Lifestyle intervention in obese Chinese adolescents with nonalcoholic fatty liver disease: A randomized controlled study (11122981)

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Background

- Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in obese children worldwide
- Higher prevalence among obese children (77% [D Chan et al, 2004])
- NAFLD is a growing problem along with the epidemic of obesity in Hong Kong (20% of primary school student are obese in 2015, FHS)

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PAPER

Hepatic steatosis in obese Chinese children

DFY Chan[1]*, AM Li[1], WCW Chu[2], MHM Chan[3], EMC Wong[4], EKH Liu[2], IHS Chan[3], J Yin[1], CWK Lam[3], TF Fok[1] and EAS Nelson[1]

- In our previous 2004 report
  - NAFLD was common among cohort of obese children referred for medical assessment
    - simple steatosis 77%
    - presumed NASH (hepatic steatosis + raised ALT) 24%

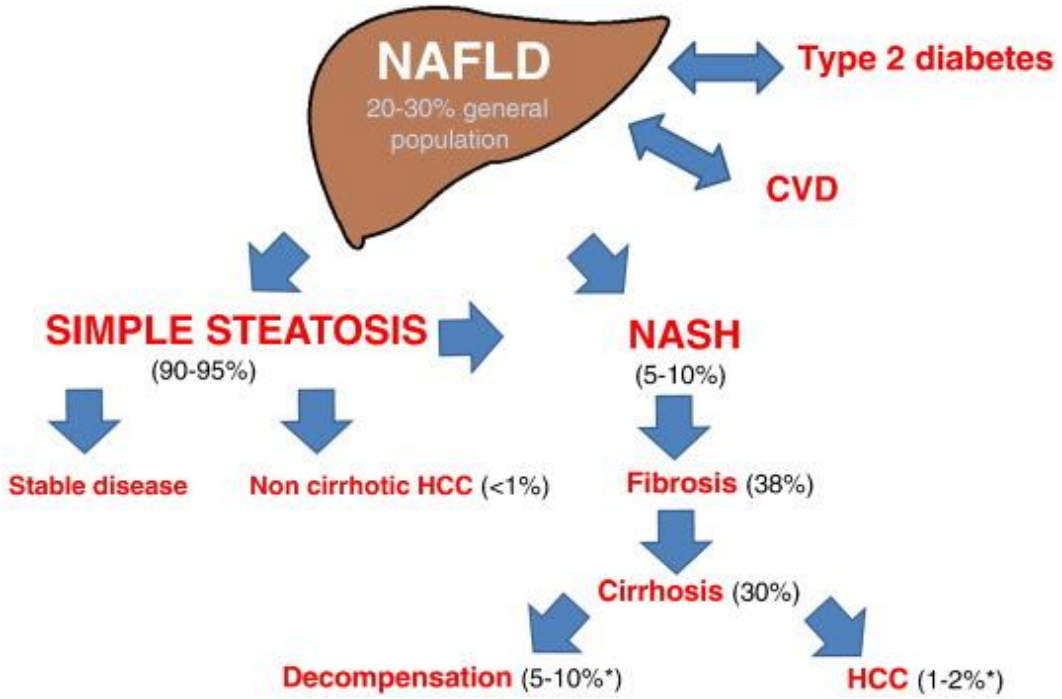


Fig. 1. Natural history of NAFLD.Abbreviations: NAFLD, non-alcoholic fatty liver disease; CVD, cardiovascular disease; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma; (% prevalence/incidence); *In 10 years from development of cirrhosis [147...

Elena Buzzetti, Massimo Pinzani, Emmanuel A. Tsochatzis

The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD)

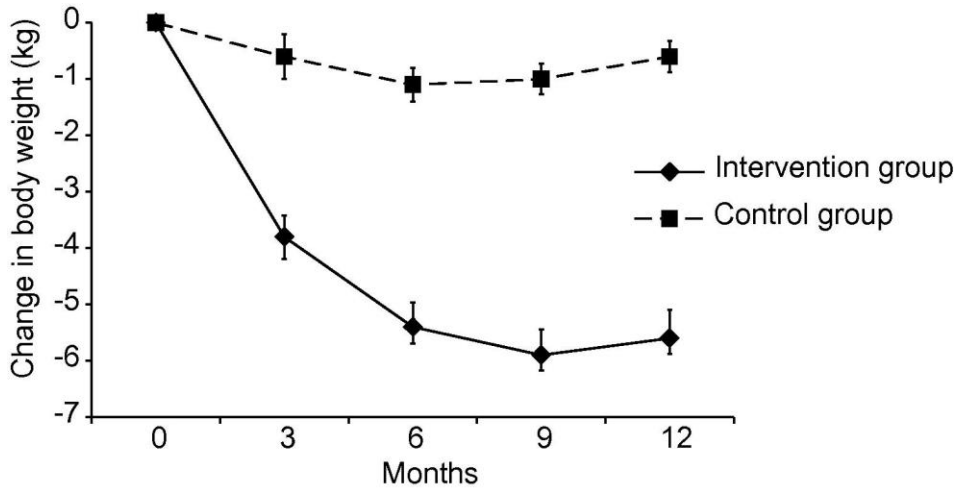
Metabolism, Volume 65, Issue 8, 2016, 1038–1048

http://dx.doi.org/10.1016/j.metabol.2015.12.012

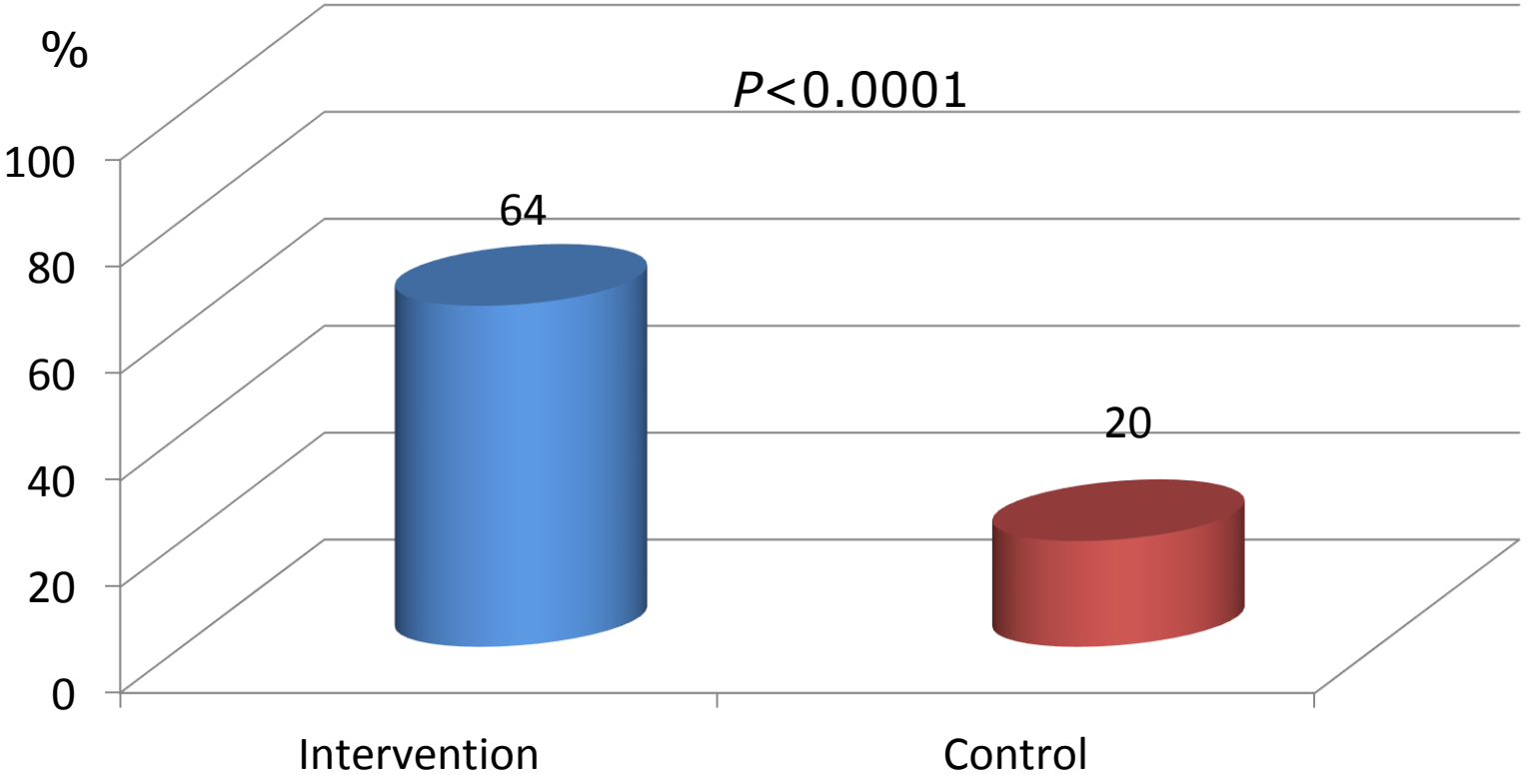
Community-based lifestyle modification programme for non-alcoholic fatty liver disease: A randomized controlled trial

Vincent Wai-Sun Wong, Ruth Suk-Mei Chan, Grace Lai-Hung Wong, Bernice Ho-Ki Cheung, Winnie Chiu-Wing Chu, David Ka-Wai Yeung, Angel Mei-Ling Chim, Jennifer Wing-Yan Lai, Liz Sin Li, Mandy Man-Mei Sea, Francis Ka-Leung Chan, Joseph Jao-Yiu Sung, Jean Woo, Henry Lik-Yuen Chan

Journal of Hepatology
Volume 59, Issue 3, Pages 536-542 (September 2013)
DOI: 10.1016/j.jhep.2013.04.013



Proportion of patients with resolved NAFLD



Nobili V *et al.* in 2008 recruited

- 53 children aged 5.7 to 18.8 years
- with mean BMIs of 24.9 to 26.8 and histological NAFLD.
- They were followed for 24 months with a monthly dietary lifestyle modification programme (low caloric diet and regular aerobic exercise) and
- supervised by a multidisciplinary team including dieticians, hepatologists, endocrinologists, psychologists, and cardiologists.
- On average, there was 4 to 6 kg drop in body weight and a significant improvement in histological findings of NAFLD over the 24 months of intervention.

Sustainability

Hypothesis	• Intrahepatic fat content will be decreased after lifestyle modification programme (LMP)
Aim	• To determine the efficacy of LMP in reducing NAFLD in obese adolescents
Primary outcome	• To determine the degree of change of intrahepatic triglyceride content of NAFLD after intervention
Secondary outcome	• To determine the effect of LMP on the obesity by assessing biochemically and by anthropometric measurements

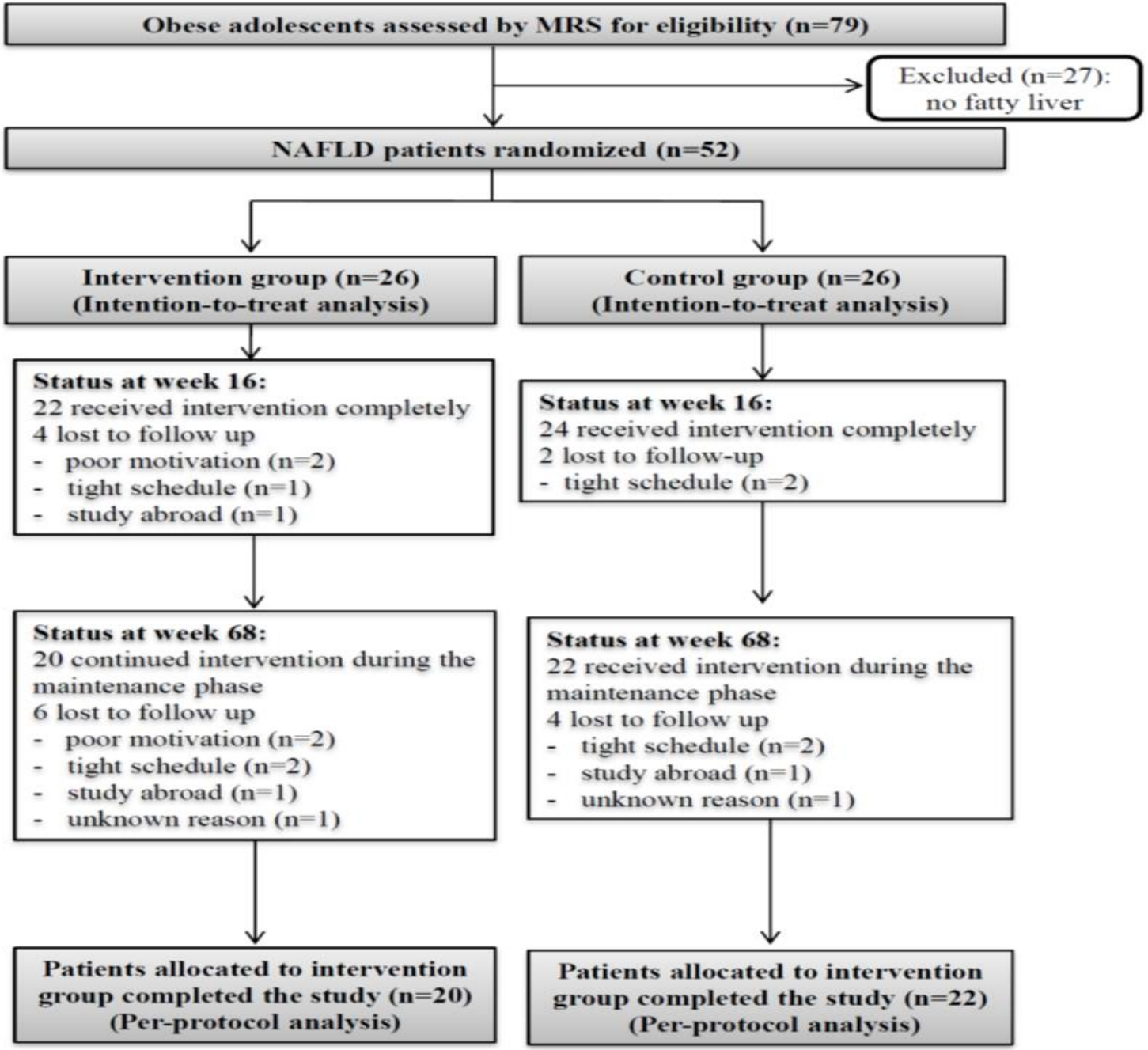
Method

- Randomized controlled trial
- Inclusion
  - Aged 14-18 post pubertal
  - Primary obesity
  - BMI >95th centile
  - MRS confirmed NAFLD
- Exclusion criteria
  - Any chronic liver disease, either clinical or biochemical
  - Alcohol consumption
  - BMI < 95th centile
  - Using steatogenic and /or antidiabetic drugs

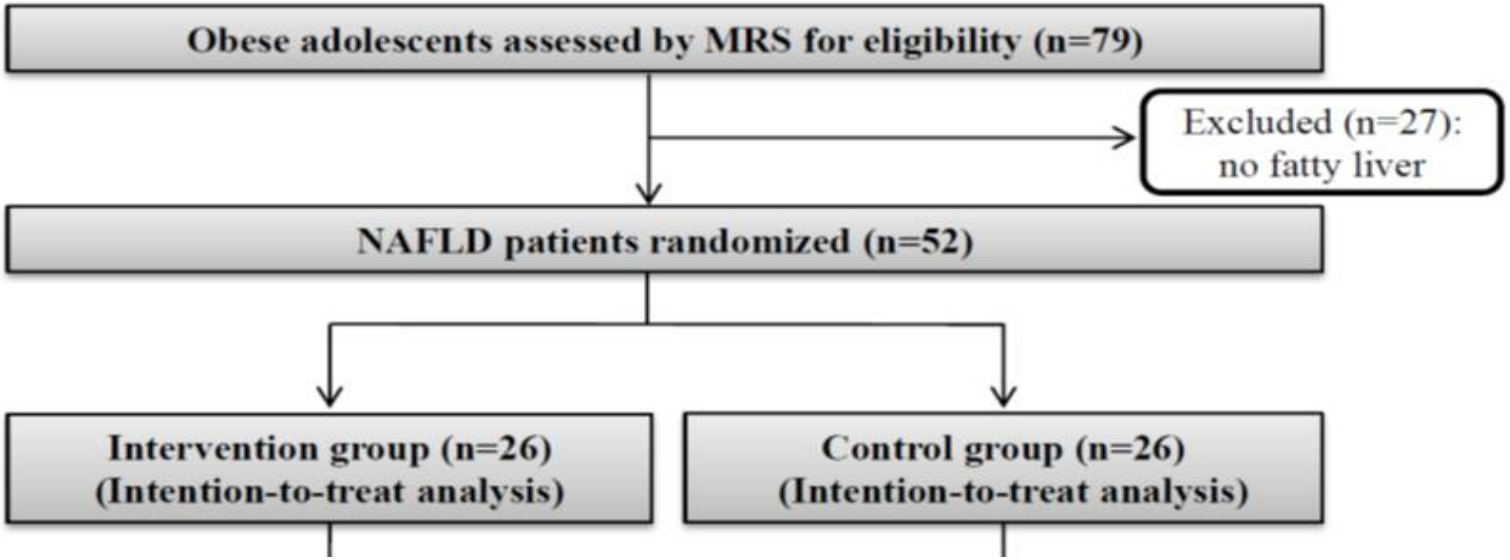
Diagnosis

- Gold Standard: liver biopsy
- Non invasive method
  - MRS
  - Diagnosis of NAFLD = intrahepatic triglycerides content **>= 5%**

Study flow diagram



Inclusion criteria and randomization



Ax T0

Ax:
MRS
Anthropometric measurements
Biochemical measurements

Variables	Intervention group (n=26)	Control group (n=26)
Age (years)	15.3 (3.4)	13.8 (5.3)
Boys, n (%)	16 (61.5)	18 (69.2)
Body weight (kg)	91.1 (9.8)	91.1 (8.0)
Boys	93.7 (7.7)	91.4 (8.2)
Girls	87.0 (11.6)	90.3 (7.8)
BMI (kg/m^2)	32.59 (3.28)	32.12 (3.12)
Boys	32.26 (3.11)	31.23 (2.92)
Girls	33.14 (3.63)	34.12 (2.75)
BMI z-score	2.32 (0.38)	2.29 (0.37)
W		
Boys	106.0 (9.8)	103.1 (8.2)
Girls	100.5 (8.8)	104.7 (7.1)
Body fat (%)	41.1 (8.5)	39.0 (9.1)
Boys	38.4 (7.4)	34.2 (5.5)
Girls	45.5 (8.7)	49.8 (5.3)
Systolic blood pressure (mmHg)	127 (19)	129 (14)
Diastolic blood pressure (mmHg)	71 (13)	71 (9)
Physical activity level (0-10)	4.8 (2.3)	6.2 (2.1)

Age & Sex

BMI

Body fat

NO Difference in all parameters between Intervention and Control

Values are mean (SD) or numbers (percentages).

Laboratory results

Variables	Intervention group (n=26)	Control group (n=26)
ALT (IU/L)	22.0 (9.5)	23.2 (9.5)
AST (IU/L)	37.6 (26.5)	36.9 (23.6)
AST/ALT ratio	0.68 (0.36)	0.79 (0.22)
Insulin (mIU/L)	27.4 (16.2)	27.8 (23.2)
Fasting glucose (mmol/L)	5.0 (0.4)	4.9 (0.5)
HOMA	6.3 (4.2)	5.3 (3.1)
QUICKI	0.50 (0.07)	0.52 (0.12)
Triglycerides (mmol/L)	1.1 (0.4)	1.1 (0.4)
Intra-hepatic triglyceride content (%)	13.1 (10.2)	13.5 (7.8)

Insulin resistance

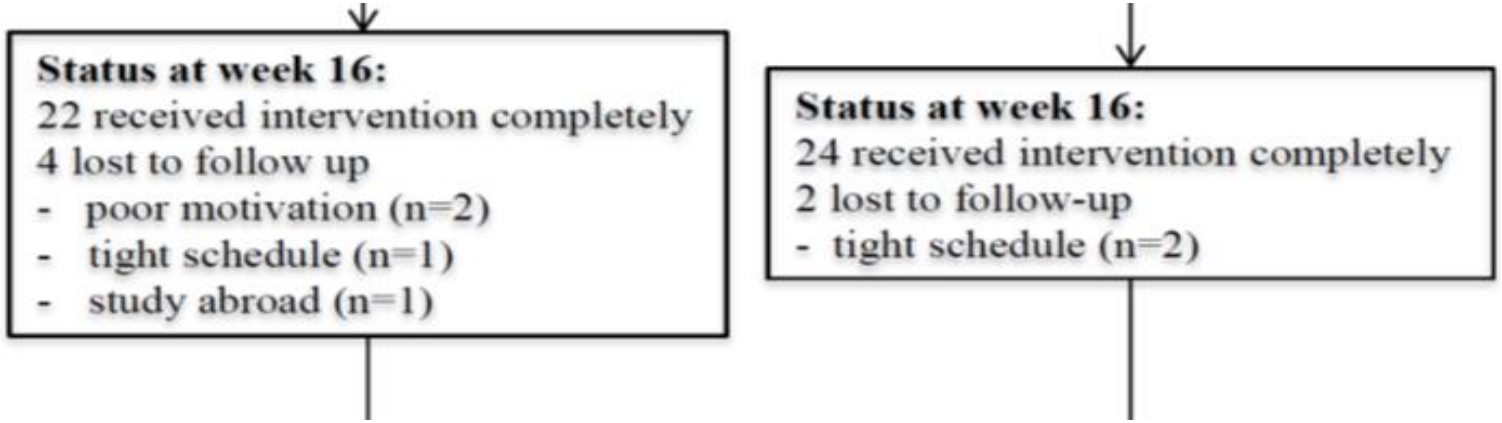
NO Difference in all parameters between Intervention and Control

IHTC

Values are mean (SD) or numbers (percentages).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high density lipoprotein; HOMA, homeostasis model assessment; LDL, low density lipoprotein; QUICKI, quantitative insulin-sensitivity check index.

PHASE I (16 weeks)



Interventional group LMP
Weekly FU by dietitian x
16 weeks

Routine regular FU
by Paediatrician
every 16 weeks

Intervention - LMP

- 16 weeks LMP
  - An evidence based method developed by the Center for Nutritional Studies
  - Based on motivational interviewing and behavioural modification
- Dietary advice based on American Dietetic Association
  - Emphasis on fruit and vegetables
  - Low fat and low glycaemic index and low caloric food
- Booklet given
- Enpower clients themselves on food selection and lifestyle modification
- Psychosocial support
- Logbook 7 days dietary record before each visit

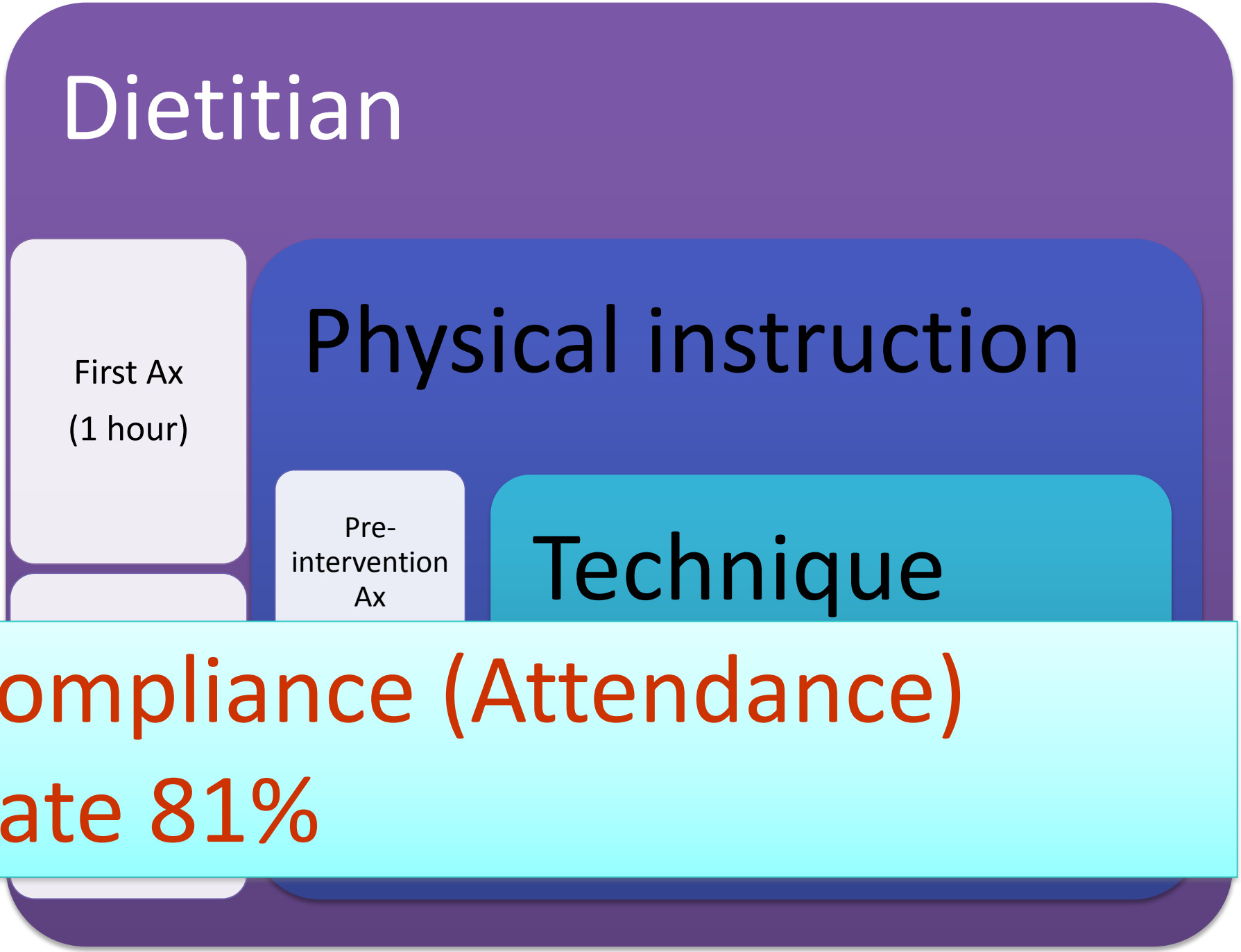
What is lifestyle modification therapy on weight management?

It is a therapeutic application of behavior shaping through operant conditioning. The key components are:

- baseline measurement
- goal-setting
- small, manageable and achievable steps (achievement serves as its own reinforcer and is likely to promote further attempts)
- reinforcement (involves notions of reward and punishment, it then ceases to be purely behavioral but invokes a range of cognitive, affective and social influences to do with motivation and compliance)

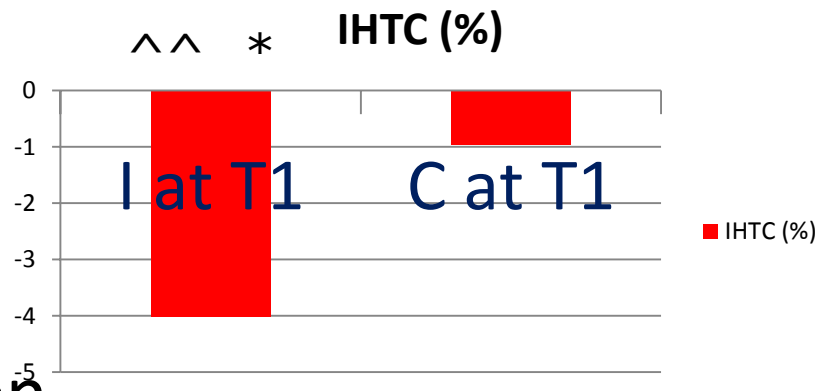
Common Strategies used in lifestyle modifications

1. Reinforcements
2. Motivation
3. Health and nutrition education
4. Empowerment


Dietitian
First Ax
(1 hour)
Physical instruction
Pre-
intervention
Ax
Technique
Compliance (Attendance)
rate 81%

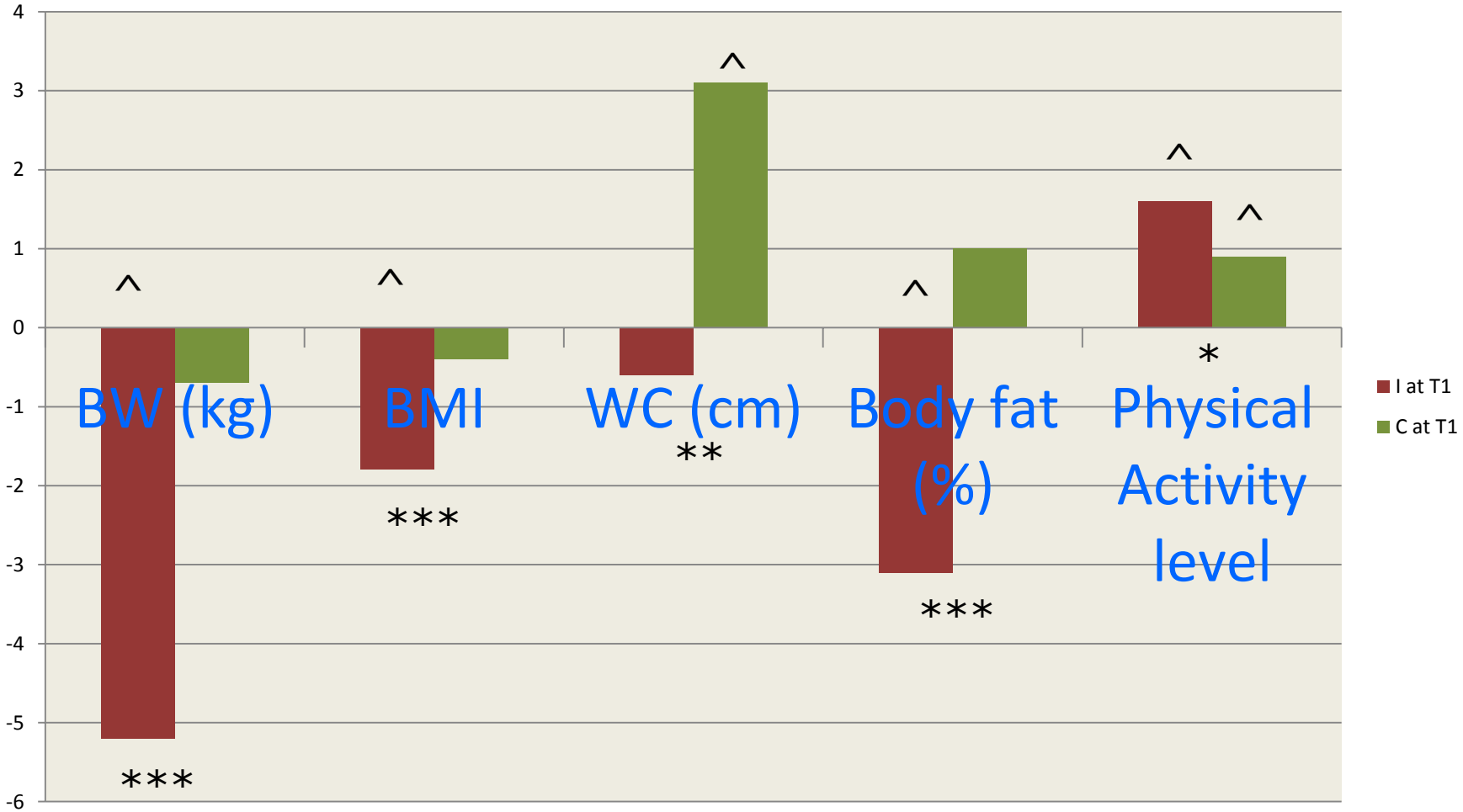
Primary Outcome: Intra-hepatic Triglyceride Content (%)

- Intervention group
  - Decreased 4.02%
  - Statistically significant decreased when compared with baseline
  - P= 0.001^^
- Control Group
  - Decreased 0.96%
  - Insignificant
- Intergroup comparison
  - P = 0.029*



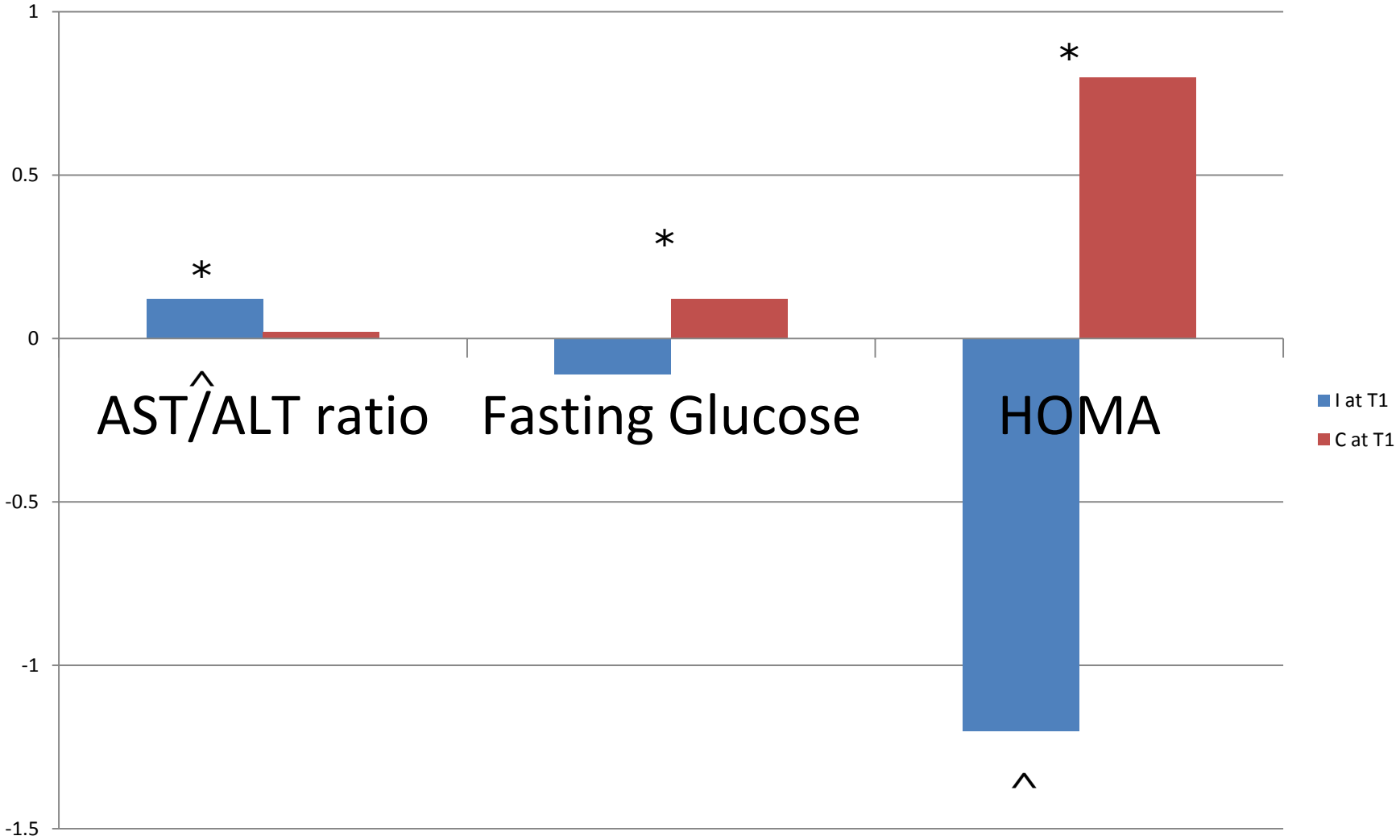
Post T1 Anthropometric Measurements

^ P<0.05 (Comparison with baseline)



Inter-group comparison
*** p<=0.001
** p<=0.01
* p<=0.05

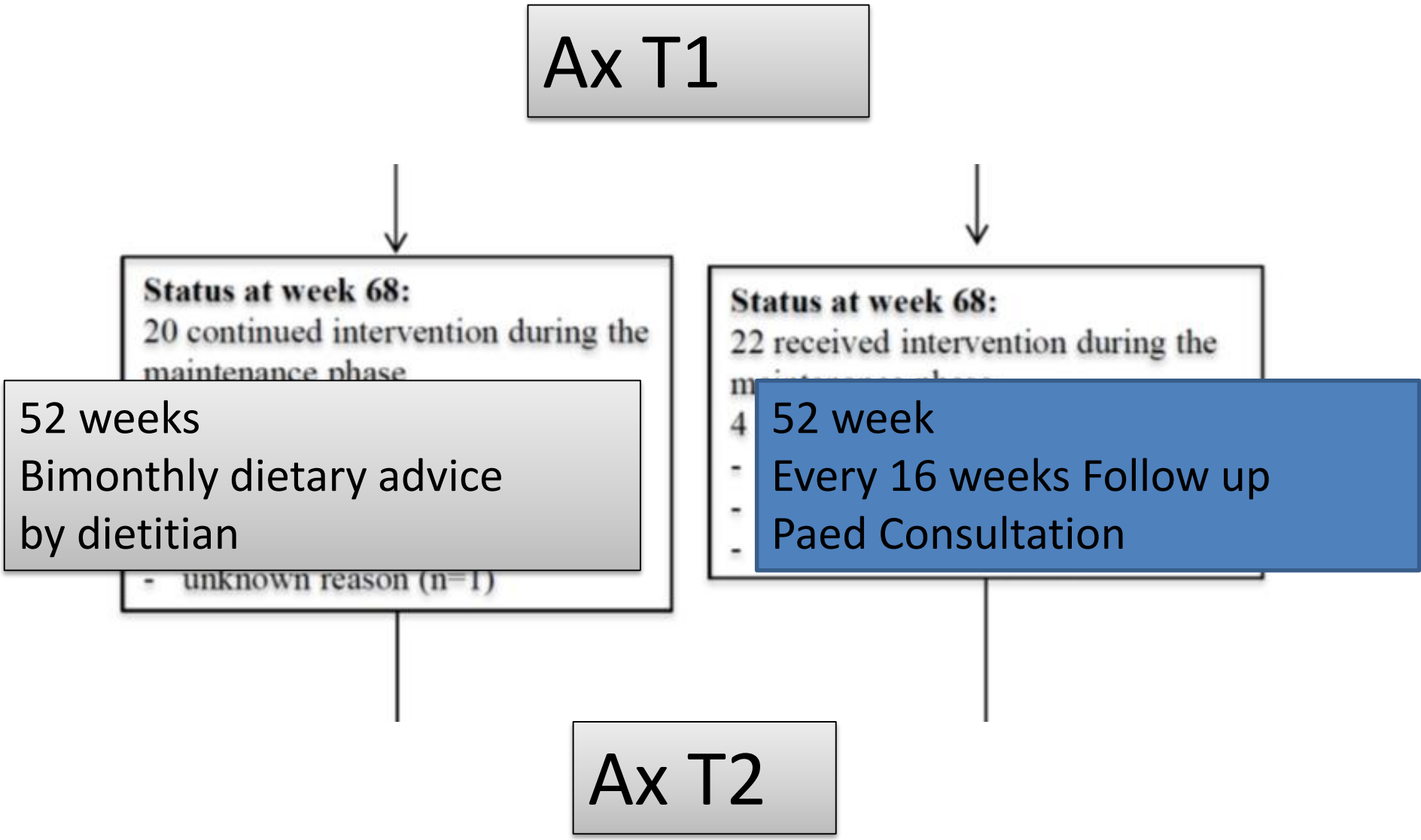
Post T1 Biochemical Measurements



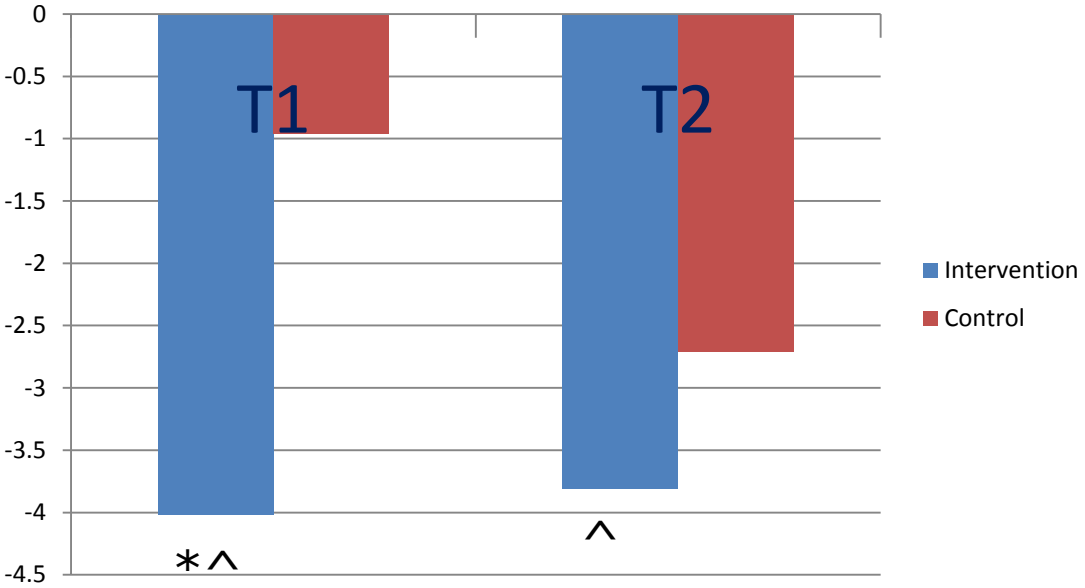
PHASE II: MAINTENANCE PHASE FOR 52 WEEKS

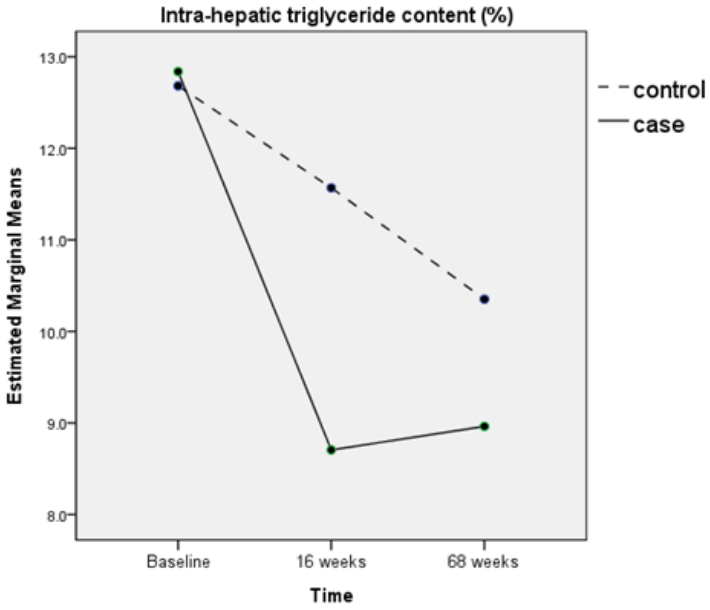
Bimonthly dietitian sessions

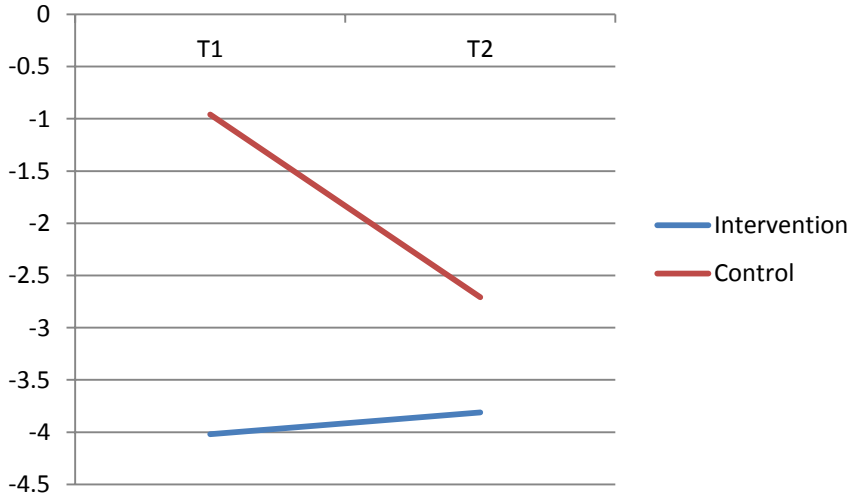
Conventional consultations


Ax T1
Status at week 68:
20 continued intervention during the
52 weeks
Bimonthly dietary advice
by dietitian
Status at week 68:
22 received intervention during the
52 week
Every 16 weeks Follow up
Paed Consultation
Ax T2

IHTC %


0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
-4.5
T1
T2
*^
^
Intervention
Control

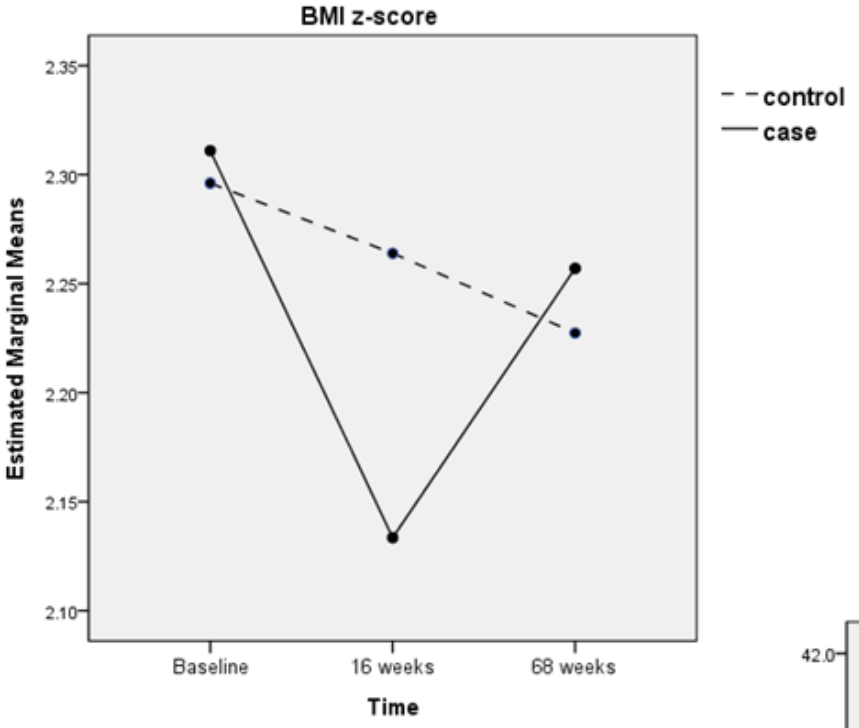

Intra-hepatic triglyceride content (%)
Estimated Marginal Means
13.0
12.0
11.0
10.0
9.0
8.0
Baseline
16 weeks
68 weeks
Time
control
case

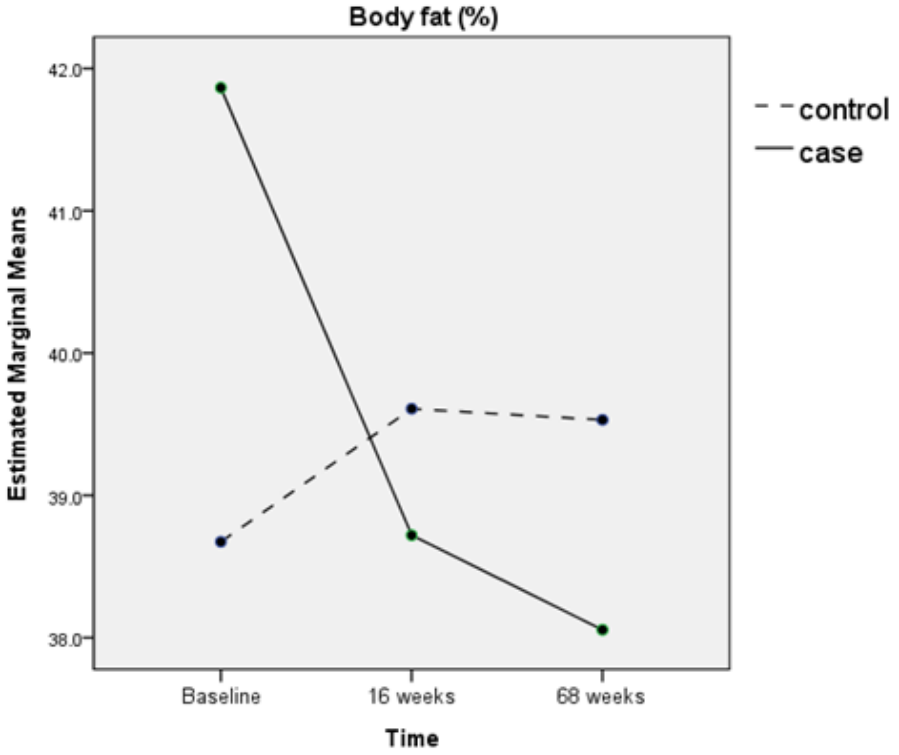

0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
-4.5
T1
T2
Intervention
Control

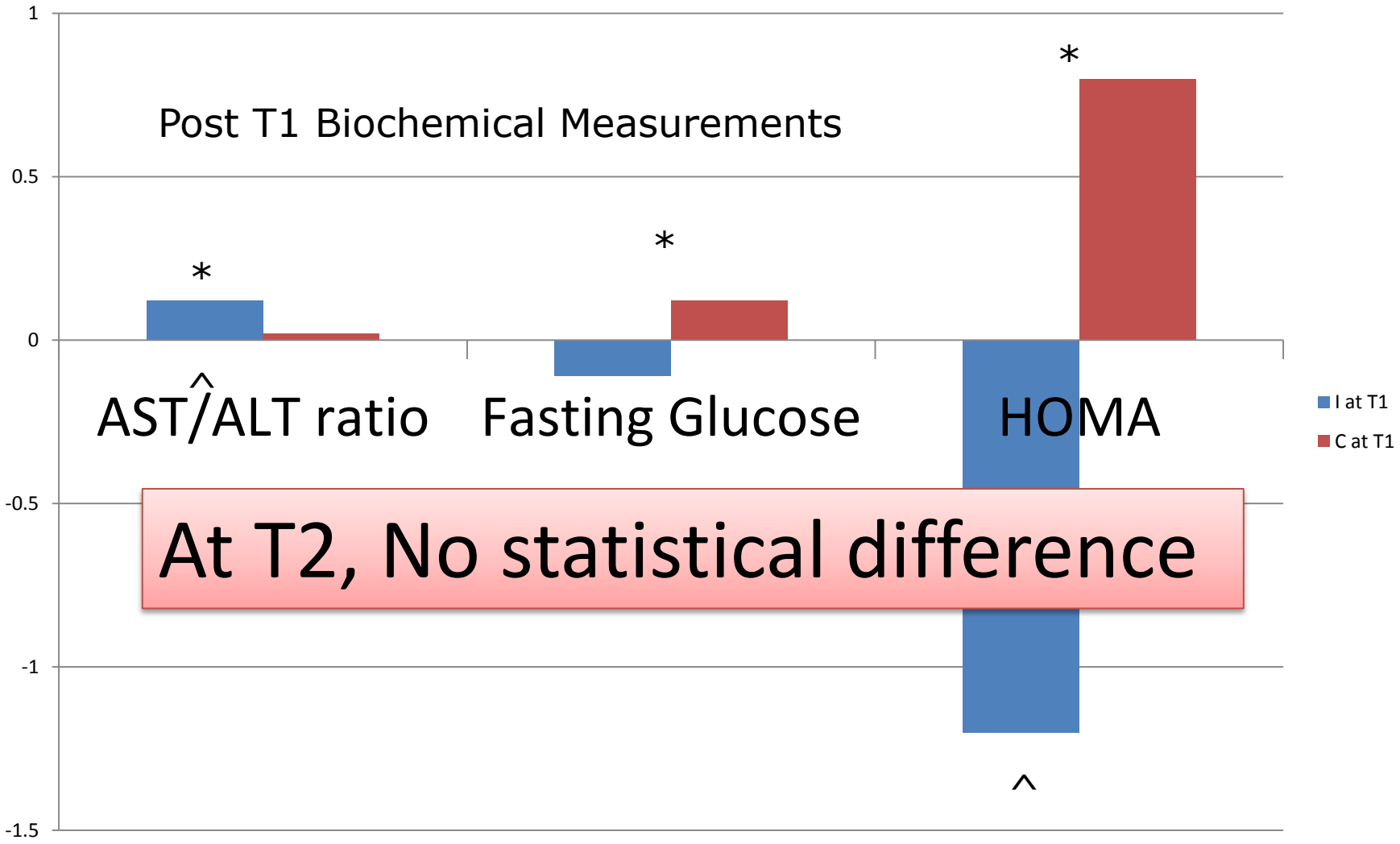
Post T2 Anthropometric Measurements

Inter-group comparison
*** p<=0.001
** p<=0.01
* p<=0.05

^ P<0.05 (Comparison with baseline)


BMI z-score
Estimated Marginal Means
2.35
2.30
2.25
2.20
2.15
2.10
Baseline
16 weeks
68 weeks
Time
control
case


Body fat (%)
Estimated Marginal Means
42.0
41.0
40.0
39.0
38.0
Baseline
16 weeks
68 weeks
Time
control
case


Post T1 Biochemical Measurements
1
0.5
0
-0.5
-1
-1.5
*
*
*
^
^
AST/ALT ratio
Fasting Glucose
HOMA
I at T1
C at T1
At T2, No statistical difference

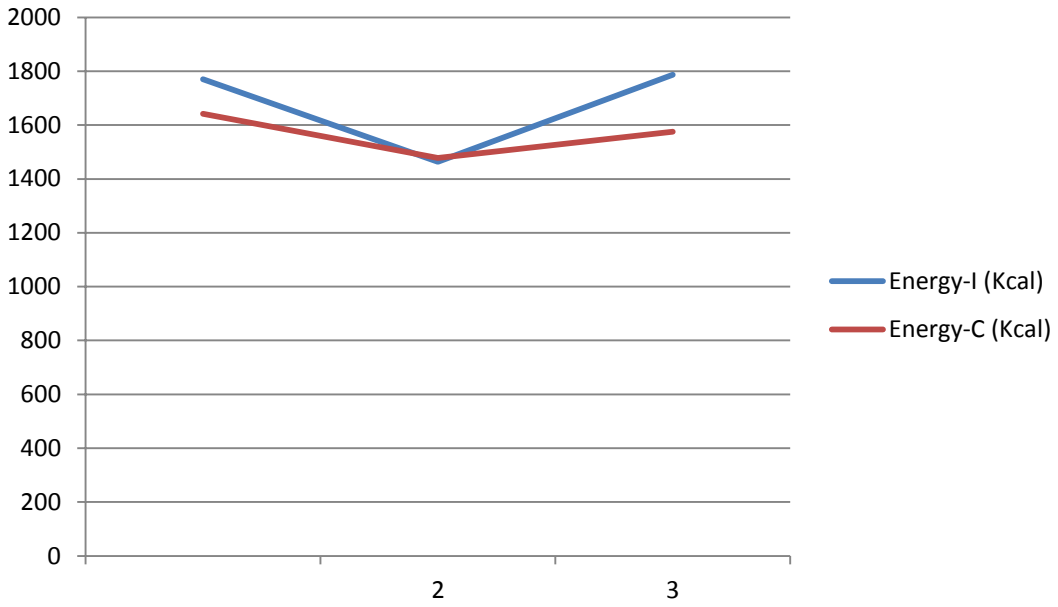
Comparisons of energy and selected nutrient intakes between the LMP group and control group in baseline, week-16 and week-68

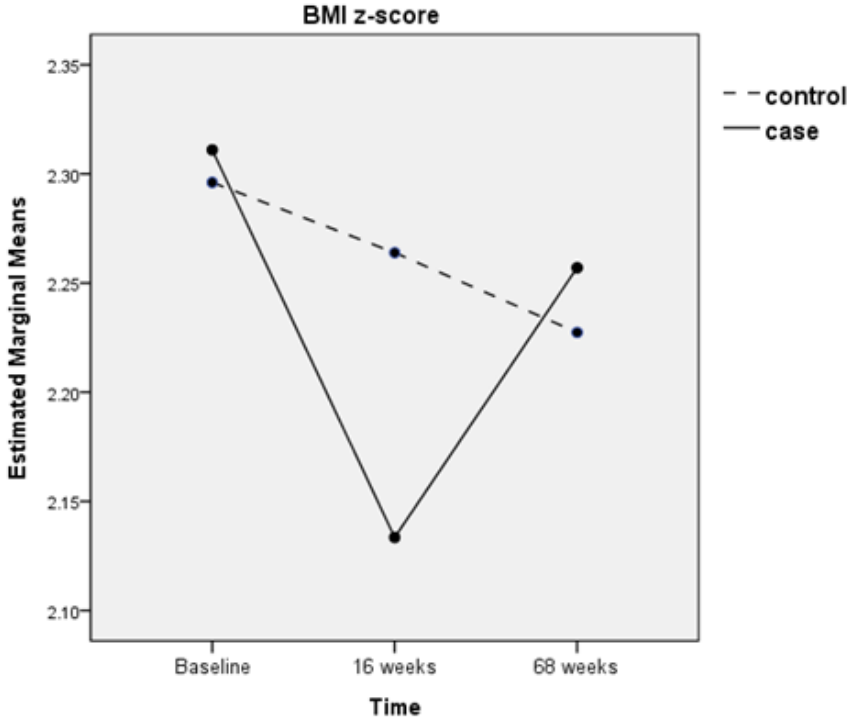
		LMP group (n=26)	Control group (n=26)	P Value[1]
Energy, Kcal	Baseline	1769.9 (516.1)	1642.1 (388.5)	0.516
	week-16	1463.0 (517.3)	1478.2 (408.9)	0.578
	week-68	1787.2 (537.2)	1575.7 (453.3)	0.180
Carbohydrate,%	Baseline	46.5 (5.7)	46.9 (6.8)	0.795
	week-16	47.4 (6.2)	46.2 (7.1)	0.520
	week-68	47.4 (6.2)	46.0 (9.9)	0.563
Fat,%	Baseline	36.2 (4.5)	34.5 (5.8)	0.247
	week-16	31.6 (6.5)	35.6 (5.3)	0.019
	week-68	34.0 (5.7)	35.2 (7.7)	0.556
Sat Fat,%	Baseline	8.3 (2.1)	8.1 (1.7)	0.660
	week-16	7.3 (2.0)	8.5 (2.1)	0.044
	week-68	8.3 (1.8)	9.3 (2.1)	0.088
Protein,%	Baseline	17.2 (3.5)	18.5 (2.8)	0.151
	week-16	20.6 (3.1)	18.2 (3.2)	0.010
	week-68	18.4 (2.3)	19.0 (4.6)	0.614
Fiber (g/1000 kcal)	Baseline	5.5 (3.0)	5.6 (2.7)	0.847
	week-16	6.6 (3.4)	6.2 (2.0)	0.586
	week-68	5.2 (2.0)	5.9 (2.2)	0.229

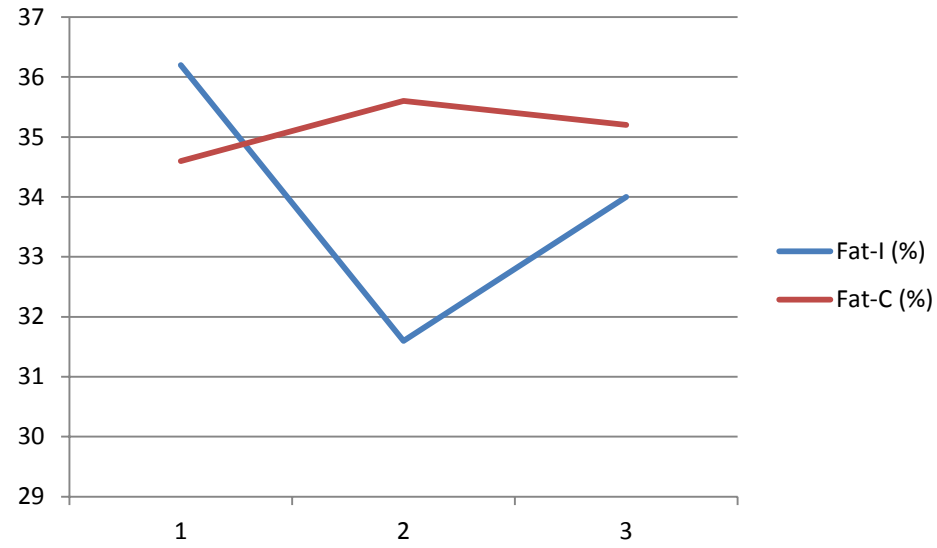
LMP = Lifestyle modification program

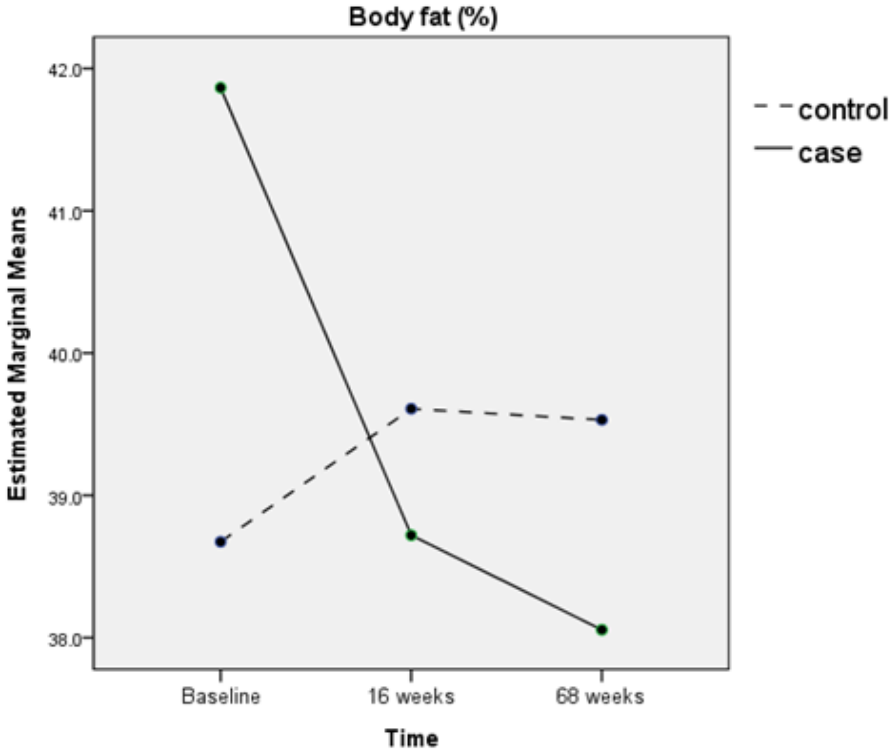
[1] Mean difference between LMP group and control group at each time point by independent t test

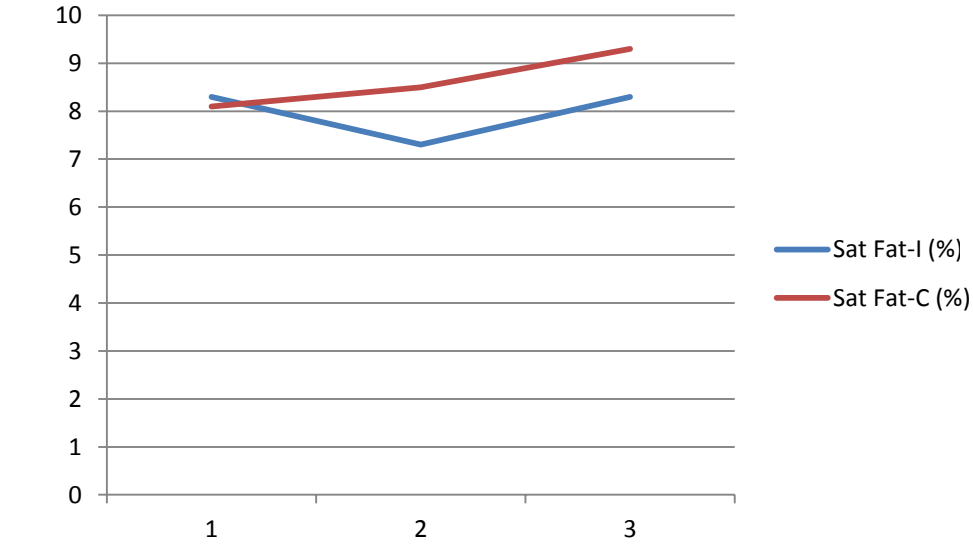
[2] Time effect and group*time interaction effect were examined by linear mixed model


2000
1800
1600
1400
1200
1000
800
600
400
200
0
2
3
Energy-I (Kcal)
Energy-C (Kcal)


BMI z-score
Estimated Marginal Means
2.35
2.30
2.25
2.20
2.15
2.10
Baseline
16 weeks
68 weeks
Time
control
case


37
36
35
34
33
32
31
30
29
1
2
3
Fat-I (%)
Fat-C (%)


Body fat (%)
Estimated Marginal Means
42.0
41.0
40.0
39.0
38.0
Baseline
16 weeks
68 weeks
Time
control
case


10
9
8
7
6
5
4
3
2
1
0
1
2
3
Sat Fat-I (%)
Sat Fat-C (%)

Discussion

- LMP
  - Phase I, significantly improvement in reduction of IHTC, BMI, body fat and insulin resistance
  - Phase II, rebound of most of the parameters
  - Persistent significant improvement of total body fat content
  - NAFLD: IHTC still significantly improved when compared with the baseline
- Convention
  - No significant change in primary and secondary outcome

Discussion

- Improvement of the total body fat and NAFLD presented as IHTC might be related to the reduction of fat content in diet

Proposed enhanced program

- Enhanced the existing LMP will be beneficial
- Extend the weekly LMP program
- Additional component in strengthen the internalization of the lifestyle modificaiton is suggested

Limitation and Discussion

- Limitations
  1. nature of the study did not allow blinding of participants
  2. liver biopsy was not performed, so not possible to evaluate necrosis & inflammation
     - However, MRS considered an accurate assessment of IHTC and technicians performing MRS were blind to grouping

Conclusion

- Weekly lifestyle intervention for intensive 16-week period reduced body weight & intra-hepatic triglyceride content in obese Chinese adolescents with NAFLD
- Additional component for internalization of the lifestyle modificaition is suggested for long term effect

BIBLIOGRAPHY

(1) Widhalm K, Ghods E. Nonalcoholic fatty liver disease: a challenge for pediatricians. Int J Obes (Lond) 2010 Oct;34(10):1451-67.

(2) Alisi A, Locatelli M, Nobili V. Nonalcoholic fatty liver disease in children. Curr Opin Clin Nutr Metab Care 2010 Jul;13(4):397-402.

(3) Chan DF, Li AM, Chu WC, Chan MH, Wong EM, Liu EK, et al. Hepatic steatosis in obese Chinese children. Int J Obes Relat Metab Disord 2004 Oct;28(10):1257-63.

(4) Hsu E, Murray K. Is nonalcoholic Fatty liver disease in children the same disease as in adults? Clin Liver Dis 2012 Aug;16(3):587-98.

(5) Lee SM. Childhood overweight and obesity. Hong kong: Student Health Service, Department of Health; 2012.

(6) Patton HM, Sirlin C, Behling C, Middleton M, Schwimmer JB, Lavine JE. Pediatric nonalcoholic fatty liver disease: a critical appraisal of current data and implications for future research. J Pediatr Gastroenterol Nutr 2006 Oct;43(4):413-27.

(7) Lee SS, Park SH, Kim HJ, Kim SY, Kim MY, Kim DY, et al. Non-invasive assessment of hepatic steatosis: prospective comparison of the accuracy of imaging examinations. J Hepatol 2010 Apr;52(4):579-85.

(8) Wong VW, Chu WC, Wong GL, Chan RS, Chim AM, Ong A, et al. Prevalence of non-alcoholic fatty liver disease and advanced fibrosis in Hong Kong Chinese: a population study using proton-magnetic resonance spectroscopy and transient elastography. Gut 2012 Mar;61(3):409-15.

(9) Liu KH, Chan YL, Chan WB, Chan JC, Chu CW. Mesenteric fat thickness is an independent determinant of metabolic syndrome and identifies subjects with increased carotid intima-media thickness. Diabetes Care 2006 Feb;29(2):379-84.

(10) Ko GT, Liu KH, So WY, Tong PC, Ma RC, Ozaki R, et al. Cutoff values for central obesity in Chinese based on mesenteric fat thickness. Clin Nutr 2009 Dec;28(6):679-83.

(11) Wong VW, Chan RS, Wong GL, Cheung BH, Chu WC, Yeung DK, et al. Community-based lifestyle modification programme for non-alcoholic fatty liver disease: a randomized controlled trial. J Hepatol 2013 Sep;59(3):536-42.

(12) Nobili V, Manco M, Devito R, Di C, V, Comparcola D, Sartorelli MR, et al. Lifestyle intervention and antioxidant therapy in children with nonalcoholic fatty liver disease: a randomized, controlled trial. Hepatology 2008 Jul;48(1):119-28.

(13) Vajro P, Franzese A, Valerio G, Iannucci MP, Aragione N. Lack of efficacy of ursodeoxycholic acid for the treatment of liver abnormalities in obese children. J Pediatr 2000 Jun;136(6):739-43.

(14) van der Heijden GJ, Wang ZJ, Chu ZD, Sauer PJ, Haymond MW, Rodriguez LM, et al. A 12-week aerobic exercise program reduces hepatic fat accumulation and insulin resistance in obese, Hispanic adolescents. Obesity (Silver Spring) 2010 Feb;18(2):384-90.

(15) Kugelmas M, Hill DB, Vivian B, Marsano L, McClain CJ. Cytokines and NASH: a pilot study of the effects of lifestyle modification and vitamin E. Hepatology 2003 Aug;38(2):413-9.

(16) Wang CL, Liang L, Fu JF, Zou CC, Hong F, Xue JZ, et al. Effect of lifestyle intervention on non-alcoholic fatty liver disease in Chinese obese children. World J Gastroenterol 2008 Mar 14;14(10):1598-602.

(17) Kong AP, Choi K.C., Chan R.S., Lok K., Li L., Ozaki R., et al. A Randomized Controlled Trial to Investigate the Impact of a Low Glycemic Index (GI) Diet on Body Mass Index in Chinese Adolescents. 2012.

(18) Leung SS, Cole TJ, Tse LY, Lau JT. Body mass index reference curves for Chinese children. Annals of Human Biology 1998;25(2):169-74.

(19) Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clinical Chemistry 1972 Jun;18(6):499-502.

(20) CUHK Discovers Low-glycemic Dietary Intervention Programme Helps Improve Non-alcoholic Fatty Liver Effectively. Press releases, CUHK 2010 Apr 2.

(21) Lok KY, Chan RS, Sea MM, Woo J. Nutritionist's variation in counseling style and the effect on weight change of patients attending a community based lifestyle modification program. Int J Environ Res Public Health 2010 Feb;7(2):413-26.

(22) Hui SC. Criterion-related validity of a 0-10 scale physical activity rating in Chinese youth.Proceedings of the 2001 Asia-Pacific Rim Conference on Exercise and Sports Science: The New Perspective of Exercise & Sports Science for the Better Life in the 21st Century. Seoul, Korea: Seoul National University; 2001.

(23) Mager DR, Patterson C, So S, Rogenstein CD, Wykes LJ, Roberts EA. Dietary and physical activity patterns in children with fatty liver. Eur J Clin Nutr 2010 Jun;64(6):628-35.

(24) Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol 1999 Sep;94(9):2467-74.

(25) Manco M, Marcellini M, Devito R, Comparcola D, Sartorelli MR, Nobili V. Metabolic syndrome and liver histology in paediatric non-alcoholic steatohepatitis. Int J Obes (Lond) 2008 Feb;32(2):381-7.

(26) Conn VS, Koopman RJ, Ruppar TM, Phillips LJ, Mehr DR, Hafdahl AR. Insulin Sensitivity Following Exercise Interventions: Systematic Review and Meta-Analysis of Outcomes Among Healthy Adults. J Prim Care Community Health 2014 Jan 27;5(3):211-22.

(27) Renjilian DA, Perri MG, Nezu AM, McKelvey WF, Shermer RL, Anton SD. Individual versus group therapy for obesity: effects of matching participants to their treatment preferences. J Consult Clin Psychol 2001 Aug;69(4):717-21.

Thank you