to lower moderation scores within the HEI-C scores (3, 7, 118). Another explanation could be that HEI-C is not able to capture DD: the Variety component of HEI-C is calculated by counting food groups from which at least one serving has been consumed during the day which fails to consider food distribution and within group diversity, a criteria that is captured in BI (1, 106). However, results from this study reinforce the first prediction in that higher DD was associated with only a few components of improved nutrient density (e.g. higher protein, vitamin E and fiber intake). Notably higher DD did not capture other important dietary practices such as a lower total and saturated fat intake and/or total sugar intake and/or higher vitamin D, folate intake and/or consumption of any food groups such as milk and alternatives. This suggests that DD score is not sufficient to capture overall

nutrient density or DQ of a child's diet. In contrast, a higher overall HV score for a child's diet and/or combining a higher DD with a higher HV (higher HFD-I) was associated with lower consumption of meat and alternatives, and higher consumption of fruits and vegetables, milk and alternatives and higher total DQ scores. A higher HV or combining DD with higher HV also captures a higher intake of vitamin D, fiber and lower intake of MUFA. However, higher HV or HFD-I was not associated with lower total and saturated fat intake and/or total sugar intake.

This study also demonstrated that obese children with NAFLD have significantly lower HV and HFD-I than children with PWS (Objective 2); thus, partially confirming our second hypothesis. However, there were no significant differences in DD between groups or in HV and HFD-I between NAFLD group and Control. While PWS children had comparable values for HFD-I as to what has been reported in the literature, the overall HFD-I scores in the cohort was low in comparison to what has been reported in the literature (1, 7, 118). The higher scores with PWS children might be related to the strong parental influences on the home food environment which may impact food availability of less healthy food items (96). A final important finding is that lower BI, HV and HFD-I scores were noted with some CMD risk factors (e.g. obesity, hyperinsulinemia/IR) (Objective 3); thus, partially confirming our third hypothesis. A summary of the study findings is presented in figure 3.6.

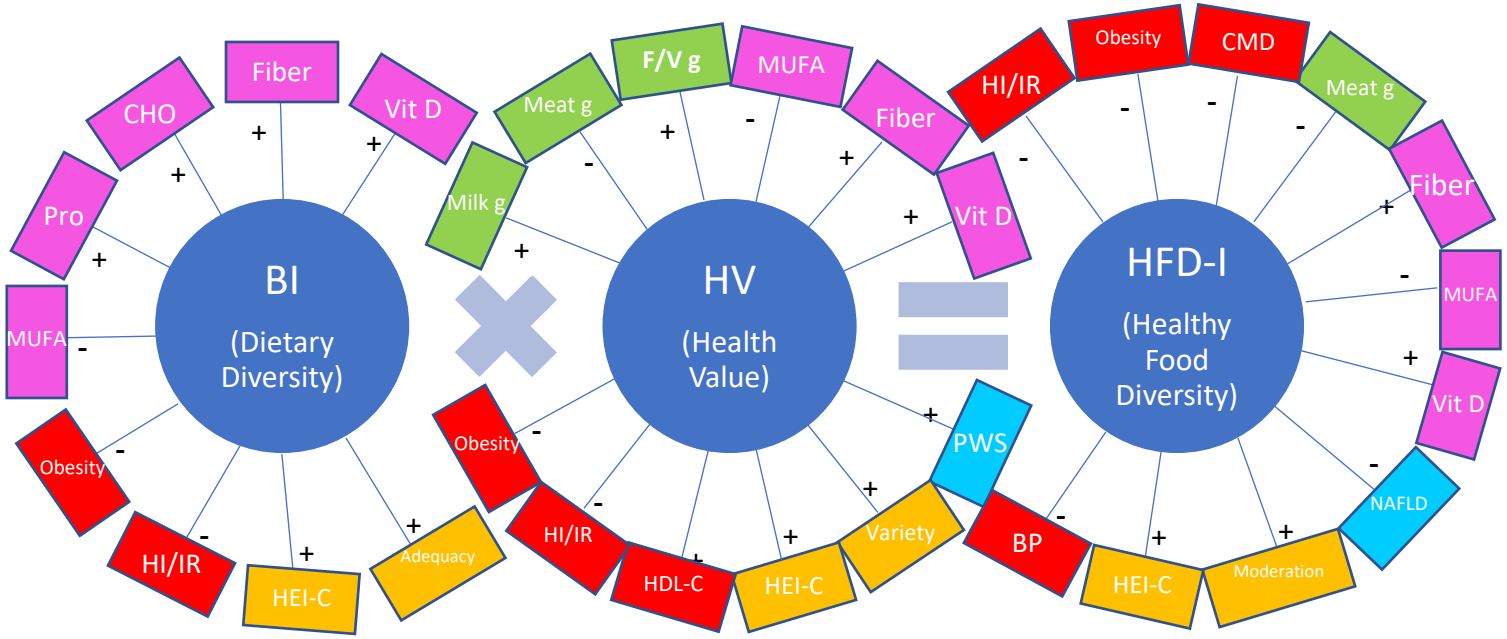


Figure 3.6 A Summary of Important Findings of the Study. Each rectangle represents a variable associated with BI, HV or HFD-I. Abbreviations: BI, Berry Index; BP, Blood Pressure; CHO, carbohydrate; CMD, cardio-metabolic dysregulation. F/V, fruits and vegetables; g, group; HDL-C high density lipoprotein Cholesterol; HEI-C, healthy eating index- Canada; HFD-I, Healthy Food Diversity Index; HI, hyperinsulinemia; HV, health value; IR, insulin resistance; MUFA, mono- unsaturated fatty acids; NAFLD, non-alcoholic fatty liver disease; Pro, protein; PWS, Prader–Willi syndrome; Vit D, vitamin D. + or – shows the direction of association between the variable and BI/HV/HFD-I scores.

Nutrients Food groups CMD and CMD related variables Diet quality indices Diagnosis group

The results of the present study examining the association of the estimated intake of some nutrients with BI, HV and HFD-I scores are similar to those previously found by Drescher et al. (1). Sugar content of the foods showed no association with HV or HFD-I. This could be attributed to the fact that it was not possible to distinguish added sugar from naturally occurring sugar in fruit and milk products in the database used to analyze nutrient intake. Higher intake of fiber in participants with higher than median scores for BI, HV and HFD-I might be explained by higher intake of fruits and vegetables, as further assessments showed that children with higher than median BI scores consumed on average about 1 serving of fruits and vegetables more than participants with lower than median scores. Additionally, fruit and vegetable intake were higher in participants with higher than median HV scores. Whole wheat grain products are not likely to be an important source of fiber in this study, since it was observed that only a small number of the study participants chose to take whole wheat grain instead of refined alternatives. This might explain the negative relationship observed between grain products intake and HV and HFD-I scores. Children with lower than median HV scores had meat and alternatives intakes almost twice the recommendations versus those with higher than median scores who consumed within the recommendation. Reviewing participants intake also showed that the majority of meat and alternatives in our cohort were higher fat choices. This is in addition to higher intake of milk and alternatives in participants with higher than median scores for HV and HFD-I. These findings underline the importance of choosing low fat protein sources, limiting the meat consumption to recommendations and obtaining protein from the choices in the milk and alternative group. Children with PWS who had the highest BI (non-significant trend) among the groups, on average consumed about 1.1 new food items per each serving of food intake in comparison to NAFLD

patients who had 0.7 new food item per each serving. Therefore, an average of 1 new food item per each serving consumed could be an optimum goal in making recommendations for increasing DD.

Lower scores for BI, HV and HFD-I observed in obese children and adolescents in compare to non- obese children contradict the results from other studies where HFD-I tool was used to measure healthy diet diversity in youth (7, 118). However, those studies either lacked a rating system to calculate health factor and could not consider healthy and unhealthy foods together when assessing the association of food variety with BMI or their tool could not capture the intakes of nutrients relevant to CMD risk factors and obesity (7, 118).

Although the scores for BI, HV and HFD-I were not significantly different when categorized according to dyslipidemia or blood pressure (according to WHO definition for CMD, see section 3.2), logistic regression analysis found significant associations between HDL-C levels and blood pressure with HV and HFD-I scores. This is in contrast to that reported by Truthmann et al. for HDL-C and blood pressure and HFD-I (118). Their participants, however, were all adolescents above 12 years old unlike our participants with ages ranging from 7 to 18 years old. They also reasoned that their indices which were based on a simple Food Frequency Questionnaire (FFQ) with only 45 food items, does not capture the intake of some nutrients such as fiber, sodium and saturated fat very accurately. The difference in nutrient intake between groups with below and above median scores for BI, HV and HFD-I shows that the 164-item nature of the tool used in the present study has been able to better capture the diversity of foods and thereby better estimate nutrient intake. In the present study higher HV and HFD-I were significantly associated with higher intakes of vitamin D, fiber, milk and fruits and vegetables, the nutrients and the food

groups believed to be protective against hypertension (33, 174, 175). Considering the effect of age and sex on CMD markers analysing data separately for girls and boys or different age group (cut-off= 13 years) would have been optimal (176, 177). However, it was not possible due to insufficient power to warrant this type of sub-analysis. It is noteworthy that only one participant had HDL levels below the 5^{th} percentile which might partly explain the discrepancy observed between logistic regression analysis and other statistical approaches.

All our participants except one, had glucose concentrations in the reference range. However, some participants, had elevated insulin concentrations. In accordance with the results of the study done by Chan She Ping-Delfos et al. participants with elevated concentration of insulin or IR had significantly lower scores for BI, HV and HFD-I (22). There are evidences relating hyperinsulinemia/IR to higher intake of refined carbohydrate and lower intakes of fruits and vegetables, fiber and vitamin E (25, 178-181). The lower BI scores in participants with obesity or hyperinsulinemia/IR is particularly important suggesting that just having healthy food choices is not sufficient for cardio-metabolic health; diversity matters as well. This can be thought as a potential intervention point for approaching NAFLD and CMD, since IR plays a fundamental role in NAFLD etiology and is considered the “primary defect” in CMD (16, 25, 27, 31, 35). In the present study, children with CMD risk, had lower scores for HFD-I.

Having shown associations with some relevant nutrients (fiber, MUFA, vitamin D and E) and food groups (meat and alternatives, milk and alternatives, fruits and vegetables), NAFLD, CMD and CMD markers (insulin status and obesity), HFD-I and its components (DD and HV) might be appropriate options for assessing the diet quality in Canadian healthy and obese youth. This contrasts the results of the study done by Truthmann et al. who found that none of their studied

indices including HFD-I were able to predict CMD risk factors (118). The ability of the present tool might be due to the fact that the food rating system in ANGCY used for adapting the tool takes many key nutrients including total fat, saturated fat, protein, sugar, fiber and sodium into account (162). Additionally, tool used in the present study was based on 164 food items (subgroups) which may enable the user to better assess DD as compared to the 45 food item in the HFD tool employed by Truthmann et al. (118).

The results of the present study suggest that a diverse and healthy diet, defined by a high HFD-I score, might be related to improved CMD markers. However, HFD-I has some limitations. First, a lower HFD-I score only shows that the diversity and/or health value of the diet is not optimum, but it does not show which food groups/items are not optimum and should be encouraged. A more important concern is that the HFD-I provides a quantitative but general overview of the HV and diversity so if an individual decides to omit one or even more food groups but still eat a wide variety of food items available in the remaining groups, they can still get a high score. For instance: one child consuming 1 serving of 11 food items (11 servings) from vegetable groups and omitting other groups would be able to get a BI= 0.90 which is an acceptable score while clearly the intake could not be considered optimal. This issue can be addressed by adding a simple component to the HFD-I: the number of food groups from which the individual has consumed ≥1 or 0.5 servings to the number of all food groups (=4 in ANGCY). In this way, the child in the above-mentioned example would have gotten a BI score= 0.9 * 0.25 = 0.23 which gives a more accurate image of his/her intake.

The present study has some limitations as well. First, the ANGCY recommendations which were used to calculate health factor (hf) have weekly basis whereas this calculated hf was used

to calculate the health value of a 3-day food record (162). Using a 7-day food record or using a food frequency questionnaire (FFQ) could be a more accurate way to calculate the health value of a diet. It was difficult to study the effect of sex and puberty stage because of too small sample size. However, PWS is a rare disorder and this contributed to small number of patients with PWS in the study. Additionally, the design of the study as cross- sectional does not allow to test causality. Future randomised clinical trials (RCTs) to study the effect of increasing DD and HV on disease status and outcome could help to approach this.

In conclusion, the results of the present study display that low DD, HV and HFD-I are associated with CMD and some CMD markers particularly obesity and hyperinsulinemia/IR in patients with NAFLD and PWS. It was also demonstrated that DD, HV and HFD-I scores are associated with intakes of some foods and nutrients such as vitamins E and D, fiber, fruits and vegetables, meat and alternatives. We observed that HFD-I and HEI-C tend to classify children quite similarly. The results also indicated that DD and HV of NAFLD patients and even children without CMD markers (controls) are not optimal and warrants intervention. Such interventions should be aimed at increasing within and between- group diversity inside the energy requirement limits and from healthy food items such as low-fat milk, whole wheat grains, fruit and vegetables and hence higher vitamin D, protein and fiber intake.

Chapter 4: Overall Conclusion

4.1 General Discussion

The present thesis studied the DD, HV and their association with cardio-metabolic risk among a cohort of children and adolescents without any cardio-metabolic risk factors or with either NAFLD or PWS. This was the first study to evaluate DD, HV and its associations between CMD in children with NAFLD and PWS. A focus on the dietary factors known to contribute to either disease etiology or overall diet quality (DQ) in childhood NAFLD and PWS (e.g. saturated fat, simple sugar and fiber intake and vitamins E, D and folate) was examined to evaluate the potential contribution of overall DQ and its sub-set components (Adequacy, Variety and Moderation) in the assessment of DD and HV and the contribution of low DD and HV to CMD in these populations. In this study, it was observed that higher intakes of fiber, carbohydrate, protein, vitamin D, vitamin E, fruit and vegetables, milk and alternatives and lower intakes of MUFA, grains, meat and alternatives were associated with higher BI, HV and HFD-I scores (Objective 1). Our results for fiber, vitamin D and vitamin E are similar to those previously found by Drescher et al. but adds to the current body of pediatric literature by expanding the examination of DD and overall HV of a diet by examining macronutrient intake in more detail and intake from the four food groups (1). This is important as it enables an overall contextual evaluation of DQ, HV and food intake and how this is related to overall changes in DD. The results of the present study indicated that DD among patients with NAFLD and controls were lower than what has been previously reported in general youth and adult population (1, 7, 118). It also displayed that DD and HV was lower in NAFLD patients compared to PWS children (Objective 2) and in children with CMD markers compered to children without CMD markers (Objective 3).

Overall study findings demonstrated that DD cannot be examined in isolation of the HV of food intake and that it is ultimately very important to evaluate DD (variation in food intake between and within food groups) together with HV at the same time, as CMD expression was related to both lower DD and lower HV, rather than lower DD alone. This has significant implications for clinical management in children with either NAFLD or PWS, as dietary interventions are the main treatment modalities in both conditions.

The present study had some limitations. These include a rather small sample size that limited the evaluation of potential impact of pubertal stage, age and sex on the results (176, 177). However, PWS is a rare genetic disorder and this contributed to small number of patients with PWS in the present study (182). Additionally, the design of the study as cross-sectional does not allow to test causality. Future randomised clinical trials (RCTs) to study the effect of increasing DD and HV on disease status and outcome could help to approach this.

To our knowledge, the present study was the first to address DD, HV and overall healthy food diversity in children and youth with either NAFLD or PWS, using an adapted tool specifically designed to measure DD while considering the HV of the food intake at the same time (1). Studying two populations (PWS and NAFLD) with different pathogenicity for obesity, body composition and cardio-metabolic risk (Table 1.3) created a unique opportunity to examine the relationship between two different obesity pathologies and DD. In addition, as parental control on food intake in children with PWS is high, it enabled us to evaluate how this might impact overall DD and HV in pediatric populations. The results of the present study might help health

professionals to design targeted diet plans aimed at specific forms of obesity and cardio-metabolic risk factors.

4.2 Clinical Relevance and Clinical Implications

Our finding that children with NAFLD, CMD risk, obesity or hyperinsulinemia/IR had lower scores for HFD-I underlines the necessity of assessing these groups of children for DD and HV. Hyperinsulinemia/IR are the main pathology of NAFLD and an important risk factor for CMD (25, 27, 31, 35). Obesity is also involved in NAFLD etiology and CMD (29-31, 108). This is critically important due to the high prevalence of obesity and obesity-related health conditions and cardio-metabolic risk in children and adolescents in Canada which influence their quality of life and may potentially increase health care costs (18-20). Lifestyle modification remains the mainstay of treatment in NAFLD and PWS (25, 89, 95). The results of the present study might be considered as a basis for developing dietary recommendations which focus on increasing DD together with dietary HV.

The fiber intake was the only nutrient associated with higher scores for both BI and HV in our cohort. Consistent with this, the intakes from fruit and vegetable group was also associated with higher HV score and children with higher than median BI scores consumed 1 more serving of fruits and vegetables in comparison to those with lower than median BI scores implying that one of the best ways to increase DD and HV might be to encourage the consumption of more fruits and vegetables. This is consistent with current dietary recommendations for Canadians (155). Whole wheat grain products were not an important source of fiber in this study, since it was observed that only a small number of the study participants chose to take whole wheat grain

instead of refined alternatives. There was a positive association of protein intake with DD (BI scores) while there was a negative association for meat and alternatives intake with HFD-I score. Children with lower than median HV scores had meat and alternatives intakes almost twice the recommendations versus those with higher than median scores who consumed within the recommendations. These results encourage limiting the intake of meat and alternatives to recommendations and increasing protein intake from sources other than meat group (i.e. dairy products). This could be another approach to improve DD and HV and was further supported by the observation that participants with higher HV scores had higher intakes from milk group. Although we did not find a significant association between intakes of total sugar, total and saturated fat with dietary scores, it would be prudent to continue to recommend these be limited in the diet of children due to their potential contribution to the etiology/pathology of NAFLD and obesity (25, 27, 58, 60). All mentioned approaches could become part of routine nutritional care for children and youth with NAFLD, obesity or CMD risk factors.

No association was found between energy intake and DD and HV whereas the intake of nutrients such as vitamin D, vitamin E, protein, carbohydrate and fiber per 1000 KCal was associated with higher BI, HV or HFD-I scores. This highlights the importance of a nutrient- dense diet as a basis for healthy eating pattern which has been addressed in the study by Hiz et al. (183). One important point that should not be overlooked is that the increase in DD should be within energy recommendations limits and closely paralleled with increase in HV since there are evidences that in instances where HV was not considered or correctly reflected in calculation of DD, DD was associated with greater BMI (7, 113, 118).

4.3 Future Directions

The present study showed that children with NAFLD, obesity and hyperinsulinemia/IR had lower HFD-I scores. It was also identified that intake of some nutrients and food groups such as fruits and vegetables, protein, fiber, vitamins D and E were associated with higher than median scores for DD, HV and HFD-I scores. The results of the present study should be confirmed in prospective studies: A cohort of general population could be divided according to their overall healthy food diversity (cut-off= median) and then followed for development of NAFLD or cardio-metabolic risk. Another example would be to follow the patients with NAFLD or CMD with defined DD and HV to monitor the disease progression and prognosis. For studying the potential associations separately for males and females or according to the puberty stage , physical activity level, disease severity and ethnicity, such studies need to have a larger sample size (33, 34, 44-48, 176, 177). As a next step, the efficacy of interventions to increase DD and HV on disease progression can be studied in a randomised clinical trial controlled for influencing factor (such as disease severity, physical activity level, etc). Increasing DD and HV could be done by encouraging intake of a variety of fruits and vegetable, substituting extra (more than recommendations) servings of meat and alternatives with low fat dairy products and choosing whole wheat grains. However, this should be with consideration of an appropriate energy intake and a low glycemic index/load (25).

In the present study it was observed that not all PWS patients were obese; in fact, only 25% of them had BMI above 95th percentile. Thus, it would be a good idea to study the DD and HV separately for obese and non- obese PWS patients. Particularly since we found a significant difference for DD and HV between obese and non- obese participants in whole cohort. This could

clarify whether the high DD and HV scores observed in PWS group is the reflection of scores related to all patients (obese and non- obese PWS) in that group.

In the present study, HFD-I was used as a diversity tool, however since it considers the dietary HV at the same time and has shown some association with HEI-C and the concepts of dietary Variety, Adequacy and Moderation, it could also be considered as a diet quality tool. However, as it was shown in chapter 3, it is possible to have a high HFD-I score while omitting a food group completely. Therefore, adding a component (the ratio of the number of food groups consumed to the number of all food groups available) to the calculations of the HFD-I score in the tool might be needed to beforehand. Additionally, a study to compare HFD-I and HEI-C regarding their association with nutrient intake, NAFLD and cardio-metabolic risk would be of interest.

4.4 Final Study Conclusions

Overall, the results of the present study indicated that DD and HV are lower in children with NAFLD, CMD, obesity and hyperinsulinemia/IR than children without NAFLD or CMD/CMD markers (obesity and hyperinsulinemia/IR). It also identified the association between DD and HV with some relevant nutrients such as fiber, vitamin D and E, MUFA and some food groups. PWS patients had higher scores for HFD-I than NAFLD patients and controls (Children with body weight within healthy range) and than that previously reported in literature (1, 7, 118). While studying two populations (PWS and NAFLD) with different pathogenicity, body composition and cardio-metabolic risk (Table 1.3) created a unique opportunity to examine the relationship between these factors and the DD, the small sample size limited our ability to develop the associations according to sex or puberty stage. This needs to be addressed in future research. The results

suggest that improving the diets in terms of increasing DD and HV mostly by encouraging fiber intake from fruit and vegetables and whole wheat grains and increasing protein intake from low fat dairy products rather than high fat meat might reduce the risk for NAFLD, CMD, obesity and their consequences. Such effect would be of interest due to high prevalence of obesity and its health- related conditions and costs in Canada. Nevertheless, the efficacy of these types of interventions must be confirmed in randomised clinical trials in advance.

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Appendix A

Table A1 Candidate Criteria for Immediate Liver Biopsy in Suspected Pediatric NAFLD (If Liver Biopsy of All Such Patients Is Not Routine)

Young age (<10-years-old)
Hepatosplenomegaly
Very elevated serum AST or ALT
Very severe insulin resistance (by HOMA-IR)
Detectable nonspecific autoantibodies
Inconclusive results from biochemical tests relating to Wilson disease
Co-morbid liver diseases such as chronic viral hepatitis or α1-antitrypsin deficiency
Hypothalamic disorder
*Family history of severe NAFLD
*Planned pharmacological intervention

Adapted with permission from Roberts EA. Pediatric nonalcoholic fatty liver disease (NAFLD): a "growing" problem? Journal of hepatology. 2007;46(6):1133-42.(38)

**performing a biopsy is not mandatory*

Table A2 Sensitivity and Specificity of ALT and Non-Invasive Imagining Technique

	Non-invasive imagining techniques*				
ALT[Ŧ]	**US**	**CT**	**MRI**	**MRS**	**Fibroscan**
Sensitivity 80%-92%	Sensitivity 60%-96%	Sensitivity 82%	Sensitivity 100%	Sensitivity 87%-100%	Sensitivity 97%-100%
Specificity 79%-85%	Specificity 84%-100%	Specificity 100%	Specificity 90.4%	Diagnostic precision 80-85%	Specificity 91%-100%

**None of these methods distinguishes NAFLD from NASH (only liver biopsy).*
Ŧ95th percentile for ALT levels in NHANES pediatric participants (normal weight, metabolically healthy, no liver disease), boys (25.8 U/L) and girls (22.1 U/L) (80).
Abbreviations: ALT, alanine aminotransferase; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy.

Obtained with permission from McDonald K. Vitamin D Status and Markers of Cardiometabolic and Liver Disease Risk in Childhood Obesit: University of Albert; 2017 (33).

Table A3 Indications for Molecular Genetic Testing for PWS

Birth to age 2 years	Hypotonia with poor suck in the neonatal period.
Age 2–6 years	Hypotonia with history of poor suck and global developmental delay.
Age 6–12 years	History of hypotonia with poor suck (hypotonia often persists), global developmental delay, and excessive eating with central obesity if diet is uncontrolled.
Age 13 years to adulthood	Cognitive impairment (usually mild intellectual disability), excessive eating with central obesity (if caloric intake is uncontrolled), hypothalamic hypogonadism, and characteristic behavior problems.

Source: Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. Genetics in medicine: official journal of the American College of Medical Genetics. 2012;14(1):10-26.

Table A4: BI Calculations for a Sample Meal

Food Consumed	**Quantity**	**Weight (g)**	**Food Ingredients**	**Servings**	**S_i**	**S_i^2**
Orange, Fresh	1 medium	131	Orange, Fresh	1	0.072	0.005
Pizza, pepperoni	288 grams	288	Tomato Sauce	0.35	0.025	0.001
			Pizza Bread	3	0.217	0.047
			Cheese	3	0.217	0.047
			pepperoni	1	0.072	0.005
			Fats & Oils	4	0.289	0.083
			Sugar	1	0.072	0.005
Lettuce, fresh	2 Cup	112.04	Lettuce	2	0.126	0.0.016
Soda, cola	120 ml	125.81	Soda, Cola	0.5	0.036	0.001
Total Servings	15.85					
$\sum Si^2$	0.165					
BI = 1- $\sum Si^2$	**0.835**					

Si = number of serving sizes consumed from food item or product i /number of all serving sizes consumed, BI= Berry Index

Table A5 HV Calculations for a Sample Meal

Food	Weight (g)	W_i	Fruits and Vegetables			Grains			Milk and Substitutes			Meat and Substitutes			Fat			Other
			Most Often	Some times	Least often	Most Often	Some times	Least often	Most Often	Some times	Least often	Most Often	Some times	Least often	Most Often	Some times	Least often	Least Often
Orange, fresh	131.000	0.199	0.199															
Pizza, pepperoni	288.000	0.438			0.016		0.087			0.269				0.045	0.016			
Soda, cola	125.810	0.192																0.192
Lettuce	112.040	0.171	0.171						.									
Sum weight	656.850																	
Sum Wi			0.370	0	0.016	0	0.087	0	0	0.269	0	0	0	0.045	0.016	0	0	0.192
hf_i			0.299	0.023	0.002	0.191	0.015	0.001	0.327	0.046	0.003	0.056	0.023	0.002	0.010	0.002	0.000	0.00
Sum $Wi*hf_i$			0.111	0	0.000	0	0.001	0	0	0.012	0	0	0	0.000	0.000	0	0	0
HV		**0.125**																
Final HV*		**0.381**																

Hf_i = corresponding health factor for each food item, HV= Health Value, w_i = the weight of the food item divided by the total weight of the all foods consumed, * Final HV was calculated as HV divided by the possible maximum Health value for the age and sex.

Table A6 Strength and Limitations of Different Definition of Cardio-metabolic Dysregulation in Children and Adolescents.

Definitions	Strength	Limitations
Cook et al.	-Considers those with elevated blood pressure in addition to those with hypertension	- It has a binary nature which makes it limited in epidemiological studies. - It does not show the severity of the problem which makes it hard to compare the results over time. - Is not for use in children under 12.
Viner et al.	-Hyperinsulinism was defined from norms for pubertal stage -can be used from the age of 2 years	- It has a binary nature which makes it limited in epidemiological studies. - It does not show the severity of the problem which makes it hard to compare the results over time. -Is based on only 103 obese children from UK and adolescents of different ethnicities -Does not consider central obesity
IDF (International Diabetes Federation)	- Considers ethnicity for WC for adolescents above 16 (adult criteria)	- Does not diagnose CMD in children under 10 - The criteria do not include insulin resistance - It has a binary nature which makes it limited in epidemiological studies and tracking the severity of the problem over time. - For adolescents above 16 uses non-standardized values rather than Z-scores or percentiles
W.H.O	- Considers known hyperinsulinemia as an alternative component for glucose levels -Impaired glucose or hyperinsulinemia is a mandatory component for defining CMD	- It has a binary nature which makes it limited in epidemiological studies. -It does not show the severity of the problem which makes it hard to compare the results over time.
NCEP ATPIII (National Cholesterol Education Program Adult Treatment Panel III)		- It has a binary nature which makes it limited in epidemiological studies. - It does not show the severity of the problem which makes it hard to compare the results over time. - Race and gender are not considered in defining the CMD, leading to under-diagnosis in specific groups.
IDEFICS (Identification and prevention of Dietary- and lifestyle-induced health Effects in Children and infants)	-It provides the results as a continuous score by standardisation Z-scores for the components. Calculates age and sex specific Z-scores which is considered an advantage for epidemiological studies and for comparisons over time. - It has insulin resistance as a component in addition to glucose levels. -Considers those with elevated blood pressure in addition to those with hypertension	

APPENDIX B

Table B.1 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Berry Index.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
BI	Group ψ	0.055		0.175	0.238	0.000	1.000	1.157	
	Group1	0.334	3.182					-1.482	0.304- 33.259
	Group2	0.069	0.227					0.788	0.046- 1.125
BI	Group ψ	0.090		0.183	0.248	0.546	0.969		
	Group1	0.448	2.585					0.950	0.222- 30.065
	Group2	0.077	0.234					-1.451	0.047- 1.172
	sex	0.557	0.623					-0.472	0.129- 3.021
BI	Group ψ	0.276		0.176	0.239	0.678	0.878		
	Group1	0.328	3.281					1.188	0.304- 35.431
	Group2	0.360	0.276					-1.286	0.018- 4.336
	BMI Classification (cut off= 95 p) £	0.865	0.799					-0.224	0.060- 10.614
BI	Glycemic Control £	0.726	1.752	0.315	0.426	1.301	0.729	0.561	0.076- 40.525
	BMI Classification (cut off= 95 p) £	0.999	0.000					-22.292	0.000-.
	Hypertension£	0.779	1.470					0.385	0.100- 21.592
	Dyslipidemia£	0.999	1.420E+9					21.074	0.000-.
BI	Glycemic Control £	0.678	1.762	0.189	0.256	2.530	0.470	0.567	0.121- 25.592
	BMI Classification (cut off= 95 p) £	0.071	0.045					-3.102	0.002- 1.304
	Hypertension£	0.134	6.190					1.823	0.572- 67.024
BI	Glycemic Control £	0.622	0.580	0.103	0.140	0.600	0.438	-0.545	0.066- 5.070
	BMI Classification (cut off= 95 p) £	0.393	0.391					-0.939	0.045- 3.371
BI	Glycemic Control£	.	0.281	0.085	0.116	0.000	.	-1.269	0.068- 1.157
BI	BMI Classification (cut off= 95 p) £	0.000	0.259	0.097	0.132	0.000	.	-1.350	0.063- 1.066
BI	Hypertension£	0.886	1.108	0.001	0.001	0.000	.	0.102	0.272- 4.509

Table B.1 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Berry Index, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
BI	Insulin levels	0.05	0.222	0.106	0.144	0.000	.	-1.504	0.049- 1.003
BI	Insulin levels	0.073	0.242	0.153	0.208	4.361	0.737	-1.418	0.051-1.143
	age	0.174	0.856					-0.156	0.684- 1.071
BI	Insulin levels	0.055	0.218	0.149	0.202	0.817	0.665	-1.525	0.046- 1.031
	sex	0.192	2.673					0.983	0.611- 11.688
BI	Insulin levels	0.083	0.241	0.203	0.276	4.326	0.742	-1.422	0.048- 1.207
	Sex	0.151	3.133					1.142	0.660- 14.863
	Age	0.138	0.837					-0.178	0.661- 1.059
BI	Insulin levels	0.723	0.582	0.226	0.306	10.282	0.173	-0.541	0.029- 11.526
	Sex	0.405	2.090					0.737	0.368- 11.866
	Age	0.198	0.852					-0.160	0.668- 1.087
	Group	0.628							
	Group1	0.561	2.390					0.871	0.127- 45.044
	Group2	0.339	5.530					1.710	0.166- 184.157
BI	Insulin levels	0.761	0.655	0.177	0.240	0.318	0.957	-0.423	0.043- 10.052
	Group $^{\psi}$	0.299							
	Group1	0.318	3.381					1.218	0.310- 36.918
	Group2	0.419	0.322					-1.133	0.021- 5.023
BI	HOMA	0.178	0.848	0.085	0.116	4.674	0.700	-0.165	0.667-1.078
BI	HOMA	0.940	0.874	0.119	0.162	2.319	0.940	-0.135	0.687- 1.111
	age		0.876					-0.132	0.700- 1.098
BI	HOMA	0.206	0.853	0.118	0.160	3.123	0.873	-0.159	0.667- 1.091
	sex	0.257	2.288					0.828	0.547- 9.572
BI	HOMA	0.339	0.887	0.162	0.220	2.162	0.950	-0.120	0.694- 1.134
	Sex	0.191	2.738					1.007	0.604- 12.407
	Age	0.188	0.853					-0.159	0.673- 1.081

Table B.1 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Berry Index, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
BI	HOMA	0.920	0.989	0.223	0.303	10.678	0.153	-0.011	0.801- 1.222
	Sex	0.445	1.942					0.664	0.354- 10.661
	Age	0.218	0.853					-0.159	0.662- 1.099
	Group $^{\Psi}$	0.275							
	Group1	0.516	2.338					0.849	0.180- 30.288
	Group2	0.231	0.286					-1.250	0.037- 2.218
BI	HOMA	0.643	0.951	0.181	0.246	5.112	0.646	-0.050	0.769- 1.176
	Group $^{\Psi}$	0.184							
	Group1	0.309	3.411					1.227	0.320- 36.332
	Group2	0.253	0.310					-1.171	0.042- 2.312
BI	Systolic Blood Pressure Percentile	0.920	1.001	0.000	0.000	8.198	0.315	0.001	0.973- 1.031
BI	Systolic Blood Pressure Percentile	0.766	0.995	0.104	0.141	7.380	0.390	-0.005	0.965- 1.026
	age	0.064	0.797					-0.226	0.628- 1.013
BI	Systolic Blood Pressure Percentile	0.790	1.004	0.046	0.062	13.469	0.061	0.004	0.975- 1.034
	sex	0.210	2.463					0.901	0.601- 10.088
BI	Systolic Blood Pressure Percentile	0.854	0.997	0.149	0.201	6.450	0.488	-0.003	0.965- 1.030
	Sex	0.192	2.721					1.001	0.605- 12.241
	Age	0.060	0.788					-0.239	0.614- 1.010
BI	Systolic Blood Pressure Percentile	0.457	1.015	0.234	0.317	12.913	0.074	0.015	0.976- 1.055
	Sex	0.416	2.034					0.710	0.367- 11.265
	Age	0.257	0.854					-0.157	0.651- 1.122
	Group $^{\Psi}$	0.181							
	Group1	0.807	1.388					0.328	0.100- 19.242
	Group2	0.094	0.182					-1.703	0.025- 1.337
BI	Systolic Blood Pressure Percentile	0.257	1.021	0.194	0.262	5.907	0.551	0.021	0.985- 1.058
	Group $^{\Psi}$	0.044							
	Group1	0.517	2.232					0.803	0.197- 25.272
	Group2	0.038	0.132					-2.024	0.020- 0.895

Table B.1 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Berry Index, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
BI	Triglycerides Levels	0.999	1.001	0.000	0.000	9.209	0.238	0.001	0.451- 2.218
BI	Triglycerides Levels	0.615	1.243	0.077	0.105	6.674	0.464	0.218	0.533- 2.902
	Age	0.105	0.826					-0.191	0.656- 1.041
BI	Triglycerides Levels	0.946		0.051	0.070	9.710	0.206	0.028	0.457- 2.318
	sex	0.176						0.958	0.651- 10.428
BI	Triglycerides Levels	0.516	1.335	0.141	0.191	10.865	0.145	0.289	0.558- 3.198
	Sex	0.121	3.286					1.190	0.729- 14.802
	Age	0.075	0.800					-0.223	0.626- 1.023
BI	Triglycerides Levels	0.163	2.103	0.266	0.361	6.761	0.454	0.743	0.740- 5.972
	Sex	0.392	2.154					0.767	0.372- 12.466
	Age	0.104	0.802					-0.220	0.615- 1.047
	Group $^{\psi}$	0.089							
	Group1	0.651	1.823					0.600	0.135- 24.556
	Group2	0.056	0.143					-1.943	0.020- 1.049
BI	Triglycerides Levels	0.343	1.602	0.197	0.267	1.559	0.980	0.471	0.605- 4.241
	Group $^{\psi}$	0.044							
	Group1	0.398	2.776					1.022	0.260-29.700
	Group2	0.047	0.148					-1.909	0.023- 0.976
BI	HDL	0.606	1.792	0.008	0.010	7.555	0.373	0.583	0.196- 16.403
BI	HDL	0.834	1.274	0.072	0.097	8.916	0.259	0.242	0.133- 12.224
	age	0.135	0.845					-0.169	0.677- 1.054
BI	HDL	0.939	1.096	0.051	0.070	9.180	0.240	0.091	0.105- 11.449
	sex	0.210	2.552					0.937	0.590- 11.031
BI	HDL	0.708	0.619	0.134	0.181	3.457	0.840	-0.480	0.050- 7.653
	Sex	0.129	3.490					1.250	0.696- 17.491
	Age	0.087	0.811					-0.209	0.638- 1.031

Table B.1 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Berry Index, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
BI	HDL	0.204	0.141	0.258	0.349	8.407	0.298	-1.960	0.007- 2.901
	Sex	0.254	2.950					1.082	0.460- 18.924
	Age	0.129	0.815					-0.204	0.626- 1.061
	Group $^{\Psi}$	0.094							
	Group1	0.615	1.971					0.678	0.141- 27.617
	Group2	0.053	0.145					-1.929	0.020- 1.029
BI	HDL	0.472	0.366	0.187	0.253	6.268	0.509	-1.005	0.024- 5.651
	Group $^{\Psi}$	0.060							
	Group1	0.362	3.016					1.104	0.281- 32.322
	Group2	0.060	0.157					-1.854	0.023- 1.082
BI	BMI Percentile	0.824	0.998	0.001	0.002	5.439	0.365	-0.002	0.978- 1.018
BI	BMI Percentile	0.746	0.997	0.073	0.099	6.336	0.501	-0.003	0.976- 1.017
	Age	0.115	0.839					-0.176	0.674- 1.044
BI	BMI Percentile	0.857	0.998	0.052	0.071	4.790	0.571	-0.002	0.978- 1.019
	Sex	0.178	2.591					0.952	0.648- 10.357
BI	BMI Percentile	0.729	0.996	0.133	0.181	4.845	0.679	-0.004	0.975- 1.018
	Sex	0.132	0.709					1.145	0.709- 13.919
	Age	0.088							0.648- 1.031
BI	BMI Percentile	0.375	1.015	0.241	0.327	10.625	0.156	0.015	0.982- 1.050
	Sex	0.438	1.963					0.674	0.356- 10.809
	Age	0.273	0.869					-0.140	0.676- 1.117
	Group $^{\Psi}$	0.128							
	Group1	0.883	1.246					0.220	0.067- 23.152
	Group2	0.104	0.112					-2.188	0.008- 1.568
BI	BMI Percentile	0.267	1.019	0.205	0.279	5.750	0.452	0.018	0.986- 1.052
	Group $^{\Psi}$	0.040							
	Group1	0.740	1.584					0.460	0.105- 23.850
	Group2	0.053	0.081					-2.513	0.006- 1.037

Table B.1 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Berry Index, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
BI	Total Fat (%AMDR)	0.445	1.053	0.323	0.438	10.227	0.176	0.052	0.922- 1.203
	Saturated Fat (%AMDR) ‡	0.519	1.020					0.020	0.960- 1.083
	PUFA (%AMDR) ‡	0.887	1.003					0.003	0.968- 1.039
	MUFA (%AMDR) ‡	0.017	0.922					-0.082	0.862- 0.986
BI	Saturated Fat (%AMDR) ‡	0.116	1.036	0.311	0.422	9.697	0.206	0.036	0.991- 1.083
	PUFA (%AMDR) ‡	0.561	1.009					0.009	0.978- 1.041
	MUFA (%AMDR) ‡	0.007	0.936					-0.066	0.892- 0.983
BI	PUFA (%AMDR) ‡	0.840	1.003	0.247	0.335	9.845	0.198	0.003	0.974- 1.033
	MUFA (%AMDR) ‡	0.008	0.959					-0.041	0.931- 0.989
BI	MUFA (%AMDR) ‡	0.008	0.960	0.246	0.334	10.741	0.150	-0.041	0.931- 0.989
BI	MUFA (%AMDR) ‡	0.021	0.962	0.270	0.366	6.144	0.523	-0.039	0.931- 0.994
	Sex	0.820	1.225					0.203	0.213- 7.037
	Age (cut-off: 13y)	0.287	0.414					-0.883	0.081- 2.104
BI	Sex	0.132	3.117	0.130	0.177	2.048	0.957	1.137	0.709- 13.710
	Age (cut-off: 13y)	0.091	0.821					-0.197	0.653- 1.032
BI	Protein (%EAR)	0.085	1.007	0.122	0.166	10.911	0.143	0.007	0.999- 1.015
	Carbohydrate (% AMDR)	0.212	1.049					0.034	0.981- 1.092
BI	Protein (%EAR)	0.063	1.008	0.141	0.191	9.777	0.202	0.008	1.000- 1.017
	Carbohydrate (% AMDR)	0.820	1.009					0.009	0.934- 1.091
	Sugar (%recommendations)	0.390	1.008					0.008	0.990- 1.025
BI	Protein (%EAR)	0.070	1.008	0.159	0.215	4.625	0.706	0.008	0.999- 1.017
	Carbohydrate (% AMDR)	0.879	1.006					0.006	0.931- 1.087
	Sugar (%recommendations) ¥	0.501	1.006					0.006	0.989- 1.023
	Sex	0.384	0.494					-0.705	0.101- 2.418

Table B.1 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Berry Index, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
BI	Protein (%EAR)	0.277	1.005	0.299	0.406	6.767	0.454	0.005	0.996- 1.014
	Carbohydrate (% AMDR)	0.631	0.979					-0.021	0.899- 1.067
	Sugar (%recommendations) ¥	0.358	1.009					0.009	0.990- 1.029
	Fiber (%AI)	0.018	1.064					0.062	1.011- 1.121
BI	Fiber (%AI)	0.006	1.068	0.268	0.364	12.914	0.074	0.066	1.019- 1.119
BI	Fiber (%AI)	0.008	1.066	0.274	0.371	7.546	0.374	0.064	1.017- 1.118
	Sex	0.598	1.544					0.434	0.307- 7.761
BI	Vitamin D (%EAR)	0.449	1.013	0.226	0.308	7.111	0.417	0.012	0.980- 1.046
	Vitamin E (%EAR)	0.079	1.036					0.035	0.996- 1.077
	Folate (%EAR)	0.458	1.006					0.006	0.990- 1.022
BI	Vitamin D (%EAR)	0.414	1.014	0.271	0.370	6.884	0.441	0.014	0.981- 1.048
	Vitamin E (%EAR)	0.075	1.039					0.038	0.996- 1.084
	Folate (%EAR)	0.327	1.008					0.008	0.992- 1.026
	Sex	0.165	0.296					-1.219	0.053- 1.649
BI	Vitamin D (%EAR)	0.249	1.016	0.39	0.053	13.288	0.065	0.16	0.989- 1.045
BI	Energy (%DRI)	0.130	1.028	0.072	0.098	10.088	0.184	0.028	0.992- 1.066
BI	Energy (%DRI)	0.082	1.041	0.151	0.205	5.883	0.554	0.040	0.995- 1.089
	sex	0.092	4.017					1.391	0.797- 20.235
BI	Grain (%Recommendations) *	0.550	1.007	0.183	0.249	7.849	0.346	0.007	0.985- 1.029
	Fruit & vegetable (%Recommendation) *	0.074	1.023					0.023	0.998- 1.049
	Milk (%Recommendations) *	0.116	1.015					0.015	0.996- 1.035
	Meat (%Recommendations) *	0.718	1.002					0.002	0.991- 1.013
BI	Grain (%Recommendations) *	0.510	1.006	0.012	0.017	10.475	0.163	0.006	0.989- 1.023
BI	Fruit & vegetable (%Recommendation) *	0.108	1.015	0.078	0.106	6.017	0.538	0.015	0.997- 1.034
BI	Milk (%Recommendations) *	0.117	1.013	0.077	0.105	7.934	0.338	0.013	0.997- 1.030
BI	Meat (%Recommendations) *	0.538	0.997	0.011	0.014	8.177	0.317	-0.003	0.990- 1.006

Table B.1 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Berry Index, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
BI	Grain (%Recommendations) * Sex	0.232 0.099	1.011 3.698	0.090	0.122	12.038	0.099	0.011 1.308	0.993- 1.031 0.784- 17.451
BI	Fruit & vegetable (%Recommendation) * Sex	0.131 0.227	1.014 2.420	0.115	0.157	6.679	0.463	0.014 0.884	0.996- 1.033 0.577- 10.154
BI	Milk (%Recommendations) * Sex	0.096 0.141	1.014 2.994	0.134	0.182	13.928	0.052	0.014 1.097	0.998- 1.031 0.696- 12.874
BI	Meat (%Recommendations) * Sex	0.551 0.179	0.998 2.598	0.061	0.082	11.302	0.126	-0.002 0.955	0.989- 1.006 0.646- 10.449
BI	HEI	0.025	1.077	0.150	0.204	5.779	0.566	0.074	1.009- 1.150
BI	HEI Sex	0.046 0.505	1.072 1.674	0.160	0.218	6.435	0.490	0.069 0.515	1.001- 1.147 0.369- 7.596
BI	HEI Sex Age (cut-off= 13y)	0.037 0.402 0.094	1.078 2.001 0.251	0.229	0.311	9.814	0.199	0.076 0.694 -1.382	1.005- 1.158 0.396- 10.125 0.050- 1.263
BI	HEI Group ψ Group1 Group2	0.158 0.213 0.668 0.124	1.054 1.734 0.270	0.222	0.301	6.722	0.458	0.053 0.551 -1.306	0.980- 1.135 0.140- 21.431 0.051- 1.433
BI	Adequacy	0.006	1.231	0.254	0.345	10.116	0.182	0.208	1.063- 1.427
BI	Moderation	0.405	1.043	0.020	0.027	2.573	0.860	0.042	0.945- 1.150
BI	Variety	0.336	1.107	0.026	0.035	5.698	0.223	0.102	0.900- 1.361

Table B.1 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Berry Index, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
BI	Adequacy	0.007	1.225	0.277	0.375	10.701	0.152	0.203	1.058- 1.419
	Sex	0.302	2.341					0.850	0.466- 11.767
BI	Moderation	0.798	1.015	0.053	0.072	2.750	0.907	0.015	0.907- 1.135
	Sex	0.271	2.375					0.865	0.509- 11.090
BI	Variety	0.376	1.100	0.072	0.098	2.948	0.708	0.096	0.890- 1.360
	Sex	0.193	2.534					0.930	0.625- 10.275
BI	Adequacy	0.006	1.354	0.304	0.412	12.850	0.076	0.303	1.091- 1.679
	Moderation	0.633	1.026					0.026	0.922- 1.142
	Variety	0.161	0.776					-0.253	0.545- 1.106
BI	Adequacy	0.007	1.335	0.314	0.426	8.777	0.269	0.289	1.080- 1.650
	Moderation	0.906	1.007					0.007	0.893- 1.136
	Variety	0.201	0.797					-0.227	0.562- 1.129
	Sex	0.465	1.995					0.691	0.312- 12.748
BI	Adequacy	0.011	1.328	0.317	0.430	9.550	0.216	0.284	1.068- 1.653
	Moderation	0.626	1.028					0.027	0.921- 1.147
	Variety	0.297	0.818					-0.201	0.561- 1.193
	Age (cut-off= 13 y)	0.407	0.474					-0.747	0.081- 2.768
BI	MUFA (%AMDR)	0.074	0.972	0.340	0.462	10.672	0.154	-0.029	0.941- 1.003
	Fiber (%AI)	0.052	1.051					0.050	1.000- 1.106
BI	MUFA (%AMDR)	0.109	0.973	0.359	0.487	8.355	0.302	-0.028	0.941- 1.006
	Fiber (%AI)	0.153	1.042					0.041	0.985- 1.102
	Group $^{\Psi}$	0.604							
	Group1	0.989	0.981					-0.019	0.069- 13.972
	Group2	0.326	0.356					-1.033	0.045- 2.793
BI	MUFA (%AMDR) ‡	0.082	0.970	0.341	0.463	12.098	0.097	-0.030	0.938- 1.004
	Fiber (%AI)	0.050	1.052					0.050	1.000- 1.106
	Sex	0.831	1.222					0.201	0.193- 7.724
BI	MUFA (%AMDR) ‡	0.092	0.973	0.358	0.486	7.469	0.382	-0.028	0.942- 1.004
	Fiber (%AI)	0.057	1.050					0.049	0.999- 1.105
	Age (cut-off= 13 y)	0.322	0.419					-0.871	0.075- 2.347

Abbreviations: AI, Adequate intake; BI, Berry Index; BMI, Body Mass Index; Cal, Calorie; F/V, fruit and vegetables; HEI-C, Healthy Eating Index; HDL: High density Lipoprotein; HOMA, Homeostasis Model Assessment for Insulin Resistance; TG, Triglycerides;
AI and EAR values were accessed from: https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/dietary-reference-intakes/tables.html
* Recommended servings for food groups were taken from Alberta Nutrition Guidelines for children and youth (ANGCY) available from https://open.alberta.ca/dataset/1c291796-4eb0-4073-be8e-bce2d331f9ce/resource/3319786c-1df1-43ca-8693-067f733682dc/download/nutrition-guidelines-ab-children-youth.pdf.
ᴪ Group was defined as having NAFLD or PWS or being Control.
£ Cardio-metabolic dysregulation components according to WHO definition (168).
‡ recommendations for SFA, MUFA and PUFA were from American Heart Association (166).
ɣ Recommendation for sugar were from WHO (167).

Table B.2 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Health Value.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HV	Group [ψ]	0.214		0.091	0.122	0.000	1.000		
	Group1	0.251	3.000					1.099	0.459- 19.592
	Group2	0.381	0.500					-0.693	0.106- 2.355
HV	Group [ψ]	0.366		0.103	0.138	2.944	0.567		
	Group1	0.385	2.405					0.878	0.332- 17.442
	Group2	0.416	0.523					-0.649	0.109- 2.498
	sex	0.489	1.682					0.520	0.386- 7.340
HV	Group [ψ]	0.368		0.170	0.226	0.423	0.936		
	Group1	0.160	5.315					1.671	0.516- 54.731
	Group2	0.378	4.124					1.417	0.176- 96.424
	BMI Classification (cut off= 95 p)	0.112	0.097					-2.335	0.005- 1.725
HV	Glycemic Control [£]	0.221	0.178	0.195	0.260	4.268	0.511	-1.728	0.011- 2.831
	BMI Classification (cut off= 95 p) [£]	0.926	0.866					-0.144	0.041- 18.117
	Hypertension[£]	0.740	1.459					0.378	0.157- 13.578
	Dyslipidemia[£]	0.549	0.521					-0.653	0.061- 4.408
HV	Glycemic Control [£]	0.185	0.164	0.187	0.249	3.403	0.333	-1.809	0.011- 2.373
	BMI Classification (cut off= 95 p) [£]	0.873	0.787					-0.239	0.042- 14.911
	Hypertension[£]	0.965	1.043					0.042	0.157- 6.945
HV	Glycemic Control[£]	0.078	0.105	0.197	0.262	0.292	0.864	-2.258	0.009- 1.283
	BMI Classification (cut off= 95 p) [£]	0.842	10277					0.245	0.114- 14.276
HV	Glycemic Control [£]	0.010	0.127	0.196	0.261	0.000	.	-2.061	0.027- 0.606
HV	BMI Classification (cut off= 95 p) [£]	0.049	0.245	0.108	0.145	0.000	.	-1.407	0.060- 0.993
HV	Hypertension[£]	0.360	0.521	0.024	0.032	0.000	.	-0.652	0.182
HV	Dyslipidemia[£]	0.089	0.289	0.082	0.109	0.000	.	-1.253	0.067- 1.212

Table B.2 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Health Value, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HV	Insulin levels	0.044	0.930	0.164	0.218	9.260	0.234	-0.073	0.866- 0.998
HV	Insulin levels age	-0.089 0.174	0.915 1.190	0.214	0.285	7.783	0.352	-0.089 0.174	0.846-0.990 0.936- 1.514
HV	Insulin levels sex	0.044 0.241	0.929 2.399	0.196	0.261	9.818	0.199	-0.074 0.875	0.865- 0.998 0.556- 10.357
HV	Insulin levels Sex Age	0.025 0.274 0.174	0.914 2.322 1.187	0.240	0.320	7.192	0.409	-0.090 0.843 0.171	0.844- 0989 0.512- 10.526 0.927- 1.519
HV	Insulin levels Sex Age Group $^{\psi}$ Group1 Group2	0.012 0.390 0.084 0.094 0.052 0.056	0.788 2.179 1.290 22.006 44.046	0.372	0.496	5.952	0.545	-0.238 0.779 0.255 3.091 3.785	0.654- 0.950 0.369- 12.865 0.967- 1.721 0.978- 494.965 0.904- 2147.253
HV	Insulin levels Group $^{\psi}$ Group1 Group2	0.028 0.112 0.043 0.091	0.825 13.139 25.141	0.289	0.386	6.535	0.479	-0.192 2.576 3.225	0.695- 0.979 1.091- 158.230 0.599- 1054.753
HV	HOMA	0.035	0.690	0.185	0.246	4.290	0.746	-0.372	0.789- 0.974
HV	HOMA age	0.021 0.145	0.638 1.201	0.236	0.315	9.462	0.221	-0.450 0.183	0.436- 0.934 0.939- 1.537
HV	HOMA sex	0.037 0.271	0.691 2.289	0.212	0.283	9.776	0.202	-0.369 0.828	0.488- 0.978 0.524- 10.003
HV	HOMA Sex Age	0.021 0.310 0.162	0.638 2.203 1.197	0.258	0.344	7.274	0.401	-0.449 0.790 0.180	0.436- 0.934 0.479- 10.140 0.930- 1.540

Table B.2 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Health Value, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HV	HOMA	0.011	0.299	0.399	0.532	2.696	0.912	-1.209	0.117- 0.758
	Sex	0.492	1.866					0.624	0.315- 11.072
	Age	0.082	1.315					0.274	0.966- 1.790
	Group $^{\Psi}$	0.084							
	Group1	0.045	28.155					3.338	0.966- 1.790
	Group2	0.049	58.717					4.073	1.023- 3370.030
HV	HOMA	0.017	0.366	0.323	0.431	5.757	0.568	-1.004	0.161- 0.836
	Group $^{\Psi}$	0.088							
	Group1	0.036	15.416					2.735	1.200-198.0.34
	Group2	0.064	39.686					3.681	0.808- 1949.569
HV	Systolic Blood Pressure Percentile	0.059	0.963	0.132	0.176	10.513	0.161	-0.038	0.925-1.001
HV	Systolic Blood Pressure Percentile	0.059	0.962	0.133	0.177	8.472	0.293	-0.039	0.925- 1.001
	age	0.909	0.987					-0.013	0.789- 1.235
HV	Systolic Blood Pressure Percentile	0.072	0.965	0.152	0.203	6.591	0.473	-0.036	0.928- 1.003
	sex	0.366	1.948					0.667	0.458- 8.277
HV	Systolic Blood Pressure Percentile	0.072	0.965	0.153	0.204	5.960	0.544	-0.036	0.927- 1.003
	Sex	0.365	1.951					0.668	0.459- 8.293
	Age	0.898	0.985					-0.015	0.785- 1.236
HV	Systolic Blood Pressure Percentile	0.098	0.962	0.187	0.249	2.701	0.911	-0.039	0.918- 1.007
	Sex	0.667	1.412					0.345	0.294- 6.781
	Age	0.919	1.013					0.013	0.786- 1.306
	Group $^{\Psi}$	0.505							
	Group1	0.253	3.653					1.295	0.397- 33.613
	Group2	0.865	1.184					0.169	0.169- 8.310
HV	Systolic Blood Pressure Percentile	0.073	0.960	0.182	0.243	11.825	0.066	-0.041	0.918- 1.004
	Group $^{\Psi}$	0.388							
	Group1	0.188	4.152					1.424	0.498- 34.598
	Group2	0.843	1.202					0.184	0.196- 7.383

Table B.2 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Health Value, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HV	Triglycerides Levels	0.156	0.498	0.066	0.088	6.380	0.496	-0.697	0.190- 1.304
HV	Triglycerides Levels	0.100	0.430	0.097	0.130	7.553	0.374	-0.844	0.157- 1.176
	Age	0.280	1.129					0.121	0.906- 1.407
HV	Triglycerides Levels	0.155	0.481	0.111	0.149	2.343	0.938	-0.732	0.176- 1.318
	sex	0.188	2.549					0.936	0.633- 10.267
HV	Triglycerides Levels	0.104	.420	0.137	0.182	6.775	0.453	-0.867	0.148- 1.195
	Sex	0.211	2.464					0.902	0.599- 10.140
	Age	0.318	1.121					0.114	0.896- 1.403
HV	Triglycerides Levels	0.131	0.395	0.190	0.253	4.957	0.665	-0.930	0.118- 1.318
	Sex	0.564	1.557					0.456	0.335- 7.430
	Age	0.215	1.161					0.150	0.917- 1.471
	Group $^{\psi}$	0.353							
	Group1	0.208	4.047					1.398	0.459- 35.703
	Group2	0.802	0.796					-0.229	0.133- 4.762
HV	Triglycerides Levels	0.203	0.472	0.140	0.186	11.402	0.122	-0.752	0.148- 1.500
	Group $^{\psi}$	0.272							
	Group1	0.167	4.096					1.410	0.556- 30.198
	Group2	0.821	0.821					-0.198	0.149- 4.533
HV	HDL	0.095	8.165	0.087	0.116	15.951	0.026	2.100	0.692- 96.297
HV	HDL	0.073	11.278	0.113	0.151	8.493	0.291	2.423	0.801- 158.697
	age	0.318	1.117					0.111	0.899- 1.389
HV	HDL	0.166	6.037	0.104	0.138	5.062	0.652	1.798	0.473- 77.077
	sex	0.416	1.810					0.593	0.434- 7.552
HV	HDL	0.130	8.238	0.124	0.165	4.555	0.714	2.109	0.538- 126.237
	Sex	0.509	1.642					0.496	0.377- 7.144
	Age	0.376	1.104					0.099	0.887- 1.374

Table B.2 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Health Value, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HV	HDL	0.143	15.006	0.186	0.248	5.086	0.649	2.708	0.400- 563.529
	Sex	0.915	0.912					-0.092	0.166- 5.012
	Age	0.229	1.158					0.146	0.912- 1.470
	Group $^{\Psi}$	0.304							
	Group1	0.163	5.275					1.663	0.509- 54.642
	Group2	0.995	0.994					-0.006	0.139- 7.110
HV	HDL	0.153	9.478	0.150	0.199	15.548	0.030	2.249	0.432- 207.856
	Group $^{\Psi}$	0.318							
	Group1	0.164	4.201					1.435	0.556- 31.737
	Group2	0.945	1.069					0.067	0.161- 7.113
HV	BMI Percentile	0.163	0.985	0.056	0.075	6.263	0.281	-0.015	0.965-1.006
HV	BMI Percentile	0.171	0.986	0.064	0.085	6.159	0.521	-0.015	0.965- 1.006
	Age	0.602	1.056					0.054	0.862- 1.293
HV	BMI Percentile	0.165	0.985	0.101	0.135	4.282	0.639	-0.015	0.965- 1.006
	Sex	0.192	2.507					0.919	0.630- 9.985
HV	BMI Percentile	0.173	0.985	0.106	0.141	3.411	0.845	-0.015	0.965- 1.006
	Sex	0.202	2.467					0.903	0.617- 9.872
	Age	0.657	1.049					0.047	0.851- 1.292
HV	BMI Percentile	0.184	0.979	0.170	0.227	12.348	0.090	-0.021	0.949- 1.010
	Sex	0.574	1.551					0.439	0.335- 7.186
	Age	0.572	1.068					0.066	0.849- 1.343
	Group $^{\Psi}$	0.297							
	Group1	0.149	5.819					1.761	0.533- 63.492
	Group2	0.770	1.431					0.358	0.129- 15.846
HV	BMI Percentile	0.133	0.977	0.153	0.204	3.006	0.808	-0.023	0.948- 1.007
	Group $^{\Psi}$	0.186							
	Group1	0.089	7.248					1.981	0.737- 71.303
	Group2	0.650	1.689					0.524	0.175- 16.301

Table B.2 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Health Value, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HV	Total Fat (%AMDR)	0.632	1.025	0.114	0.152	4.487	0.722	0.025	0.927- 1.134
	Saturated Fat (%AMDR) ‡	0.321	0.977					-0.023	0.934- 1.023
	PUFA (%AMDR) ‡	0.845	0.997					-0.003	0.968- 1.027
	MUFA (%AMDR) ‡	0.325	0.981					-0.020	0.943- 1.020
HV	Saturated Fat (%AMDR) ‡	0.325	0.985	0.108	0.144	7.291	0.399	-0.015	0.957- 1.015
	PUFA (%AMDR) ‡	0.933	1.001					0.001	0.977- 1.026
	MUFA (%AMDR) ‡	0.346	0.987					-0.013	0.962- 1.014
HV	PUFA (%AMDR) ‡	0.732	1.004	0.082	0.110	2.503	0.927	0.004	0.981- 1.028
	MUFA (%AMDR) ‡	0.094	0.981					-0.020	0.958- 1.003
HV	MUFA (%AMDR) ‡	0.100	0.981	0.079	0.106	4.434	0.729	-0.019	0.959- 1.004
HV	MUFA (%AMDR) ‡	0.158	0.982	0.111	0.148	5.066	0.652	-0.018	0.957- 1.007
	Sex	0.598	1.500					0.405	0.332- 6.769
	Age (cut-off: 13y)	0.388	1.895					0.639	0.444- 8.092
HV	PUFA (%AMDR) ‡	0.895	0.999	0.049	0.065	5.797	0.564	-0.001	0.976- 1.021
	Sex	0.184	2.489					0.912	0.648- 9.566
HV	Sex	0.206	2.388	0.056	0.075	0.474	0.789	0.870	0.620- 9.202
	Age (cut-off: 13y)	0.593	1.444					0.368	0.375- 5.566
HV	Protein (%EAR)	0.598	1.002	0.074	0.098	7.601	0.369	0.002	0.995- 1.009
	Carbohydrate (% AMDR)	0.127	1.043					0.042	0.988- 1.100
HV	Protein (%EAR)	0.577	1.002	0.047	0.099	1.816	0.969	0.002	0.995- 1.009
	Carbohydrate (% AMDR)	0.341	1.037					0.037	0.962- 1.119
	Sugar (%recommendations) ¥	0.853	1.002					0.002	0.985- 1.018
HV	Protein (%EAR)	0.634	1.002	0.092	0.123	8.094	0.324	0.002	0.994- 1.009
	Carbohydrate (% AMDR)	0.369	1.035					0.035	0.960- 1.117
	Sugar (%recommendations) ¥	0.994	1.000					0.000	0.983- 1.017
	Sex	0.408	0.538					-0.619	0.124- 2.337

Table B.2 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Health Value, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HV	Protein (%EAR)	0.870	0.999	0.181	0.241	8.271	0.309	-0.001	0.991- 1.008
	Carbohydrate (% AMDR)	0.674	1.017					0.017	0.940- 1.100
	Sugar (%recommendations) ¥	0.901	1.001					0.001	0.984- 1.019
	Fiber (%AI)	0.054	1.042					0.041	0.999- 1.087
HV	Fiber (%AI)	0.023	1.045	0.165	0.220	5.489	0.601	0.044	1.006- 1.086
HV	Fiber (%AI)	0.039	1.042	0.173	0.231	9.110	0.245	0.041	1.002- 1.084
	Sex	0.541	1.583					0.459	0.363- 6.907
HV	Vitamin D (%EAR)	0.043	1.036	0.148	0.197	2.928	0.892	0.035	1.001- 1.071
	Vitamin E (%EAR)	0.192	0.994					-0.006	0.984- 1.003
	Folate (%EAR)	0.652	0.997					-0.003	0.984- 1.010
HV	Vitamin D (%EAR)	0.042	1.036	0.184	0.246	4.582	0.711	0.036	1.001- 1.072
	Vitamin E (%EAR)	0.160	0.993					-0.007	0.983- 1.003
	Folate (%EAR)	0.818	0.998					-0.002	0.984- 1.012
	Sex	0.224	2.566					0.942	0.561- 11.731
HV	Vitamin D (%EAR)	0.064	1.028	0.107	0.142	5.310	0.622	0.028	0.998- 1.059
HV	Energy (%DRI)	0.329	0.985	0.028	0.037	8.084	0.325	-0.015	0.955- 1.016
HV	Energy (%DRI)	0.393	0.987	0.068	0.091	5.382	0.613	-0.013	0.957- 1.017
	sex	0.221	2.338					0.849	0.601- 9.097
HV	Grain (%Recommendations) *	0.214	0.985	0.263	0.351	5.565	0.591	-0.015	0.962- 1.009
	Fruit & vegetable (%Recommendation) *	0.207	1.016					0.016	0.991- 1.041
	Milk (%Recommendations) *	0.131	1.015					0.015	0.996- 1.034
	Meat (%Recommendations) *	0.228	0.993					-0.007	0.981- 1.005
HV	Grain (%Recommendations) *	0.192	0.989	0.049	0.065	11.368	0.123	-0.011	0.972- 1.006
HV	Fruit & vegetable (%Recommendation) *	0.032	1.021	0.147	0.196	4.930	0.668	0.021	1.002- 1.042
HV	Milk (%Recommendations) *	0.336	1.007	0.027	0.035	4.467	0.725	0.007	0.993- 1.021
HV	Meat (%Recommendations) *	0.026	0.989	0.162	0.216	12.503	0.085	-0.011	0.979- 0.999

Table B.2 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Health Value, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HV	Grain (%Recommendations) * Sex	0.345 0.340	0.991 1.992	0.072	0.097	5.898	0.552	-0.009 0.689	0.974- 1.009 0.484- 8.207
HV	Fruit & vegetable (%Recommendation) * Sex	0.038 0.255	1.021 2.315	0.177	0.237	10.036	0.187	0.021 0.840	1.001- 1.041 0.546- 9.819
HV	Milk (%Recommendations) * Sex	0.278 0.159	1.008 2.689	0.081	0.107	9.526	0.217	0.008 0.989	0.994- 1.022 0.678- 10.665
HV	Meat (%Recommendations) * Sex	0.025 0.158	0.988 2.966	0.210	0.279	4.668	0.700	-0.012 1.087	0.977- 0.998 0.656- 13.401
HV	HEI	0.004	1.120	0.277	0.370	2.557	0.923	0.114	1.037- 1.211
HV	HEI Sex	0.007 0.856	1.118 1.164	0.278	0.371	3.221	0.864	0.111 0.152	1.031- 1.212 0.226- 6.003
HV	HEI Sex Age (cut-off= 13y)	0.007 0.880 0.690	1.119 1.135 1.507	0.283	0.378	9.350	0.228	0.112 0.127 0.410	1.031- 1.214 0.219- 5.875 0.313- 7.248
HV	HEI Group $^{\psi}$ Group1 Group2	0.011 0.945 0.978 0.741	1.117 0.970 0.736	0.280	0.373	3.192	0.867	0.111 -0.031 -0.307	1.026- 1.216 0.110- 8.556 0.119- 4.553
HV	Adequacy	0.047	1.131	0.118	0.157	3.400	0.846	0.123	1.001- 1.277
HV	Moderation	0.014	1.177	0.205	0.273	6.935	0.327	0.163	1.033- 1.340
HV	Variety	0.042	1.270	0.124	0.165	11.701	0.020	0.2390	1.009- 1.598

Table B.2 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Health Value, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HV	Adequacy	0.063	1.123	0.146	0.195	8.525	0.289	0.116	0.994- 1.269
	Sex	0.282	2.177					0.778	0.527- 8.992
HV	Moderation	0.025	1.174	0.205	0.274	6.301	0.390	0.160	1.020- 1.350
	Sex	0.920	1.085					0.081	0.222- 5.3060
HV	Variety	0.046	1.274	0.163	0.217	5.592	0.348	0.242	1.004- 1.615
	Sex	0.208	2.518					0.924	0.598- 10.607
HV	Adequacy	0.364	1.076	0.290	0.387	9.188	0.239	0.073	0.919- 1.259
	Moderation	0.027	1.162					0.150	1.017- 1.327
	Variety	0.380	1.140					0.131	0.851- 1.529
HV	Adequacy	0.366	1.076	0.290	0.387	9.226	0.237	0.073	0.918- 1.261
	Moderation	0.044	1.163					0.151	1.004- 1.347
	Variety	0.382	1.140					0.131	0.850- 1.529
	Sex	0.977	0.975					-0.026	0.168- 5.644
HV	Adequacy	0.326	1.088	0.293	0.391	7.090	0.420	0.085	0.919- 1.288
	Moderation	0.027	1.160					0.149	1.017- 1.324
	Variety	0.483	1.117					0.111	0.819- 1.524
	Age (cut-off= 13 y)	0.693	1.409					0.343	0.257- 7.733
HV	MUFA (%AMDR) ‡	0.541	0.992	0.173	0.231	12.417	0.088	-0.008	0.968- 1.017
	Fiber (%AI)	0.069	1.039					0.039	0.997- 1.083
HV	MUFA (%AMDR) ‡	0.650	0.994	0.185	0.247	18.218	0.011	-0.006	0.969- 1.020
	Fiber (%AI)	0.129	1.035					0.034	0.990- 1.081
	Group ψ	0.782							
	Group1	0.556	1.841					0.611	0.242- 14.029
	Group2	0.833	0.830					-0.186	0.147- 4.694
HV	MUFA (%AMDR) ‡	0.661	0.994	0.178	0.237	15.697	0.028	-0.006	0.968- 1.021
	Fiber (%AI)	0.078	1.038					0.038	0.996- 1.083
	Sex	0.666	1.412					0.345	0.296- 6.742
HV	MUFA (%AMDR) ‡	0.452	0.990	0.198	0.264	9.217	0.237	-0.010	0.965- 1.016
	Fiber (%AI)	0.067	1.041					0.040	0.997- 1.087
	Age (cut-off= 13 y)	0.308	2.219					0.797	0.479- 10.275

Abbreviations: AI, Adequate intake; BMI, Body Mass Index; Cal, Calorie; F/V, fruit and vegetables; HEI-C, Healthy Eating Index; HDL: High density Lipoprotein; HOMA, Homeostasis Model Assessment for Insulin Resistance; HV: Health Value; TG, Triglycerides;
AI and EAR values were accessed from: https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/dietary-reference-intakes/tables.html
* Recommended servings for food groups were taken from Alberta Nutrition Guidelines for children and youth (ANGCY) available from https://open.alberta.ca/dataset/1c291796-4eb0-4073-be8e-bce2d331f9ce/resource/3319786c-1df1-43ca-8693-067f733682dc/download/nutrition-guidelines-ab-children-youth.pdf.
ᴪ Group was defined as having NAFLD or PWS or being healthy.
£ Cardio-metabolic dysregulation components according to WHO definition (168).
‡ recommendations for SFA, MUFA and PUFA were from American Heart Association (166).
ɣ Recommendation for sugar were from WHO (167).

Table B.3 Multiple Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Healthy Food Diversity.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HFD-I	Group ψ	0.093		0.159	0.213	0.000	1.000		
	Group1	0.152	5.444					1.695	0.537- 55.203
	Group2	0.234	0.389					-0.944	0.082- 1.840
HFD-I	Group ψ	0.148		0.164	0.219	1.264	0.868		
	Group1	0.209	4.664					1.540	0.421- 51.649
	Group2	0.252	0.401					-0.914	0.084- 1.915
	sex	0.639	1.436					0.362	0.316- 6.515
HFD-I	Group ψ	0.260		0.188	0.251	2.176	0.537		
	Group1	0.121	7.686					2.039	0.584- 101.175
	Group2	0.821	1.386					0.327	0.081- 23.581
	BMI Classification (cut off= 95 p)	0.282	0.236					-1.446	0.017- 3.278
HFD-I	Glycemic Control £	0.286	0.235	0.176	0.235	3.406	0.638	-1.449	0.016- 3.363
	BMI Classification (cut off= 95 p) £	0.793	0.673					-0.396	0.035- 13.011
	Hypertension£	0.641	1.710					0.536	0.180- 16.266
	Dyslipidemia £	0.599	0.571					-0.561	0.071- 4.606
HFD-I	Glycemic Control £	0.240	0.209	0.169	0.226	2.301	0.512	-1.563	0.015- 2.836
	BMI Classification (cut off= 95 p) £	0.778	0.657					-0.421	0.035- 12.183
	Hypertension £	0.814	1.254					0.226	0.191- 8.234
HFD-I	Glycemic Control £	0.105	0.133	0.175	0.235	0.509	0.775	-2.018	0.012- 1.528
	BMI Classification (cut off= 95 p) £	0.901	1.164					0.152	0.105- 12.861
HFD-I	Glycemic Control£	0.013	0.150	0.175	0.234	0.000	.	-1.897	0.034- 0.667
HFD-I	BMI Classification (cut off= 95 p) £	0.056	0.257	0.102	0.136	0.000	.	-1.358	0.064- 1.035
HFD-I	Hypertension£	0.459	0.593	0.016	0.021	0.000	.	-0.522	0.149- 2.365
HFD-I	Dyslipidemia£	0.126	0.333	0.065	0.087	0.000	.	-1.099	0.081- 1.364

Table B.3 Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Healthy Food Diversity, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HFD-I	Insulin levels	0.029	0.923	0.194	0.260	9.048	0.249	-0.081	0.858- 0.992
HFD-I	Insulin levels	0.024	0.917	0.204	0.273	4.721	0.694	-0.086	0.851- 0.989
	age	0.515	1.079					0.076	0.858- 1.358
HFD-I	Insulin levels	0.028	0.922	0.225	0.301	10.512	0.161	-0.081	0.857- 0.991
	sex	0.244	2.451					0.897	0.543- 11.066
HFD-I	Insulin levels	0.025	0.917	0.232	0.311	8.471	0.293	-0.087	0.0850- 0.989
	Sex	0.263	2.380					0.867	0.522- 10.856
	Age	0.574	1.070					0.067	0.846- 1.353
HFD-I	Insulin levels	0.021	0.805	0.366	0.490	2.027	0.958	-0.217	0.670- 0.968
	Sex	0.494	10836					0.608	0.322- 10.457
	Age	0.264	1.171					0.158	0.888- 1.544
	Group $^{\psi}$	0.102							
	Group1	0.039	37.540					3.625	1.206- 1168.523
	Group2	0.098	25.428					3.236	0.550- 1174.971
HFD-I	Insulin levels	0.034	0.830	0.332	0.444	3.732	0.810	-0.186	0.698- 0.986
	Group $^{\psi}$	0.094							
	Group1	0.031	23.499					3.157	1.324- 417.047
	Group2	0.135	16.769					2.820	0.416- 675.391
HFD-I	HOMA	0.021	0.659	0.221	0.295	5.908	0.551	-0.417	0.463- 0.939
HFD-I	HOMA	0.018	0.642	0.231	0.309	4.927	0.669	-0.444	0.445- 0.926
	age	0.493	1.086					0.082	0.858- 1.373
HFD-I	HOMA	0.022	0.662	0.246	0.330	10.252	0.175	-0.413	0.464- 0.943
	sex	0.279	2.321					0.842	0.505- 10.671
HFD-I	HOMA	0.019	0.644	0.254	0.340	6.740	0.456	-0.439	0.446- 0.931
	Sex	0.301	2.249					0.810	0.483- 10.462
	Age	0.544	1.077					0.074	0.848- 1.368

Table B.3 Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Healthy Food Diversity, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HFD-I	HOMA	0.015	0.319	0.401	0.537	3.946	0.786	-1.144	0.127- 0.801
	Sex	0.616	1.575					0.454	0.267- 9.302
	Age	0.248	1.189					0.173	0.886- 1.595
	Group $^{\Psi}$	0.086							
	Group1	0.034	53.474					3.979	1.362- 2098.735
	Group2	0.074	39.416					3.674	0.704- 2206.994
HFD-I	HOMA	0.019	0.361	0.371	0.497	4.296	0.745	-1.019	0.154- 0.846
	Group $^{\Psi}$	0.074							
	Group1	0.026	30.586					3.421	1.512- 618.553
	Group2	0.087	30.822					3.428	0.610- 1557.981
HFD-I	Systolic Blood Pressure Percentile	0.088	0.966	0.107	0.143	10.689	0.153	-0.034	0.929- 1.005
HFD-I	Systolic Blood Pressure Percentile	0.067	0.963	0.128	0.170	2.941	0.890	-0.038	0.925- 1.003
	age	0.369	0.901					-0.104	0.719- 1.131
HFD-I	Systolic Blood Pressure Percentile	0.109	0.969	0.130	0.173	3.631	0.821	-0.032	0.932- 1.007
	sex	0.342	2.004					0.695	0.478- 8.401
HFD-I	Systolic Blood Pressure Percentile	0.079	0.965	0.152	0.203	17.166	0.016	-0.035	0.928- 1.004
	Sex	0.323	2.086					0.735	0.485-8.968
	Age	0.348	0.895					-0.111	0.710- 1.128
HFD-I	Systolic Blood Pressure Percentile	0.131	0.964	0.215	0.287	5.000	0.660	-0.037	0.918- 1.011
	Sex	0.735	1.317					0.275	0.267- 6.505
	Age	0.615	0.936					-0.066	0.724- 1.211
	Group $^{\Psi}$	0.326							
	Group1	0.161	6.385					1.854	0.478- 85.345
	Group2	0.956	0.948					-0.054	0.139- 6.483
HFD-I	Systolic Blood Pressure Percentile	0.140	0.967	0.208	0.278	7.362	0.289	-0.034	0.924- 1.011
	Group $^{\Psi}$	0.203							
	Group1	0.120	7.157					1.968	0.599- 85.525
	Group2	0.793	0.787					-0.239	0.132- 4.686

Table B.3 Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Healthy Food Diversity, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HFD-I	Triglycerides Levels	0.108	0.449	0.086	0.115	7.744	0.356	-0.800	0.169- 1.193
HFD-I	Triglycerides Levels	0.102	0.432	0.088	0.118	4.770	0.688	-0.840	0.158- 1.181
	Age	0.746	1.036					0.035	0.836- 1.283
HFD-I	Triglycerides Levels	0.106	0.427	0.132	0.176	3.560	0.829	-0.851	0.152- 1.198
	sex	0.181	2.647					0.973	0.635- 11.033
HFD-I	Triglycerides Levels	0.104	0.416	0.133	0.178	4.902	0.672	-0.877	0.145- 1.197
	Sex	0.188	2.616					0.961	0.625- 10.949
	Age	0.829	1.024					0.024	0.823- 1.275
HFD-I	Triglycerides Levels	0.137	0.373	0.227	0.304	7.848	0.346	-0.987	0.102- 1.367
	Sex	0.671	1.413					0.345	0.287- 6.950
	Age	0.555	1.074					0.071	0.848- 1.360
	Group $^{\psi}$	0.200							
	Group1	0.123	7.765					2.050	0.575- 104.853
	Group2	0.673	0.685					-0.379	0.118- 3.985
HFD-I	Triglycerides Levels	0.165	0.407	0.214	0.287	12.187	0.095	-0.899	0.114- 1.449
	Group $^{\psi}$	0.140							
	Group1	0.095	8.279					2.114	0.692- 99.068
	Group2	0.660	0.679					-0.387	0.121- 3.802
HFD-I	HDL	0.065	13.066	0.113	0.151	17.221	0.016	2.570	0.851- 200.575
HFD-I	HDL	0.066	14.110	0.115	0.153	16.301	0.023	2.647	0.841- 236.852
	age	0.806	1.027					0.027	0.829- 1.273
HFD-I	HDL	0.113	9.671	0.126	0.169	10.425	0.166	2.269	0.586- 159.575
	sex	0.468	1.716					0.540	0.399- 7.370
HFD-I	HDL	0.118	10.084	0.126	0.169	10.837	0.146	2.311	0.555- 183.217
	Sex	0.488	1.690					0.525	0.384- 7.429
	Age	0.906	1.013					0.013	0.816- 1.259

Table B.3 Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Healthy Food Diversity, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HFD-I	HDL	0.121	22.047	0.231	0.309	12.883	0.075	3.093	0.441- 1102.428
	Sex	0.754	0.749					-0.288	0.123- 4.555
	Age	0.535	1.081					0.078	0.845- 1.382
	Group $^{\Psi}$	0.176							
	Group1	0.091	10.627					2.363	0.687- 164.399
	Group2	0.935	0.922					-0.081	0.132- 6.452
HFD-I	HDL	0.122	13.843	0.222	0.297	14.595	0.042	2.628	0.497- 385.353
	Group $^{\Psi}$	0.179							
	Group1	0.092	8.182					2.102	0.709- 94.414
	Group2	0.923	0.911					-0.094	0.135- 6.140
HFD-I	BMI Percentile	0.271	0.988	0.035	0.047	4.076	0.538	-0.012	0.968- 1.009
HFD-I	BMI Percentile	0.265	0.988	0.037	0.050	8.327	0.305	-0.012	0.968- 1.009
	Age	0.786	0.973					-0.028	0.795- 1.189
HFD-I	BMI Percentile	0.280	0.989	0.081	0.108	3.737	0.712	-0.012	0.968- 1.009
	Sex	0.191	2.501					0.917	0.633- 9.883
HFD-I	BMI Percentile	0.270	0.988	0.085	0.113	8.049	0.328	-0.012	0.968- 1.009
	Sex	0.183	2.563					0.941	0.641- 10.245
	Age	0.702	0.960					-0.041	0.780- 1.183
HFD-I	BMI Percentile	0.378	0.987	0.183	0.245	8.213	0.314	-0.013	0.958- 1.017
	Sex	0.665	1.406					0.341	0.301- 6.568
	Age	0.975	0.996					-0.004	0.790- 1.256
	Group $^{\Psi}$	0.203							
	Group1	0.132	7.715					2.043	0.542- 109.788
	Group2	0.846	0.800					-0.224	0.083- 7.685
HFD-I	BMI Percentile	0.358	0.987	0.179	0.240	2.013	0.847	-0.014	0.958- 1.015
	Group $^{\Psi}$	0.127							
	Group1	0.095	8.897					2.186	0.686- 115.423
	Group2	0.815	0.775					-0.255	0.092- 6.564

Table B.3 Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Healthy Food Diversity, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HFD-I	Total Fat (%AMDR)	0.934	1.004	0.118	0.158	10.025	0.187	0.004	0.908- 1.110
	Saturated Fat (%AMDR) ‡	0.651	0.990					-0.010	0.947- 1.035
	PUFA (%AMDR) ‡	0.750	1.005					0.005	0.974- 1.037
	MUFA (%AMDR) ‡	0.313	0.980					-0.020	0.943- 1.019
HFD-I	Saturated Fat (%AMDR) ‡	0.546	0.991	0.118	0.157	6.564	0.476	-0.009	0.963- 1.020
	PUFA (%AMDR) ‡	0.667	1.006					0.006	0.980- 1.033
	MUFA (%AMDR) ‡	0.176	0.981					-0.019	0.955- 1.008
HFD-I	PUFA (%AMDR) ‡	0.562	1.008	0.108	0.145	3.613	0.823	0.008	0.982- 1.034
	MUFA (%AMDR) ‡	0.058	0.977					-0.023	0.954- 1.001
HFD-I	MUFA (%AMDR) ‡	0.068	0.979	0.100	0.133	7.278	0.401	-0.022	0.956- 1.002
HFD-I	MUFA (%AMDR) ‡	0.142	0.981	0.110	0.147	6.718	0.459	-0.019	0.956- 1.006
	Sex	0.576	1.545					0.435	0.336- 7.114
	Age (cut-off: 13y)	0.838	1.162					0.150	0.275- 4.922
HFD-I	PUFA (%AMDR) ‡	0.958	1.001	0.049	0.066	10.037	0.187	0.001	0.978- 1.024
	Sex	0.187	2.493					0.913	0.643- 9.665
HFD-I	Sex	0.181	2.531	0.050	0.067	0.371	0.831	0.929	0.649- 9.878
	Age (cut-off: 13y)	0.878	0.899					-0.107	0.231- 3.501
HFD-I	Protein (%EAR)	0.459	1.002	0.083	0.111	5.004	0.659	0.002	0.995- 1.009
	Carbohydrate (% AMDR)	0.113	1.045					0.044	0.990- 1.103
HFD-I	Protein (%EAR)	0.538	1.002	0.083	0.111	6.881	0.441	0.002	0.995- 1.010
	Carbohydrate (% AMDR)	0.238	1.048					0.047	0.969- 1.113
	Sugar (%recommendations) ¥	0.914	0.999					-0.001	0.983- 1.016
HFD-I	Protein (%EAR)	0.594	1.002	0.102	0.137	3.900	0.791	0.002	0.995- 1.009
	Carbohydrate (% AMDR)	0.265	1.045					0.044	0.967- 1.130
	Sugar (%recommendations) ¥	0.771	0.997					-0.003	0.981- 1.015
	Sex	0.385	0.516					-0.662	0.116- 2.296

Table B.3 Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Healthy Food Diversity, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HFD-I	Protein (%EAR)	0.973	1.000	0.149	0.199	9.585	0.213	0.000	0.992- 1.008
	Carbohydrate (% AMDR)	0.445	1.032					0.031	0.952- 1.118
	Sugar (%recommendations) ¥	0.880	0.999					-0.001	0.982- 1.016
	Fiber (%AI)	0.121	1.032					0.032	0.992- 1.075
HFD-I	Fiber (%AI)	0.042	1.038	0.126	0.169	6.484	0.484	0.037	1.001- 1.076
HFD-I	Fiber (%AI)	0.075	1.035	0.139	0.186	8.092	0.325	0.034	0.997- 1.074
	Sex	0.465	1.719					0.542	0.402- 7.354
HFD-I	Vitamin D (%EAR)	0.046	1.036	0.149	0.200	2.759	0.906	0.036	1.001- 1.074
	Vitamin E (%EAR)	0.135	0.992					-0.008	0.983- 1.002
	Folate (%EAR)	0.848	0.999					-0.001	0.986- 1.011
HFD-I	Vitamin D (%EAR)	0.046	1.037	0.188	0.252	5.174	0.639	0.036	1001- 1.075
	Vitamin E (%EAR)	0.113	0.992					-0.009	0.981- 1.002
	Folate (%EAR)	0.950	1.000					0.000	0.987- 1.014
	Sex	0.209	2.700					0.993	0.573- 12.735
HFD-I	Vitamin D (%EAR)	0.074	1.027	0.100	0.133	5.615	0.585	0.027	0.997- 1.058
HFD-I	Energy (%DRI)	0.403	0.987	0.020	0.027	5.710	0.574	-0.013	0.958- 1.017
HFD-I	Energy (%DRI)	0.475	0.989	0.063	0.084	5.018	0.658	-0.011	0.960- 1.019
	sex	0.210	2.392					0.872	0.611- 9.359
HFD-I	Grain (%Recommendations)	0.235	0.986	0.237	0.318	7.642	0.365	-0.014	0.963- 1.009
	Fruit & vegetable (%Recommendation)	0.365	1.011					0.011	0.987- 1.035
	Milk (%Recommendations)	0.100	1.016					0.016	0.997- 1.036
	Meat (%Recommendations)	0.213	0.993					-0.007	0.981- 1.004
HFD-I	Grain (%Recommendations)	0.234	0.990	0.040	0.054	11.541	0.117	-0.010	0.973- 1.007
HFD-I	Fruit & vegetable (%Recommendation)	0.074	1.017	0.098	.131	2.231	0.946	0.017	0.998- 1.035
HFD-I	Milk (%Recommendations)	0.225	1.009	0.044	0.058	3.068	0.879	0.009	0.994- 1.024
HFD-I	Meat (%Recommendations)	0.032	0.990	0.145	0.194	10.664	0.154	-0.010	0.980- 0.999

Table B.3 Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Healthy Food Diversity, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HFD-I	Grain (%Recommendations) Sex	0.418 0.317	0.993 2.071	0.067	0.089	7.356	0.393	-0.007 0.728	0.975- 1.010 0.497- 8.629
HFD-I	Fruit & vegetable (%Recommendation) Sex	0.089 0.242	1.016 2.326	0.132	0.177	8.437	0.296	0.016 0.844	0.998- 1.035 0.565- 9.569
HFD-I	Milk (%Recommendations) Sex	0.184 0.152	1.010 2.781	0.099	0.132	6.862	0.443	0.010 1.023	0.995- 1.025 0.686- 11.282
HFD-I	Meat (%Recommendations) Sex	0.031 0.164	0.989 2.887	0.192	0.256	4.222	0.754	-0.011 1.060	0.979- 0.999 0.647- 12.876
HFD-I	HEI	0.010	1.094	0.205	0.274	5.483	0.601	0.090	1.021- 1.172
HFD-I	HEI Sex	0.018 0.646	1.090 1.435	0.210	0.281	5.699	0.575	0.086 0.361	1.015- 1.170 0.308- 6.685
HFD-I	HEI Sex Age (cut-off= 13y)	0.018 0.633 0.810	1.090 1.458 0.832	0.211	0.282	5.678	0.578	0.086 0.377 -0.184	1.015- 1.170 0.310- 6.850 0.186- 3.723
HFD-I	HEI Group $^{\Psi}$ Group1 Group2	0.067 0.953 -0.697	1.073 2.592 0.498	0.242	0.324	13.125	0.069	0.070 0.953 -0.697	0.995- 1.157 0.218- 30.791 0.093- 2.666
HFD-I	Adequacy	0.089	1.106	0.084	0.113	7.780	0.352	0.100	0.985- 1.241
HFD-I	Moderation	0.023	1.154	0.171	0.228	10.393	0.109	0.143	1.020- 1.305
HFD-I	Variety	0.132	1.177	0.065	0.087	7.997	0.092	0.163	0.952- 1.456

Table B.3 Logistic Regression Models for Predicting the Likelihood of Having Above/ Below Median Scores for Healthy Food Diversity, Continued.

Dependent Variable	Independent Variable(s)	p- value for variable(s)	Exp (B)	Cox & Snell r Square	Nagelkerke r Square	Chi-Square	Model P-value	B	CI
HFD-I	Adequacy	0.117	1.098	0.116	0.156	12.956	0.072	0.094	0.977- 1.234
	Sex	0.260	2.240					0.806	0.550- 9.124
HFD-I	Moderation	0.042	1.146	0.172	0.231	9.781	0.134	0.136	1.005- 1.307
	Sex	0.781	1.246					0.220	0.265- 5.865
HFD-I	Variety	0.148	1.175	0.106	0.142	5.825	0.213	0.161	0.945- 1.461
	Sex	0.207	2.455					0.898	0.609- 9.904
HFD-I	Adequacy	0.354	1.073	0.221	0.297	6.421	0.492	0.070	0.925- 1.244
	Moderation	0.037	1.142					0.133	1.008- 1.293
	Variety	0.692	1.057					0.056	0.803- 1.392
HFD-I	Adequacy	0.362	1.072	0.222	0.298	8.172	0.318	0.069	0.924- 1.243
	Moderation	0.061	1.136					0.127	0.994- 1.298
	Variety	0.685	1.059					0.057	0.804- 1.395
	Sex	0.836	1.187					0.172	0.234- 6.024
HFD-I	Adequacy	0.439	1.064	0.223	0.299	6.076	0.531	0.062	0.909- 1.246
	Moderation	0.038	1.145					0.135	1.008- 1.300
	Variety	0.639	1.073					0.071	0.799- 1.441
	Age (cut-off= 13 y)	0.774	0.786					-0.241	0.151- 4.080
HFD-I	MUFA (%AMDR) ‡	0.306	0.987	0.152	0.204	7.515	0.377	-0.013	0.962- 1.012
	Fiber (%AI)	0.161	1.029					0.028	0.989- 1.070
HFD-I	MUFA (%AMDR) ‡	0.453	0.990	0.206	0.275	5.639	0.582	-0.010	0.965- 1.016
	Fiber (%AI)	0.429	1.017					0.017	0.975- 1.062
	Group ψ	0.355							
	Group1	0.300	3.581					1.276	0.321- 39.898
	Group2	0.456	0.522					-0.651	0.094- 2.885
HFD-I	MUFA (%AMDR) ‡	0.401	0.989	0.156	0.209	11.379	0.123	-0.012	0.962- 1.015
	Fiber (%AI)	0.180	1.028					0.027	0.987- 1.070
	Sex	0.684	1.382					0.323	0.292- 6.549
HFD-I	MUFA (%AMDR) ‡	0.290	0.986	0.155	0.207	8.582	0.284	-0.014	0.961- 1.012
	Fiber (%AI)	0.161	1.029					0.028	0.989- 1.071
	Age (cut-off= 13 y)	0.741	1.281					0.247	0.296- 5.539

Abbreviations: AI, Adequate intake; BMI, Body Mass Index; Cal, Calorie; F/V, fruit and vegetables; HEI-C, Healthy Eating Index; HDL: High density Lipoprotein; HOMA, Homeostasis Model Assessment for Insulin Resistance; HFD-I: Healthy Food Diversity Index, HV: Health Value; TG, Triglycerides;
AI and EAR values were accessed from: https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/dietary-reference-intakes/tables.html

* Recommended servings for food groups were taken from Alberta Nutrition Guidelines for children and youth (ANGCY) available from https://open.alberta.ca/dataset/1c291796-4eb0-4073-be8e-bce2d331f9ce/resource/3319786c-1df1-43ca-8693-067f733682dc/download/nutrition-guidelines-ab-children-youth.pdf.

ᴪ Group was defined as having NAFLD or PWS or being healthy.

£ Cardio-metabolic dysregulation components according to WHO definition (168).

ǂ recommendations for SFA, MUFA and PUFA were from American Heart Association (166).

ɣ Recommendation for sugar were from WHO (167).

Table B.4 Post- hoc Power Analysis for CMD and CMD Markers Association with Berry Index, Health Value and Healthy Food Diversity Index Scores

Variable*	Power		
	BI	HV	HFD-I
CMD vs No CMD	30.0	46.3	48.1
Normal vs Abnormal Insulin Status	77.0	85.2	89.5
Obese vs Non- Obese	80.5	61.0	66.6
Elevated vs Normal Blood pressure	8.1	17.6	14.4
Normal vs Abnormal Lipid Profile	2.8	11.1	12.1

Abbreviation: BI, Berry Index; CMD, Cardio-metabolic Dysregulation; HFD-I, Healthy Food Diversity Index; HV, Health Value. * CMD and cut-off for CMD markers were defined by WHO Criteria (168)

Table B.5 Post- hoc Power Analysis for Nutrient Intake Association with Berry Index, Health Value and Healthy Food Diversity Index Scores

Variable	Power		
	Below/above median BI Scores	Below/above median HV Scores	Below/above median HFD Scores
Fat (g)	9.9	30.9	41.5
Saturated Fat (g)	3.0	28.9	34.5
PUFA (g)	13.4	39.4	44.1
MUFA (g)	38.0	44.1	54.0
Carbohydrate (g)	9.6	5.8	14.4
Sugar (g)	6.2	3.6	7.0
Protein (g)	3.1	7.0	11.1
Fiber (g)	83.2	58.4	4.4
Vitamin D (IU)	18.7	52.2	51.5
Vitamin E (mg)	60.0	5.3	9.0
Folate DFE (microg)	5.0	4.7	8.1
Energy (KCal)	2.9	19.8	29.7

Abbreviation: BI, Berry Index; CMD, Cardio-metabolic Dysregulation; HFD-I, Healthy Food Diversity Index; HV, Health Value.

Table B.6 Post- hoc Power Analysis for Total Healthy Eating Index- Canada and Its Sub-components with Berry Index, Health Value and Healthy Food Diversity Index Scores

Variable	Power		
	Below/above median BI Scores	Below/above median HV Scores	Below/above median HFD Scores
HEI-C	66.9	96.2	85.3
Adequacy	88.6	57.5	42.2
Moderation	13.5	84.3	75.9
Variety	15.4	60.3	34.3

Abbreviation: BI, Berry Index; HEI, Healthy Eating Index (106); HFD-I, Healthy Food Diversity Index; HV, Health Value.

Table B.7 Effect Size Analysis for Significant Association of CMD, CMD Markers and Having NAFLD or PWS with Berry Index, Health Value and Healthy Food Diversity Index Scores

Variable*	Effect Size (Cohen's d)		
	BI	HV	HFD-I
CMD vs No CMD	ND	ND	0.7
Normal vs Abnormal Insulin Status	1.0	1.1	1.1
Obese vs Non- Obese	0.9	0.8	0.8
Elevated vs Normal Blood pressure	ND	ND	ND
Normal vs Abnormal Lipid Profile	ND	ND	ND
PWS vs NAFLD	ND	1.8	1.9
Control vs NAFLD	ND	ND	0.8
Control vs PWS	ND	ND	ND

Abbreviation: BI, Berry Index; CMD, Cardio-metabolic Dysregulation; HFD-I, Healthy Food Diversity Index; HV, Health Value; NAFLD, non-alcoholic fatty liver disease; ND, Non-defined; PWS, Prader-Willi syndrome. * CMD and cut-off for CMD markers were defined by WHO Criteria (168)

Table B.8 Effect Size Analysis for Nutrient Intake Association with Berry Index, Health Value and Healthy Food Diversity Index Scores

Nutrients*	Effect Size (Cohen's d)		
	Below/above median BI Scores	Below/above median HV Scores	Below/above median HFD Scores
Fat	ND	ND	ND
Saturated Fat	ND	ND	ND
PUFA	ND	ND	ND
MUFA	1.0	ND	ND
Carbohydrate	ND	ND	ND
Sugar	ND	ND	ND
Protein	0.6	ND	ND
Fiber	1.0	0.9	0.9
Vitamin D	ND	0.8	0.9
Vitamin E	0.7	ND	ND
Folate DFE	ND	ND	ND
Energy	ND	ND	ND

Abbreviation: BI, Berry Index; CMD, Cardio-metabolic Dysregulation; HFD-I, Healthy Food Diversity Index; HV, Health Value; ND, Non-defined (no significant association was observed). * Nutrients are shown as % recommendations per 1000 Kcal(164-167, 184).

Table B.9 Effect Size Analysis for Food Groups Intake Association with Berry Index, Health Value and Healthy Food Diversity Index Scores

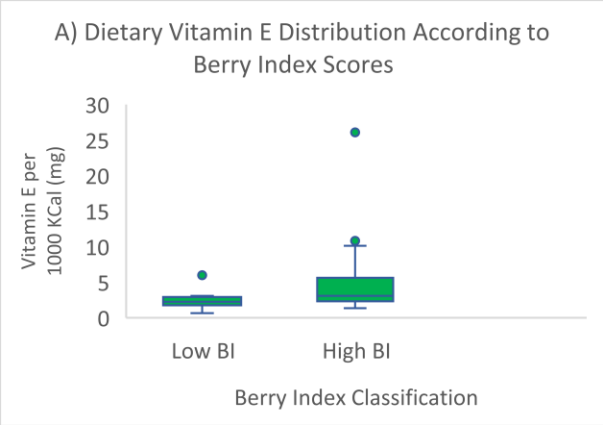
Food Groups		Effect Size (Cohen's d)		
		Below/above median BI Scores	Below/above median HV Scores	Below/above median HFD Scores
Fruits and Vegetables	% Recommendations*	ND	0.8	ND
	Servings	ND	0.8	ND
Grains	% Recommendations*	ND	ND	ND
	Servings	ND	ND	ND
Milk and Alternatives	% Recommendations*	ND	0.7	ND
	Servings	ND	ND	ND
Meat and Alternatives	% Recommendations*	ND	0.9	0.8
	Servings	ND	ND	ND

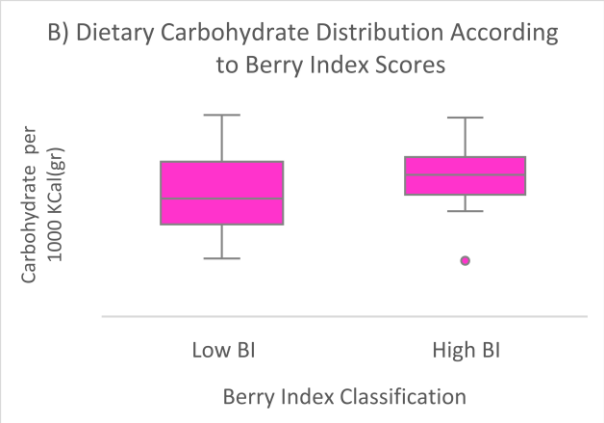
Abbreviation: BI, Berry Index; CMD, Cardio-metabolic Dysregulation; HFD-I, Healthy Food Diversity Index; HV, Health Value; ND, Non-defined (No significant association was observed). *Recommendations are based on Alberta Nutrition Guidelines for Children and Youth (162).

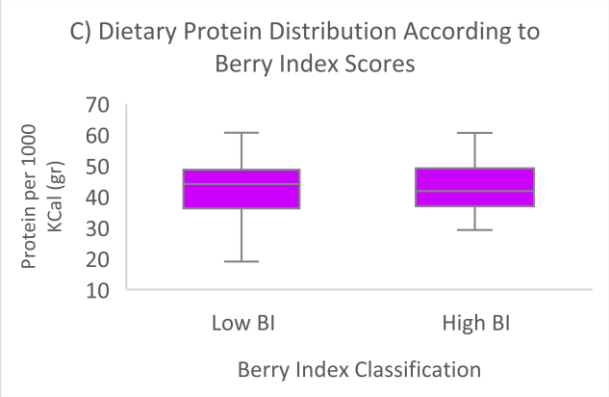
Table B.10 Effect Size Analysis for Total Healthy Eating Index-Canada and Its Sub-components with Berry Index, Health Value and Healthy Food Diversity Index Scores

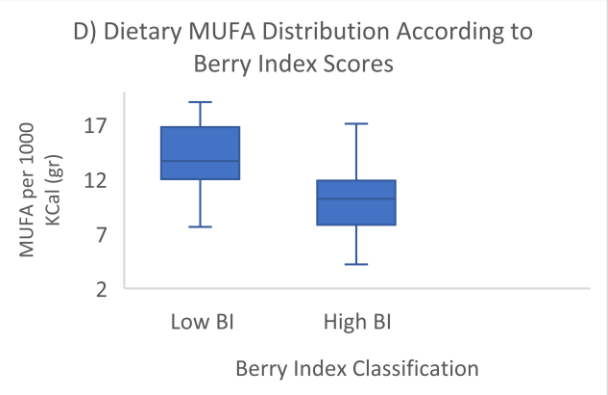
Variable	Effect Size (Cohen's d)		
	Below/above median BI Scores	Below/above median HV Scores	Below/above median HFD Scores
HEI-C	0.8	1.2	1.0
Adequacy	1.1	ND	ND
Moderation	ND	ND	0.8
Variety	ND	0.6	ND

Abbreviation: BI, Berry Index; HEI, Healthy Eating Index (106); HFD-I, Healthy Food Diversity Index; HV, Health Value; ND, Non-defined (No significant association was observed) .









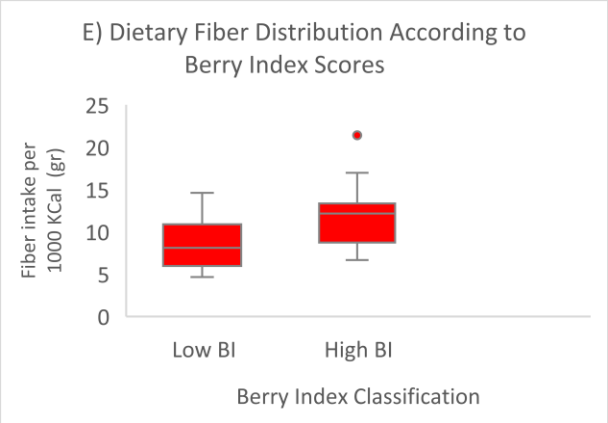
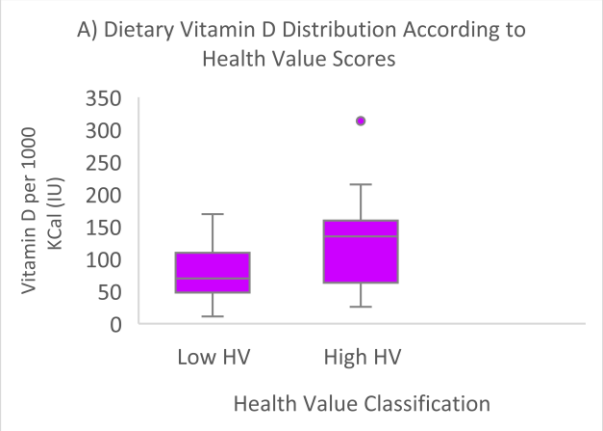
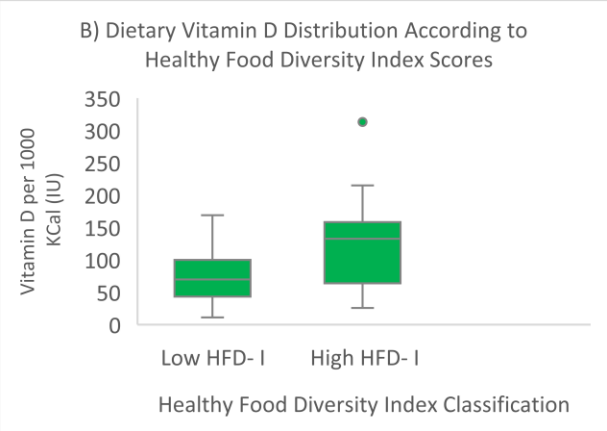
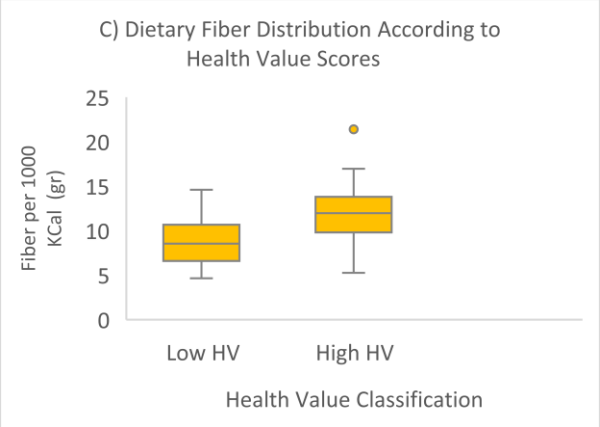
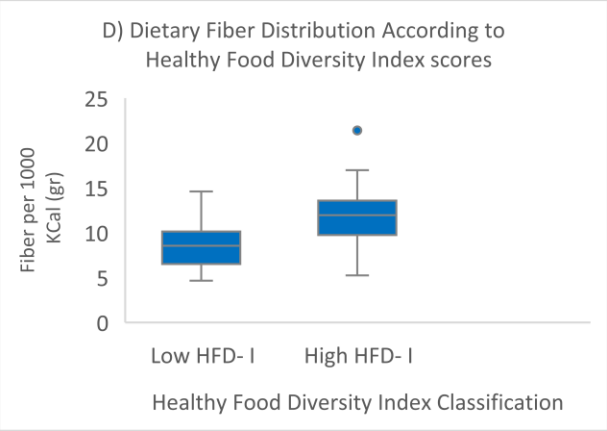


Figure B.1 Distribution of Intakes from Nutrients According to Berry Index Scores. Distribution of dietary 1A) vitamin E (p= 0.022), 1B) carbohydrate (p= 0.018), 1C) protein (p= 0.045), 1D) MUFA (p= 0.002) and 1E) Fiber (p= 0.01) intakes according to BI scores. Classification of participants into lower BI scores (n= 14) was based on the median of scores. Nutrients were compared between the categories as amount in 1000 Kcals. Abbreviations: BI, Berry Index. gr, Grams. MUFA, Monounsaturated Fatty Acid. For comparing vitamin E values between groups, Man- Whitney and for other comparisons, Independent Sample t-test was used.









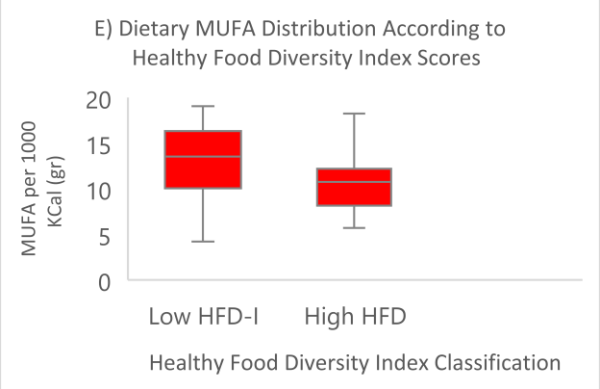


Figure B.2 Distribution of Intakes from Nutrients According to Health Value and Healthy Food Diversity Index Scores. Distribution of dietary vitamin D intake according to HV (2A, p= 0.019) and HFD-I (2B, p= 0.017) scores, distribution of dietary fiber intake according to HV (2C, p= 0.007) and HFD-I (2D, p= 0.009) scores, distribution of dietary MUFA intake according to HFD-I score (2E, p= 0.049). Classification of participants into lower and higher HV or HFD-I scores was based on the median of scores. Nutrients were compared between the categories as amount in 1000 Kcals. Abbreviations: BI, Berry Index; gr, Grams; HFD-I, Healthy Food Diversity; HV, Health Value; MUFA, Mono Unsaturated Fatty Acid. Data were analysed using Independent Sample t-test.

B.1 Association of Dietary Diversity and Dietary Intake with BI, HV and HFD-I

Relationship Between Absolute Nutrient Intake, Dietary Diversity and Health Value

The absolute intake of fiber (g) and vitamin E (mg) were significantly higher (p= 0.005 and p= 0.014, respectively) and MUFA significantly (g) (p= 0.044) lower in participants with higher than median BI scores. A significant (p= 0.015) sex- BI interaction was observed for vitamin D (IU)intake. Absolute fiber intake (g) was significantly (p= 0.037) higher in participants with higher than median HV scores. A non-significant trend (p= 0.052) was observed for absolute vitamin D intake (IU) across HV groups. Absolute MUFA intake (g) was significantly (p= 0.035) lower in participants with higher than median HFD-I scores. No other difference in absolute nutrient intake was observed between participants with BI, HV and HFD-I scores above and below median.

Nutrient Intake per 1000 KCal, Dietary Diversity and Health Value

The differences in intakes of carbohydrate, protein, fiber, MUFA, vitamins E and D per 1000 KCal between participants with lower and higher than median scores for BI, HV and HFD-I are shown in figures B.1-B.2. A significant sex-BI interaction was observed for intakes of carbohydrate (p= 0.031) and protein (p= 0.01) per 1000 Kcal.

Nutrient Intake as DRI Coverage, Dietary Diversity and Health Value

Fiber (%AI) (164) and vitamin E (%EAR) (165) were significantly (p= 0.001 and p= 0.004, respectively) higher and MUFA (% AHA recommendations (166), see Methods section) significantly (p= 0.002) lower in participants with higher than median BI against those with lower than median BI scores. A significant (p= 0.015) interaction between sex with BI was observed for vitamin D intake. Those with higher than median HV and HFD-I scores had higher percentage of AI coverage for fiber (p= 0.013 and p= 0.033, respectively). A non-significant trend (p= 0.052) was

observed for EAR coverage for vitamin D between HV classes and for MUFA (% AHA recommendations) between HFD-I groups.

BI, HV and HFD-I scores were significantly lower in participants who met the recommendations (15% of energy intake) for MUFA ($p= 0.035$, $p= 0.014$ and $p= 0.009$) and in children who did not met the recommendations for protein intake ($p< 0.001$). HV and HFD-I scores were significantly lower in participants who exceeded the mean recommendation amount (30% of energy intake) for total fat intake ($p= 0.005$ and $p= 0.004$, respectively). No significant difference was observed for BI, HV and HFD-I scores between participants who met the recommendations for other nutrients versus who did not.

Logistic Regression was performed to ascertain the effect of different variables on likelihood of having lower or higher than median BI, HV and HFD-I Scores (Tables B.2- B.4 in Appendix B). Studied nutrients (%EAR/ AI/ AHA or WHO recommendations) were put into models (in combination with each other and with sex, age and group or individually) to predict the likelihood of having a higher than median BI scores (logistic regression). MUFA (% AHA recommendations) and fiber (% AI) were significantly predictors of having a higher than median BI scores when they were the only independent variable in the model ($p= 0.008$ and $p= 0.006$, respectively). However, the overall model was not significant for these two nutrients and for other nutrients studied (Table B.1 in Appendix B). Fiber (% AI) was associated with the likelihood of having a higher than median HV scores when it was the only independent variable in the model ($p= 0.023$) or in combination with sex ($p= 0.039$) (Table B.2 in Appendix B). Vitamin D (% EAR) was also associated with the likelihood of having a higher than median HV score in combination with folate and vitamin E (% EAR) ($p= 0.043$) and folate, vitamin E (% EAR) and sex ($p= 0.042$). However,

the overall model p- value was not significant for any models consisting of vitamin D or fiber. The overall model p- value was significant for two models: MUFA, fiber and group (p= 0.011) and MUFA, fiber and sex (p= 0.028). However, none of the variables in these two models were individually associated with the likelihood of having higher than median HV scores. No other significant association was found for other nutrients regarding HV and BI. Fiber intake (%AI) was significantly associated with the likelihood of having a higher than median HFD-I scores (p= 0.042) when it was the only independent variable in the model but the p- value for overall model was not significant. Such significant association was not seen when other variables such as sex, sugar and macronutrients were added to models. The observed pattern for predicting HFD-I scores based on vitamin D status was similar to what found for HV scores (Table B.3 in Appendix B).