Title
Diet and Exercise in Pediatric Liver Transplant Recipients

Permalink
https://escholarship.org/uc/item/9dr9600g

Journal
Journal of Pediatric Gastroenterology and Nutrition, 68(1)

ISSN
0277-2116

Authors
Chambers, Julia H
Zerofsky, Melissa
Lustig, Robert H
et al.

Publication Date
2019

DOI
10.1097/mpg.0000000000002150

Peer reviewed

Diet and exercise in pediatric liver transplant recipients: behaviors and association with metabolic syndrome

Julia H. Chambers, BS[1], **Melissa Zerofsky, PhD**[2], **Robert H. Lustig, MD MSL**[2], **Philip Rosenthal, MD**[2,3], **Emily R. Perito, MD MAS**[2,4]

[1]School of Medicine, University of California, San Francisco, San Francisco, CA

[2]Department of Pediatrics, UCSF Benioff Children's Hospital, University of California, San Francisco, San Francisco, CA

[3]Department of Surgery, UCSF Benioff Children's Hospital, University of California, San Francisco, San Francisco, CA

[4]Department of Epidemiology and Biostatistics, UCSF Benioff Children's Hospital, University of California, San Francisco, San Francisco, CA

Abstract

Objective: To analyze the impact of physical activity and eating behaviors on precursors of cardiovascular disease—including overweight/obesity, hypertension, low HDL, and impaired glucose tolerance—in pediatric liver transplant (LT) recipients and matched controls.

Method: Cross-sectional study of pediatric LT recipients 8–30 years, matched to controls from NHANES. Dietary intake assessed with 24-hour recall. Physical activity assessed by standardized questionnaires. LT recipients 12 years completed a confidential survey on alcohol consumption.

Results: LT recipients (n=90) were 0.9–24.7 years post-transplant. LT recipients and controls were equally likely to consume excess carbohydrates (32% vs 34%) and sugar, per age and gender-specific recommended dietary intake (RDA) guidelines. LT recipients spent more hours sedentary or on the computer daily and fewer days each week physically active for >60 minutes than controls. More overweight/obese LT recipients spent 3+ hours at the computer than non-overweight LT recipients (49% vs 27%; p=0.02). Normal weight LT recipients spent more days doing vigorous activity each week (median 5 days, IQR 2–6) than did the overweight/obese LT recipients (median 3 days, IQR 2–4; p=0.01). Among LT recipients, neither dietary intake nor physical activity were consistently associated with measures of hypertension, glucose intolerance, or dyslipidemia. Among LT adolescents and young adults (n=38), 36% reported ever consuming alcohol; 38% of these reported significant alcohol consumption by frequency or quantity.

Address for correspondence: Emily R. Perito, MD MAS, 550 16th Street, 5th Floor Box 0136, SF, CA 94143, Ph: 415 467 5892, Fax: 415 476 1343, emily.perito@ucsf.edu.

Julia H. Chambers BS[1] – Data analysis and interpretation, drafting manuscript, final approval for publishing

Melissa Zerofsky, PhD[2] – Data acquisition, Data analysis and interpretation, drafting manuscript, final approval for publishing

Robert H. Lustig, MD, MSL[2] – Project conception and design, data interpretation, manuscript revision, final approval for publishing

Philip Rosenthal, MD[2,3] – Project conception and design, data interpretation, manuscript revision, final approval for publishing

Emily R. Perito, MD MAS[2,4] – Project conception and design, data analysis and interpretation, manuscript drafting and revision, final approval for publishing

Conclusions: Additional counseling during routine post-LT care on the importance of physical activity and healthy diet may be useful. However, it is unlikely that these factors alone explain the increased prevalence of metabolic syndrome components in pediatric LT recipients.

Keywords

obesity; hypertension; glucose intolerance; long-term outcomes; cardiovascular risk; alcohol use

INTRODUCTION

Since ten-year survival after pediatric liver transplant (LT) now surpasses 80%, attention to long-term outcomes and the factors that influence them is key to optimal care (1). In adult LT recipients, cardiovascular disease is a leading cause of morbidity and mortality (2). In these adults, post-transplant metabolic syndrome (PTMS) is a significant risk factor for cardiovascular events (2,3). In pediatric LT recipients, we have recently shown that the components of PTMS—including overweight/obesity, hypertension, low HDL, and impaired glucose metabolism—are highly prevalent (4,5,6). This raises concern for accelerated cardiovascular disease and eventual cardiovascular morbidity in these children and adolescents (4,7,8,9,10).

Large, population-based, prospective studies demonstrate that a sedentary lifestyle and unhealthy diet increase the risk for metabolic syndrome and its components (11,12,13). In non-transplanted individuals, increased physical activity can lower blood pressure and improve lipid profiles (14). Sugar-sweetened beverages and other processed foodstuffs have also been linked to metabolic syndrome components (12,15). Given the high prevalence of metabolic syndrome components in our pediatric LT population, we wanted to explore whether physical activity and diet might be modifiable risk factors for these conditions.

Although previous studies have described the physical activity of pediatric LT recipients (16,17,18,19) and dietary behaviors (20), none have reported on associations with components of PTMS. In this analysis, we (1) compare the physical activity and dietary behaviors of pediatric LT recipients to non-transplanted peer controls from the National Health and Nutrition Examination Survey (NHANES) database and (2) evaluate whether these behaviors are associated with PTMS components in the LT recipients. Additionally, this is the first study to describe alcohol consumption in pediatric LT recipients—another lifestyle behavior that has potential long-term impact on the health of the patient and their transplanted liver.

METHODS

This study was approved by UCSF's Committee on Human Research (IRB 12–10290). Our LT cohort was evaluated in a cross-sectional study of pediatric LT recipients aged 8–30 years at the time of study visit. All subjects underwent first LT prior to age 18, were on stable immunosuppressive regimens at study visit, and had no known diabetes at time of enrollment.

Study visit:

After age-appropriate consent and assent were obtained, subjects were evaluated in UCSF's Pediatric Clinical Research Center or during inpatient admission for a surveillance liver biopsy. Data on demographics, family history, and medications were collected and managed using REDCap electronic data capture tools hosted at UCSF (21). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies.

Height and weight were measured using protocols from the NHANES 2011 Anthropometry Procedures (22). Blood pressure was measured three times sitting, using a digital sphygmomanometer, with at least 5 minutes of rest preceding each measurement, following NHANES 2011 protocols; the mean value was calculated for both systolic and diastolic blood pressured and was used in all analyses. Fasting serum was obtained after at least an 8-hour fast. Oral glucose tolerance testing was performed with weight-based glucose load (1.75 gram/kg to maximum 75 grams), following the NHANES 2011 Oral Glucose Tolerance Testing (OGTT) protocols (22).

Control matching:

LT recipients were matched by gender, race/ethnicity, and age with up to 3 controls from NHANES 2011–2012 and 2013–2014 cohorts. NHANES is a bi-annual, nationally representative cross-sectional study of children and adults in the U.S. administered by the Centers for Disease Control and Prevention. We used publically available, person-level data from these surveys (23). NHANES protocols were approved by the National Center for Health Statistics, with informed consent obtained from all participants. NHANES only performs oral glucose tolerance testing on children 12 years and older. Thus, only LT recipients and controls 12 years of age were included in the analysis of impaired glucose tolerance.

PTMS component definitions:

For subjects younger than 18 years at study visit, BMI percentile for age and gender was calculated based on 2000 CDC growth chart data (24). Subjects were classified as overweight if their BMI percentile was 85th-94th percentile for age and gender and obese if their BMI percentile was 95th percentile (25). Systolic and diastolic hypertension were defined as use of anti-hypertensives or blood pressure greater than the 95th percentile for gender, age, and height; pre-hypertension included those with blood pressure percentiles 90–94th percentile (26,27).

Obesity and hypertension in subjects 18 years or older were classified according to adult guidelines. Overweight was considered BMI 25–29.9kg/m^2, and obese BMI 30 kg/m^2. Hypertension was defined as use of anti-hypertensives, systolic blood pressure 140 mmHg, or diastolic 90mmHg. Pre-hypertension included those with systolic 120 mmHg; diastolic 80mmHg (26).

Elevated lipids for all subjects represented values at or above the 75th percentile for children and young adults (26). The cutoffs for elevated/borderline lipids were: triglycerides

75mg/dL for children 9 or younger, 90 mg/dL for those 10 or older, 115 mg/dL for those 20 or older; low-density lipoprotein (LDL) 110 mg/dL for <20 years of age and 120 for those 20 and older, and total cholesterol 170mg/dL for those <20 years of age and 190 for those 20 and older. Low high density lipoprotein (HDL) was 40 mg/dL, which represents the 10th percentile (26). Elevated fasting glucose was considered at least 100 mg/dL and IGT 140mg/dL two hours after glucose load, following American Diabetes Association definitions (28). Borderline elevated values were used as cutoffs since cardiovascular risk due to lipids is continuous and cumulative.

We defined metabolic syndrome in children as the presence of three or more of the following: (1) elevated waist circumference, (2) systolic or diastolic hypertension, (3) elevated triglycerides, (4) low HDL, (5) elevated fasting glucose or IGT (26,29).

Physical activity assessment:

LT recipients answered select questions on physical activity from the NHANES 2011–2012 surveys. Answers were entered directly into the study REDCap survey by subjects or parents/guardians or by the research coordinator during subject interview. NHANES asks different physical activity questions depending on age; this limited n for some variables in the comparison between LT recipients and controls, as detailed in Table 3.

Dietary assessment:

LT recipients, with assistance from the parent/guardian and/or research coordinator as needed, completed one 24-hour dietary recall for the day prior to study visit using the ASA-24 Kids on-line interface, which guides subjects through a detailed review with prompts about all meals and snacks, specific food types, portion sizes, and additives (30). Dietary recalls were analyzed by the ASA-24 system using the Food and Nutrient Database for Dietary Studies (FNDDS), and the resultant Daily Total Nutrients from Foods and Supplements file was downloaded for each subject and used for data analysis.

For NHANES controls, the "Dietary Interview—Total Nutrient Intake, First Day" files were used for analysis of dietary intake. These files also represent a 24-hour recall of intake in for the day prior to survey, done in in-person interviews, using the What We Eat in America interface analyzed through the FNDDS (31).

To evaluate insufficient or excess consumption of macro and micro-nutrients, we used the 2015–2020 Dietary Guidelines for Americans (32), which provides ranges for recommended daily allowance (RDA) based on age and gender. We evaluated excess or insufficiency of subjects and controls based on age and gender-appropriate RDA guidelines, and calculated percent who reported excess or insufficient consumption for each group.

Alcohol use:

We assessed alcohol use in subjects 12 years old using the validated, 10-item Alcohol Use Disorders Identification-Consumption short form (AUDIT-C) survey (33,34). Subjects entered their answers directly into the database while alone in an exam or hospital room This survey was hosted on a de-identified, RedCap database that was separate from that used for

the other study surveys to aid confidentiality. We also retrospectively reviewed the medical record to see if recipients were asked about alcohol in follow-up appointments, if they had consistent responses between the two modalities, and if there were elevations in AST or ALT that might be related to alcohol use.

Statistical analyses:

A p-value < 0.05 was considered statistically significant in all analyses. Categorical variables were compared using McNemar's chi-squared tests; continuous variables were compared using Student's t-test with equal or unequal variances for normally distributed variables and Kruskal-Wallis tests for skewed variables. All statistical analysis was done with Stata 12 (College Station, TX).

RESULTS

The cohort included 90 pediatric LT recipients and 243 matched non-LT NHANES controls (Table 1). LT recipients ranged from 8.0–30.2 years of age, and were 0.9–24.7 years from transplant at study visit. Six subjects were re-transplanted, all within 6 months of initial liver transplant—5 hepatic artery thrombosis, 1 cholangitis. LT recipients on tacrolimus (n=72) had a mean trough of 4.4 mg/dL at study visit (range 0.0–9.7 mg/dL). Median aspartate aminotransferase (AST) was 32 IU/L (IQR 24–46), alanine aminotransferase (ALT) 30 IU/L (IQR 21–45), gamma-glutamyl transpeptidase (GGT) 21 IU/L (IQR 13–51), total bilirubin 0.8 mg/dL (IQR 0.6–1.2), and creatinine 0.57 mg/dL (IQR 0.48–0.79).

Despite a similar prevalence of overweight/obesity between LT recipients and NHANES controls, LT recipients had a higher prevalence of hypertension, impaired glucose tolerance, and low HDL and lower prevalence of other dyslipidemia (Table 1), as we have described previously (4). Prevalence of metabolic syndrome components did not differ significantly by transplant indication (data not shown).

Dietary behaviors:

LT recipients reported consuming fewer total calories than matched controls, including less carbohydrates, fewer grams of fiber, and less total cholesterol (Table 2). Although the differences did not reach statistical significance, LT recipients reported consuming less sugar than controls, despite their higher prevalence of glucose intolerance. And though LT recipients had a higher prevalence of hypertension, they did not report consuming more sodium than controls (Table 1, 2).

Based on age and gender-appropriate RDA guidelines, LT recipients and controls were equally likely to consume excess carbohydrates (32% vs 34%), sugar (92% vs. 95%), and saturated fat (Figure 1). LT recipients were less likely to report excess total caloric intake (38% vs. 49% of controls, p=0.06), insufficient vitamin E (74% vs. 87% of controls, p=0.005) and vitamin D (89% vs. 95% of controls, p=0.04). LT recipients were more likely to report insufficient calcium (81% vs. 63% of controls, p=0.002) intake than controls. The groups were equally likely to consume excess sodium (77% vs. 74%) (Figure 1).

Among LT recipients, 56% reported taking vitamin or mineral supplements. Of those 50 subjects, 52% took a daily multivitamin, 22% vitamin D, 8% calcium, and 16% supplemental iron.

Physical activity:

LT recipients reported more sedentary hours and more daily hours on the computer than controls. Thirty-five percent of LT recipients spent 3+ hours on the computer daily, compared to 22% of non-transplanted peers (p=0.002) (Table 3).

LT recipients spent fewer days each week physically active for >60 minutes than controls (Table 3). LT recipients reported spending a median 40 minutes (IQR 40–120) daily in vigorous or moderate physical activity, versus median of 60 minutes in controls (IQR 30–120, p=0.10) Twenty-four percent of LT recipients reported spending zero days of the preceding week active for >60 minutes (vs 2% of controls, p<0.001).

Liver transplant recipients: Association between behaviors and PTMS components

Overweight/obesity: Among LT recipients, reported intake of calories, protein, total fat, total saturated fat, carbohydrates, sugar, fiber, cholesterol, and sodium did not differ between overweight/obese (n=43) and normal weight recipients (n=47) (data not shown). The prevalence of normal weight and overweight/obese LT recipients that reported consuming excess carbohydrates, excess sugar, excess saturated fats, excess sodium or insufficient amounts of fiber based on RDA for age and gender did not differ significantly (data not shown). Based on RDA for age and gender, normal weight LT recipients were more likely than overweight/obese LT recipients to report consuming excess calories (49% vs. 26%, p=0.02).

Overweight/obese LT recipients were more sedentary and less active than non-overweight LT recipients. A greater proportion of overweight/obese LT recipients spent 3+ hours at the computer than non-overweight LT recipients (49% vs 27%; p=0.02). Normal weight LT recipients spent more days doing vigorous activity each week (median 5 days, IQR 2–6) than did the overweight/obese LT recipients (median 3 days, IQR 2–4; p=0.01). There were no differences by weight status in daily hours of TV watched, sitting time, or in days spent doing moderate physical activity (data not shown).

Blood pressure: LT recipients with systolic hypertension/prehypertension reported consuming more cholesterol than those who were normotensive (346 mg vs. 227 mg, p=0.02). The dietary intake of recipients with systolic (n=29) or diastolic (n=8) hypertension/prehypertension was not different from that of normotensive controls for sodium or any other consumption variable by total intake or by RDA for age/gender. There were no differences in reported physical activity between these groups (data not shown).

Dyslipidemia: LT recipients with low/borderline low HDL (n=52) did not have significantly different reported intake of any micro- or macro-nutrient reviewed compared to those with normal HDL, based on total intake or RDA levels (data not shown). Those who had low/borderline HDL were more likely to have performed no moderate activity each

week (61% vs 29%, p=0.006). The groups had no differences in daily hours spent sitting, watching TV, or at the computer (data not shown).

Glucose tolerance and fasting glucose: Glucose-intolerant LT recipients (n=25) had no reported differences in dietary behaviors or physical activity compared to those that had normal glucose tolerance (n=59, data not shown). Similarly, LT recipients with elevated/ borderline elevated fasting glucose (n=17) had no reported differences in dietary behaviors or physical activity by any of the survey measures compared to those that had normal fasting glucose (n=72).

Hypertriglyceridemia: LT recipients with elevated/borderline elevated triglycerides (n=16) had no differences in reported dietary intake compared to those without hypertriglyceridemia (n=72). Otherwise there were no differences in reported physical activity (data not shown).

PTMS: LT recipients who met criteria for PTMS (n=19) did not have significantly different reported dietary intake or physical activity measures compared to those that did not meet criteria for PTMS (data not shown).

Alcohol consumption among LT recipients:

Liver transplant recipients aged 12 years or older (n = 59) were confidentially surveyed about alcohol use. Sixty-four percent of LT recipients surveyed reported never consuming alcohol. All LT recipients denied daily drinking. Of the 36% who had consumed alcohol (n=21), most had their first drink at age 17 or older (n=12), but the youngest reported age was 11–12 years old (n=2). Twenty-two percent reported having at least 1 drink each month (n=13); 9 consumed alcohol monthly and four consumed 2–4 times per month.

Eight patients were categorized as having more significant alcohol consumption based on number of days they had 1 drink, any binge drinking (6 in one day), or frequency of alcohol use during the average month. Three were males and 5 females. Most (n = 7) were 17 – 22 years old at study visit; one was 28. All were >10 years from transplant. At study visit, all had stable and normal AST, ALT, and GGT and no documented recent transaminase elevations. On retrospective comparison with medical records, 7 of these 8 had been asked about alcohol consumption during clinical encounters. Only 1 of the 7 had denied alcohol. The other 6 reported alcohol use patterns that were consistent with the research survey. Two had clinical documentation of elevated AST/ALT related to alcohol use; none appeared to have unexplained elevations of AST/ALT during follow-up.

DISCUSSION

This analysis provides novel insight into diet and physical activity patterns in pediatric LT recipients compared to healthy, non-LT peers. Even though LT recipients reported lower intake of calories, carbohydrates, and cholesterol compared to controls, a majority still exceeded the recommended daily intake of carbohydrates, fat, and sugar. Despite similar proportions of LT recipients and controls reporting excess sodium intake, LT recipients had a higher prevalence of hypertension. Similarly, LT recipients were more likely to have glucose

intolerance although they were equally likely to report consuming excess sugar when compared to controls. Although this suggests room for improved dietary behaviors in pediatric LT recipients, the increased prevalence of PTMS components in our LT cohort—including hypertension, glucose intolerance, and low HDL—did not appear to be explained by differences in dietary intake.

Our previous work suggests that immunosuppressive medications, specifically CNIs as well as corticosteroids, contribute to the high prevalence of hypertension, IGT, and low HDL amongst LT recipients. CNIs can affect blood pressure due to their nephrotoxicity and IGT due to its impairment of pancreatic ß cell function (4). More research needs to be done to better understand how providers can adjust immunosuppression regimens, utilizing CNI minimization or adjunct medications, to stave off rejection and optimize long term cardiovascular outcomes. Other transplant or graft-related factors—i.e. changes in vascular flow and pressures or in the patient's sugar and lipid metabolism—may also be related but have been minimally studied to date.

LT recipients reported significantly more sedentary and computer time than their matched controls. They were less likely to achieve the recommended 60 minutes of daily physical activity. Notably, LT recipients with overweight/obesity and those with low HDL reported less physical activity than LT recipients without these conditions. Although educational or other interventions to improve diet and increase exercise in LT recipients may be helpful for overall health, these data suggest that they are unlikely to completely ameliorate these PTMS components.

Our findings regarding dietary behaviors were consistent with a smaller, previously published study of LT recipients aged 2–18 years (n=27) compared to healthy children (n=28) (20). These pediatric LT recipients also reported diets relatively similar to their "healthy" counterparts. They also found that LT recipients consumed insufficient amounts of vitamin D and calcium. These studies suggest an enhanced need to counsel pediatric LT recipients about the negative health outcomes associated with poor diet since this population has an increased risk for developing components of PTMS.

Four previous studies analyzed physical activity in smaller LT cohorts, but none have investigated associations with PTMS components (16,17,18,19). Only one of these studies (19) compared physical activity of LT recipients to controls. Unnithan et al. (19) found that pediatric LT recipients (n=29) had reduced cardio-respiratory fitness compared to controls (n=34), and many were unable to meet standards for abdominal strength and endurance. Of interest, those LT recipients reported physical activity levels comparable to their peers, although they did not outline the actual patterns of behavior. Three additional small studies (16,17,18) found reduced levels of physical fitness or activity in children after LT. Both our study and that of Unnithan et al. stress that effectively moderate and vigorous physical activity need to be pro-actively encouraged for stable patients in this population.

Our study provides additional evidence that many LT recipients have relatively low levels of physical activity and high levels of sedentary behavior—even many years post-transplant when they are medically stable. LT recipients might benefit from specific education about

the importance, and safety, of regular moderate to vigorous physical activity. Interventions to increase physical activity may be particularly important for overweight/obese patients, and potentially for those with low HDL. Patterson et al. suggested that frequent fatigue and low self-efficacy could be at fault for low physical activity (16). As such, promoting self-confidence and coaching LT recipients about safe ways for them to be physically active is important in this population. Similar to our findings on dietary intake, physical activity did not appear to entirely account for the increased prevalence of hypertension, glucose intolerance, or low HDL in LT recipients.

This study is the first to report on alcohol use in pediatric LT recipients. Our data highlights the importance of screening these patients for substance use. Just over 1/3 reported any alcohol consumption and 1/3 of those reported more regular consumption. Avoiding binge or frequent drinking could specifically be protective for the liver graft. In our small sample of more frequent drinkers, pediatric LT recipients appeared willing to discuss alcohol use in clinical encounters when they were asked—suggesting that the discussion is feasible for pediatricians and other providers to initiate.

This was a single-center cross-sectional study, which may limit the generalizability of our results. To increase power given our relatively small sample size, we matched LT recipients to multiple controls. Controls were not recruited or assessed at our center, but we did use the same physical activity questions used by the NHANES cohort, and only reported on answers in LT recipients for whom age-matched controls had answered the same questions. Under-reporting of dietary consumption is a concern for the 24-hour dietary recall that we used, particularly of sugar-containing foods (35); it is a potential explanation for the lower caloric intake in our LT recipients compared to their controls. Our dietary assessments were completed with a validated tool and with assistance from our research coordinator to try and avoid under-reporting. Repeated assessments of diet and exercise in these patients would help to validate our findings.

As with all children, counseling about the importance of healthy diet and regular physical activity is an important part of preventive care in pediatric LT recipients. Adopting healthy habits during childhood and adolescence may help optimize their long-term health, and it may specifically help protect the liver, i.e. by preventing non-alcoholic fatty liver disease. But given the severe illness, surgeries, and other complications that these children have survived, routine attention to diet and exercise may not be a priority for families. There may be additional unaddressed barriers for LT recipients or parents, such as deconditioning that may occur with transplantation and hospitalization, the fear of injuring the transplanted liver, or the fear of impairing growth potential. Additional education for families and primary care pediatricians about the high prevalence of cardiovascular risk conditions may also help increase awareness and motivate change. However, although healthier diets and increased physical activity may help optimize long-term cardiovascular health in pediatric LT recipients—as with the general pediatric population—it is uncertain from our data if they on their own will ameliorate metabolic syndrome or its components so this merits further research.

Acknowledgments

Abbreviations

ALT	alanine aminotransferase
ASA-24	Automated self-administered 24-hour dietary assessment
AST	Aspartate aminotransferase
AUDIT-C	Alcohol Use Disorders Identification-Consumption
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CNI	Calcineurin Inhibitor
FNDDS	Food and Nutrient Database for Dietary Studies
GGT	Gamma-glutamyl transpeptidase
HDL	High-density lipoprotein
IGT	Impaired glucose tolerance
IQR	Interquartile range
LDL	Low-density lipoprotein
LT	Liver transplant
NHANES	National Health and Nutrition Examination Survey
OGTT	Oral glucose tolerance testing
PTMS	Post-transplant metabolic syndrome
RDA	Recommended dietary intake
REDCap	Research Electronic Data Capture

REFERENCES

1. Ng VL, Alonso EM, Bucuvalas JC, et al. Health status of children alive 10 years after pediatric liver transplantation performed in the US and Canada: Report of the studies of pediatric liver transplantation experience. J Pediatr 2012;160:820–826.e3 [PubMed: 22192813]

2. Laish I, Braun M, Mor E, et al. Metabolic syndrome in liver transplant recipients: Prevalence, risk factors, and association with cardiovascular events. Liver Transpl 2011;17(1):15–22. [PubMed: 21254340]

3. Johnston SD, Morris JK, Cramb R, et al. Cardiovascular morbidity and mortality after orthotopic liver transplantation. Transplantation 2002;73(6):901–906. [PubMed: 11923689]

4. Perito ER, Lustig RH, Rosenthal P. Metabolic Syndrome Components After Pediatric Liver Transplantation: Prevalence and the Impact of Obesity and Immunosuppression. Am J Transplant 2016;16(6):1909–16. [PubMed: 26751054]

5. Kosola S, Lampela H, Makisalo H, et al. Metabolic syndrome after pediatric liver transplantation. Liver Transpl 2014;20:1185–1192. [PubMed: 24923737]

6. Dagher M, Ng VL, Carpenter A, et al. Overweight, central obesity, and cardiometabolic risk factors in pediatric liver transplantation. Pediatr Transplant 2015;19:175–181. [PubMed: 25581506]

7. Weiss R, Bremer AA, Lustig RH. What is metabolic syndrome, and why are children getting it? Ann N Y Acad Sci 2013;1281:123–140. [PubMed: 23356701]

8. Steinberger J, Daniels SR, Eckel RH, et al. Progress and challenges in metabolic syndrome in children and adolescents: A scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism. Circulation 2009;119:628–647. [PubMed: 19139390]

9. Satapathy SK, Charlton MR. Posttransplant metabolic syndrome: New evidence of an epidemic and recommendations for management. Liver Transpl 2011;17(1):1–6. [PubMed: 21254337]

10. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics 2011;128 Suppl 5:S213–56. [PubMed: 22084329]

11. Pan Y, Pratt CA. Metabolic Syndrome and Its Association with Diet and Physical Activity in US Adolescents. J Am Diet Assoc 2008;108(2):276–86 [PubMed: 18237576]

12. Bremer AA, Auinger P, Byrd RS. Relationship between insulin resistance-associated metabolic parameters and anthropometric measurements with sugar-sweetened beverage intake and physical activity levels in US adolescents: findings from the 1999–2004 National Health and Nutrition Examination Survey. Arch Pediatr Adolesc Med 2009;163(4):328–35 [PubMed: 19349561]

13. Gustat J, Srinivasan SR, Elkasabany A, et al. Relation of self-rated measures of physical activity to multiple risk factors of insulin resistance syndrome in young adults: The Bogalusa Heart Study. J Clin Epidemiol 2002;55(10):997–1006 [PubMed: 12464376]

14. McMurray RG, Ondrak KS. Cardiometabolic Risk Factors in Children: The Importance of Physical Activity. Am J of Lifetstyle Medicine 2013;7(5):292–303.

15. Steffen LM, Van Horn L, Daviglus ML, et al. A modified Mediterranean diet score is associated with a lower risk of incident metabolic syndrome over 25 years among young adults: the CARDIA (Coronary Artery Risk Development in Young Adults) study. Br J Nutr 2014;112(10):1654–61. [PubMed: 25234439]

16. Patterson C, So S, Schneiderman JE, et al. Physical activity and its correlates in children and adolescents post-liver transplant. Pediatr Transplant 2016;20(2):227–34. [PubMed: 26893138]

17. Maria da Silva R, Brunow de Cavalho W, Johnston C, et al. Functional capacity after pediatric liver transplantation: a pilot study. Pediatr Transplant 2014;8(6):586–93.

18. Krasnoff JB, Mathias R, Rosenthal P, et al. The comprehensive assessment of physical fitness in children following kidney and liver transplantation. Transplantation 2006; 82(2): 211–7. [PubMed: 16858284]

19. Unnithan VB, Veehof SH, Rosenthal P, et al. Fitness testing of pediatric liver transplant recipients. Liver Transpl 2001;7(3):206–12. [PubMed: 11244161]

20. Alzaben AS, MacDonald K, Robert C, et al. Diet quality of children post-liver transplantation does not differ from healthy children. Pediatr Transplant 2017;21:e12944 10.1111/petr.12944

21. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG, Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support, J Biomed Inform 2009 4;42(2):377–81. [PubMed: 18929686]

22. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES). Anthropometry Procedures Manual https://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/Anthropometry_Procedures_Manual.pdf. Published January 2011.

23. Centers for Disease Control and Prevention. National Health and Nutrition Examination. Questionnaires, Datasets, and Related Documentation http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm, accessed 7/11/2017.

24. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11 2002 May;(246)(246):1–190. –24

25. Barlow SE, Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics 2007 12;120 Suppl 4:S164–92. [PubMed: 18055651]

26. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 2011 12;128 Suppl 5:S213–56. [PubMed: 22084329]

27. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004 8;114(2 Suppl 4th Report):555–576. [PubMed: 15286277]

28. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2012 1;35 Suppl 1:S64–71. [PubMed: 22187472]

29. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009 10 20;120(16):1640–1645. [PubMed: 19805654]

30. National Institutes of Health. National Cancer Institute Automated Self-Administered 24-Hour Dietary Assessment Tool (ASA24) https://epi.grants.cancer.gov/asa24. Updated November 6, 2017.

31. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey. 2011–2012 Data Documentation, Codebook, and Frequencies https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/DR1TOT_G.htm. Published September 2014.

32. Office of Disease Prevention and Health Promotion. 2015–2020 Dietary Guidelines for Americans Eighth Edition https://health.gov/dietaryguidelines/2015/. Published December 2015.

33. Knight JR, Sherritt L, Harris SK, Gates EC, Chang G. Validity of brief alcohol screening tests among adolescents: A comparison of the AUDIT, POSIT, CAGE, and CRAFFT. Alcohol Clin Exp Res 2003;27(1):67–73. [PubMed: 12544008]

34. Frank D, DeBenedetti AF, Volk RJ, Williams EC, Kivlahan DR, Bradley KA. Effectiveness of the AUDIT-C as a screening test for alcohol misuse in three race/ethnic groups. J Gen Intern Med 2008;23(6):781–787. [PubMed: 18421511]

35. Rangan A, Allman-Farinelli M, Donohoe E, et al. Misreporting of energy intake in the 2007 Australian Children's Survey: differences in the reporting of food types between plausible, under- and over-reporters of energy intake. J. Hum. Nutr. Diet 2014;27:450–458 [PubMed: 24206056]

What is known

- Components of metabolic syndrome—including hypertension, low HDL, and impaired glucose tolerance—are more prevalent in pediatric liver transplant (LT) recipients than in their peers.

- Low physical activity and poor diet have been associated with increased prevalence of metabolic syndrome in non-LT children.

What is new

- Physical activity and diet did not entirely account for the increased prevalence of hypertension, glucose intolerance, or low HDL in LT recipients.

- More than 1/3 of pediatric LT recipients 12 years and older consume alcohol.

- Although healthier diets and increased physical activity may help optimize long-term cardiovascular health in pediatric LT recipients, they are unlikely to completely ameliorate components of metabolic syndrome.
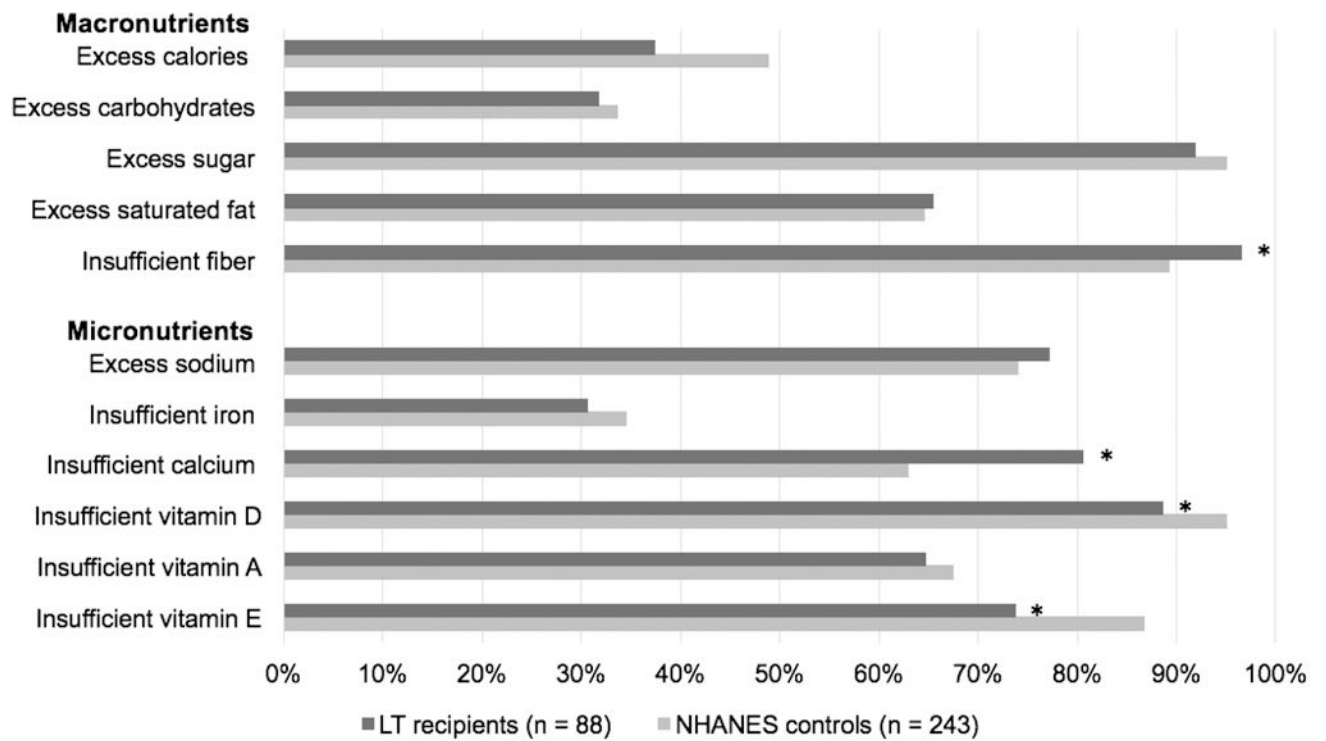
Figure 1:
Prevalence of over or under-consumption of nutrients in LT recipients and NHANES controls, based on recommended daily allowance (RDA) for age and gender. Data reflects reported consumption from 24-hour dietary recall. * p<0.05 for comparison of prevalence in LT recipients vs. controls.

Table 1:

Demographics, clinical characteristics, and metabolic syndrome components[*]

	LT (n = 90)	NHANES controls (n = 243)	p
Age at visit (y)	15.6 ± 4.8	15.4 ± 4.8	0.71
Female	46%	44%	0.86
Race/ethnicity			
White	27%	30%	0.67
Black	8%	8%	
Hispanic	40%	43%	
Other/multiracial	26%	19%	
Years since transplant	10.9 (6.5–15.3)		
Transplant indication[†]			
Biliary atresia	32%		
Metabolic disease	15%		
Cholestatic conditions	6%		
Other	47%		
Glucocorticoids at visit	7%		
CNI			
Tacrolimus	80%		
Cyclosporine	10%		
Not taking CNI	10%		
Tacrolimus trough at visit (n = 72)	4.4 ± 2.2		
Mean recent tacrolimus trough (n = 70)[‡]	5.0 ± 2.8		
Cyclosporine trough at visit (n = 9)	69 ± 52		
Mean recent cyclosporine trough (n = 8)[‡]	96 ± 63		
BMI	21.8 (18.9–26.4)	20.3 (17.6–24.8)	0.02
Weight status by BMI/BMI percentile			0.30
Normal weight	52%	43%	
Overweight	13%	14%	
Obese	35%	43%	
Systolic prehypertension or hypertension	32%	11%	<0.001
Diastolic prehypertension or hypertension	9%	2%	0.01
Fasting labs[¶]			
Elevated fasting glucose (100 mg/dL)	18%	23%	0.41
IGT (2-h glucose 140 mg/dL)[§]	34%	5%	<0.001
Low/borderline low HDL[‖]	46%	27%	0.006
Elevated/borderline elevated triglycerides	20%	30%	0.17
Elevated/borderline elevated LDL[‖]	5%	18%	0.01

	LT (n = 90)	NHANES controls (n = 243)	p
Elevated/borderline elevated total cholesterol ‖	8%	27%	0.001
Metabolic syndrome	21%	14%	0.14

*
Categorical variables reported as proportion with p-value by McNemar's $\chi 2$ test. Continuous variables reported as mean ± SD with p-value by t-test with equal variances or median (IQR).

†
Metabolic disease includes alpha-1-antitrypsin deficiency, Crigler–Najjar syndrome, cystic fibrosis, glycogen storage disease, inborn errors in bile acid metabolism, neonatal hemochromatosis, primary hyperoxaluria, tyrosinemia, urea cycle defects, and Wilson disease. Cholestatic conditions includes Alagille syndrome, Byler disease, progressive intrahepatic cholestatic syndromes, total parenteral nutrition cholestasis, sclerosing cholangitis, and idiopathic cholestasis. Other diagnoses include congenital hepatic fibrosis, Budd–Chiari syndrome, autoimmune hepatitis cirrhosis, drug toxicity, hepatitis C cirrhosis, and unknown cirrhosis.

‡
Mean of three most recent trough levels before study visit.

¶
Data only available on patients 12 years. LT (n = 66); NHANES controls (n = 182)

§
4 LT recipients did not complete the IGT

‖
1 LT recipient did not have a lipid panel (HDL, LDL, and total cholesterol) drawn.

Table 2:

Reported daily dietary intake in LT recipients versus matched NHANES controls

	LT (n = 88)[*]	NHANES controls (n = 243)	p
Macronutrients[†]			
Energy (kcal)	1877.3 ± 695.3	2104.5 ± 858.2	0.01
Protein (g)	72.7 ± 33.6	79.1 ± 40.3	0.15
Total fat (g)	73.0 ± 33.2	80.5 ± 39.3	0.09
Fatty acids, total saturated (g)	24.4 ± 13.4	26.8 ± 14.1	0.16
Carbohydrate (g)	236.3 ± 104.5	267.9 ± 112.6	0.02
Sugars, total (g)	108.2 ± 67.1	120.2 ± 64.0	0.15
Fiber, total dietary (g)	13.1 ± 7.0	15.8 ± 9.4	0.007
Cholesterol (mg)	133.4 ± 26.5	159.6 ± 30.4	<0.001
Micronutrients[‡]			
Calcium (mg)	783.8 (523.8–1125.5)	944.0 (580.0–1473.0)	0.01
Iron (mg)	15.2 (10.3–21.0)	14.0 (9.2–21.0)	0.33
Sodium (mg)	3085.7 (2421.7–3920.5)	3149.0 (2244.0–4435.0)	0.43
Zinc (mg)	11.4 (7.6–16.2)	10.5 (6.1–14.8)	0.08
Vitamin C (mg)	49.5 (18.9 –117.7)	39.4 (17–107)	0.36
Vitamin B-12 (mcg)	5.0 (2.8–8.2)	4.4 (2.4–6.9)	0.12
Vitamin A, RAE (mcg)	554.1 (341.3–991.8)	494 (273–805)	0.10
Vitamin E, α-tocopherol (mg)	7.5 (5.0–13.9)	6.3 (4.4–10.3)	0.04
Vitamin K (mg)	54.0 (29.1–107.2)	59.1(32.1–95.6)	0.82
Vitamin D (D2 + D3) (mcg)	3.8 (1.1–10.1)	4.0 (1.6–7.7)	0.88

[*] 2 LT recipients were missing dietary recall data.

[†] Data reported as mean ± SD with p by t-test with unequal variances.

[‡] Data represent median (interquartile range) with p by Kruskal–Wallis due to more significant skewing of data.

Table 3:

Physical activity in LT recipients versus matched NHANES controls[*]

	LT (n = 90)		NHANES controls (n = 243)		p
Sedentary activity					
Daily hours of TV					0.85
Less than 1 hour	15%		15%		
1–2 hours	56%		51%		
3–4 hours	21%		25%		
5 or more hours	8%		9%		
Daily hours of computer					0.002
Less than 1 hour	46%		37%		
1–2 hours	19%		41%		
3–4 hours	20%		14%		
5 or more hours	15%		8%		
	LT 15 years old		NHANES controls 15 years old		p
	n	%	n	%	
Days physically active for 60 minutes[†]					<0.001
0 days per week	9	24%	2	2%	
−3 days per week	12	33%	17	20%	
4–7 days per week	16	43%	66	78%	
School sports or physical activity club[‡]	12	31%	25	44%	0.20
Weekly active video games					0.10
0 days per week	32	84%	37	65%	
1–3 days per week	4	11%	16	28%	
4–7 days per week	2	5%	4	7%	
	LT 12 years old		NHANES controls 12 years old		
	n	% or median (IQR)	n	% or median (IQR)	p
Sedentary activity					
Daily hours sitting	65	10 (8–12)	182	8 (6–9)	0.0001
Physical activity during sports, fitness, or recreational activities					
Weekly vigorous activity 10 min					0.98
0 days per week	34	52%	95	52%	
1–3 days per week	16	25%	43	24%	
4–7 days per week	15	23%	44	24%	
Minutes vigorous activity/week	31	60 (40–120)	87	60 (30–120)	0.81
Weekly moderate activity 10 min					0.76
0 days per week	31	48%	93	51%	
1–3 days per week	16	24%	47	26%	
4–7 days per week	18	28%	42	23%	

	LT (n = 90)		NHANES controls (n = 243)		p
Minutes moderate activity/week	34	40 (25–60)	89	60 (30–120)	0.10
Physical activity during work					
Weekly vigorous work ≥ 10 min					0.26
0 days per week	61	94%	157	86%	
1–3 days per week	2	3%	14	8%	
4–7 days per week	2	3%	11	6%	
Minutes of vigorous work/week	4	52.5 (30–90)	25	120 (45–120)	0.29
Weekly moderate work ≥ 10 min					0.04
0 days per week	31	48%	120	66%	
1–3 days per week	14	21%	26	14%	
4–7 days per week	20	31%	36	20%	
Minutes moderate work/week	34	55 (30–120)	62	60 (40–120)	0.09

*
Categorical variables reported as proportion with p-value by McNemar's $\chi 2$ test. Continuous variables reported as median (interquartile range) with p by Kruskal–Wallis.

†
NHANES 2011–12 set only asked 2–11 year olds and NHANES 2013–14 asked 2–15 years. Missing data n=23.

‡
Data represents respondents from NHANES 2013–14. Missing data n=51.